

## 2004

1. Jonathan Widdicombe, PhD, University of Davis, Davis, California, Principal Investigator

“Technical Support for Production of Primary Cultures of Human Tracheal Epithelium”

This grant is to provide funding to maintain a CORE facility for the supply of primary cultures of airway epithelium. These researchers were the first to show that airway epithelial cells could be grown in culture with retention of vectorial Cl secretion.

They then used these cells to provide the first demonstration of reduced Cl conductance of the apical membrane of airway epithelium in CF. Additionally, cells grown using their technique have been widely used by others.

Amount Funded: \$30,000.00

2. Dennis Nielson, MD, PhD, University of California San Francisco, San Francisco, California, Principal Investigator and

Daniel Salinas, MD, Post Doctoral Fellow

“Novel Methods to Study the Link Between the Gene Defect and the Pathophysiology of CF” The purpose of this study is to determine the link between the CF gene defect and clinical disease. This is of critical importance in developing therapies to treat CF. New biophysical measurement methods and model systems will be used to define the role of the ASL and submucosal glands in CF. So far, researchers have found that the pH of submucosal gland fluid from nasal biopsies is more acidic in CF than in non-CF patients. Further research could help in understanding airway pH regulation, which could be key to understanding airway defenses and chronic infection in CF. Additionally, researchers have successfully demonstrated that submucosal gland dysfunction can be considered a primary defect in CF. Other results indicate that the fluid secretion rate from submucosal glands was reduced 2.7-fold and secreted fluid viscosity was elevated 2.2-fold in early CF. These results provide evidence for submucosal gland dysfunction as an intrinsic defect in CF, furthering earlier findings supporting the involvement of CFTR in gland fluid secretion in intact airways, and of reduced fluid secretion and hyperviscosity in severely diseased CF airways.

Amount Funded: \$33,333.34

3. Ron Kopito, PhD, Stanford University, Principal Investigator and Wei Zhang, PhD, Post Doctoral Fellow

“Small Molecule Screening Approach to Search for Suppressors of Delta508”

The purpose of this study is to identify small molecules capable of enhancing the folding and/or stability of misfolded Delta F508-CFTR. Another goal is to develop ultra-sensitive high throughput homogeneous assay for detecting the cell surface expression of CFTR. As of now researchers have generated a reporter that not only contains live cell surface displayed S-tags, but also maintains Delta F508-CFTR

folding and traffics defective properties. Also, the proposed assay was demonstrated to be valid. Further research is required to finish up the experiment, specifically generating a stable CHO cell line expressing Delta F508-4S-CFTR. This stable cell line will then be tested on the optimized assay, and then they will set up a homogenous cell-based assay for screening small molecules capable of enhancing folding, cell surface delivery, stability and functional expression of Delta F508-CFTR.

Amount Funded: \$40,000.00

4. Beate Illek, PhD, Children's Hospital Oakland Research Institute, Oakland, California, Principal Investigator

“Vitamin C Uptake into Cystic Fibrosis Airways”

The purpose of this study is to introduce Vitamin C to CF airways in hopes of easing airflow through CF lungs once again. CF lungs produce a thickened airway mucus that inhibits transport of sputum, forming plugs that partially block airways. Recent studies have shown that Vitamin C replenishes local Vitamin C deficits that contribute to the inhibition of normal hydration of airway surface liquid/mucus. Another aspect has been added to the study and that is to examine the properties of Vitamin C that act as an antioxidant by scavenging free radicals. Researchers recently started to study the effects of an oxidizing environment on CFTR Cl transport and found that an oxidizing environment blocked CFTR Cl transport across human tracheal cultures. The goal of this project is to determine the beneficial effects of Vitamin C and the combination of Vitamin C with other antioxidants during oxidative stress of the airways.

Amount Funded: \$20,000.00