

# Biomedical Research Funded in 2005

## *Elizabeth Nash Memorial Fellowship Program*

- 1) George Caughey, MD, Principal Investigator - University of California, San Francisco  
Xiang Xu, MD, PhD – Post Doctoral Fellow

*“Probing the role of Hepatocyte Growth Factor (HGF) regulation by neutrophil secretions”*

This project studies the regulation of CF epithelial function by neutrophil peptidase-generated antagonists of HGF: Hepatocyte growth factor (HGF) is essential for epithelial development and repair. HGF can be induced in damaged tissue including the lung, and has been shown in an animal model to decrease airway inflammation and remodeling, e.g. fibrosis. Preliminary studies for this project have found that enzymes released during inflammation in the CF lung inactivated HGF by cleaving the protein. Furthermore, this cleavage of HGF produces a fragment that functions to oppose epithelial repair. The goal of this project is to further understand the function of these HGF fragments generated by cleavage and their effect on CF epithelial cell function. This study will provide insight into the chronic epithelial wounding seen in CF and may identify strategies to limit this airway damage.

*Amount Funded: \$40,000.00*

- 2) Ron Kopito, PhD, Principal Investigator – Stanford University, and John Christianson, PhD,  
Post Doctoral Fellow

*“Elucidation of the Ubiquitin Pathway involved in degradation of delta F508 CFTR”*

This project focuses on the identification of genes involved in degradation of CFTR  $\Delta$ F508: All cells have a quality control check point for the synthesis of proteins. Proteins that do not fold properly are recognized by the cell as misfolded and subsequently these proteins are degraded by the cell. How the cell carries out this quality control check and the proteins involved in this process is not clearly understood. The goal of this project is to use a fluorescent-based screening assay to identify specific proteins involved in the recognition of the misfolded CFTR  $\Delta$ F508 protein. The identification of these specific proteins for mutant CFTR will become the target of a rationale therapeutic design to enhance CFTR maturation.

*Amount Funded: \$40,000*

- 3) Jeffrey Wine, PhD, Principal Investigator - Stanford University, and Jae Young Choi, MD, PhD  
Post Doctoral Fellow

*“Development of methods to test longevity of mucus plugs in airway glands in CF and imaging of glandular secretion and single-cell secretion”*

This project studies the mucus structure in normal, CF and pharmacologically treated airways: The goal of this project is to investigate if airway gland dysfunction plays a role in CF lung disease. The role of the airway gland in CF has become controversial. The findings published by Boucher and colleagues from the University of North Carolina, Chapel Hill show that CFTR protein expression in the airway gland is significantly lower than previously reported. Mucous secretion is important for normal lung function, and is altered in CF lungs. Thus the question of the role of airway glands in CF lungs needs to be understood in order to identify important treatments to combat CF lung disease.

*Amount Funded: \$40,000*

- 4) Beate Illek, PhD, Principal Investigator - Children's Hospital Oakland Research Institute, Oakland, California, Eun Jin Kim, PhD, Post Doctoral Fellow.

*"Vitamin C Uptake into Cystic Fibrosis Airways"*

This study is on role of vitamin C on CFTR transport and *Pseudomonas aeruginosa*-induced oxidative stress in cystic fibrosis airways: Vitamin C is a normal component of the airway, and concentrations of this natural antioxidant are decreased during oxidative stress - a condition that occurs in the CF lung. Interestingly, Dr. Illek and colleagues have demonstrated that vitamin C activates both the wild type and the corrected mutant CFTR protein. Thus, the goal of this project is to determine the beneficial effects of vitamin C in protecting the airways from pyocyanin-induced inhibition of CFTR channel activity. In other words, in the presence of a *Pseudomonas* infection, will vitamin C and/or other antioxidants protect the airways and preserve CFTR channel activity? This study will have a direct application to the design of future preclinical studies.

*Amount Funded: \$40,000.00*