NIH Award from the National Institute of Allergy and Infectious Diseases

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- **Project:** Arachidonic Acid Mediated Regulation of Secretory IgA Levels in the Airways
- **Start Date:** August 13, 2009
- **Total Award Amount:** $228,750

**How the results of this project will benefit society:**
Secretory IgA (SIgA) is an important mediator of mucosal immunity. Strategies that boost SIgA production in the airways will benefit patients who have become susceptible to infections caused by airborne pathogens. These studies will provide valuable information supporting the goal of the National Institutes of Health to prevent disease and promote health.

**The problem the project is trying to solve:**
These studies indicate that the arachidonic acid metabolizing enzymes, 12/15-lipoxygenase and 5-lipoxygenase regulate the first-line defense molecule secretory IgA in the conducting airways. We hypothesize that this is due to their ability to produce cysteinyi leukotrienes and the effects of the cysteinyl leukotrienes are mediated by nitric oxide. Manipulation of this pathway would be predicted to result in induction of secretory IgA and decreased susceptibility to pulmonary infections.

**How this project will work:**
Our studies point to a novel molecular pathway by which arachidonic acid metabolism regulates the basal rate of SIgA production in the airways. As such our studies might support the development of a medicine that can be used as a co-therapy with mucosal vaccines to permanently boost the levels of SIgA in the airways; thus providing a very long-lived pathogen-specific protection. However, because of the polyreactivity of innate SIgA and the ability of its oligosaccharide side-chains to bind directly to bacteria, our studies might also support the development of a stand-alone therapy to boost the generally protective mucosal immunity that is afforded by SIgA. Our preliminary studies support a working model in which the magnitude of SIgA production in the airways is largely dependent upon the levels of constitutive generation of 12/15-lipoxygenase (LO) and 5-LO metabolites produced by airway epithelial cells and their downstream ability to induce nitric oxide (NO) production by dendritic cells.

We will test this hypothesis by completing two specific aims. Specific aim 1: To determine if cysteinyi leukotrienes (CysLTs) mediate baseline NO and SIgA production in the airways of wild-type mice and if increased CysLTs mediate the increase of NO and SIgA observed in the airways of 12/15-LO-/- mice. Specific aim 2: To determine if NO mediates baseline SIgA production in the airways of wild-type mice and if increased NO mediates the increase of SIgA production observed in the airways of 12/15-LO-/- mice. We estimate that our proposed studies will be complete in approximately two years and we anticipate that they will lead to additional questions regarding the basic mechanisms by which SIgA is regulated in the airways. Our proposed mouse studies will utilize very well characterized genetic and pharmacologic approaches. Medicines that target the LO and NO pathways are already developed or emerging. Thus, we believe that our proposed studies will reveal a novel mechanistic pathway that can be readily manipulated to dramatically boost SIgA levels in the airways.

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