

Biomedical Research Funded in 2010

New Horizons Research

1) Terry Machen, Ph.D., Principle Investigator - University of California Berkeley

“Mechanism and JNK Control of Flagellin-Stimulated Inflammation and CL Secretion by Airway Epithelia”

To aid Cystic Fibrosis research, it is necessary to understand the specific chemicals and agents that are responsible for the inflammatory response pathways. It was determined that the flagellin-stimulated inflammatory response which includes the activation of a slow increase in transepithelial chloride secretion results from activation of CFTR gene creating a cascade of responses. However, for CF patients the absence of this chloride secretion might reduce bacterial clearance in the lungs thus hindering normal activity. An inhibitor of the normal inflammatory response is JNK which reduces IL8 secretion and thus increase chloride secretion.

The flagellin activates CFTR-dependent initiates chloride secretion by activating CFTR or related ion transport pathways, and that JNK inhibits this response. Therefore, by identifying ion transport pathways involved in CFTR-dependent chloride secretion as well as testing the role of JNK in regulating both the inflammatory response and chloride secretion this research is hoping to find a method to aid Cystic Fibrosis patients. Inflamed airways in CF may benefit from treatment with JNK blockers because these should reduce inflammation and increase chloride secretion in CF patients with the G551D deletion who express CFTR in the plasma membrane or in patients treated with correctors to increase delta F508 CFTR in the membrane.

Amount Funded: \$75,000.00

2) Forest Rohwer, Ph.D., Principle Investigator- San Diego State University

“Metagenomic Analysis of Viral and Microbial Communities in Cystic Fibrosis Lungs”

Metagenomics is a field of study investigating community genetic information obtained from a particular environment. For a CF airway infection, this means a metagenomic study would include the study of all the microbial, viral and fungal populations present in the airway of the patient and not just the species that the clinical lab can culture and identify. Identifying all members of these populations is important because the immune system mounts an inflammatory response to the entire community (i.e. microbial, viral and fungal) and not just *Pseudomonas* or *Staphylococcal* species that are typically cultured.

Dr. Rohwer’s proposed work approaches the CF airway infection as a complex and dynamic ecosystem composed of interacting microbial populations competing in an environment of limited resources (i.e. oxygen, nutrients etc). The environment also poses challenges for these microbial communities because of the actions of the immune system and the effects of therapies such as antibiotics and chest physiotherapy.

Amount Funded: \$75,000.00

3) Dieter Gruenert, Ph.D., Principle Investigator - University of California San Francisco

“CFTR expression levels and CFTR function; transgene versus endogenous.”

A protein called CFTR is an ion channel that allows for Chloride molecules to be transported through channels in the intestine, lung, pancreas and sweat glands. This makes sure that the salt concentrations remain steady throughout the body. However if there is a defect with the CFTR, there are unstable salt concentrations throughout the body causing Cystic Fibrosis. Bicarbonate is a huge molecule that is needed for normal body function. As a result, it was determined that cell signals are required for normal body function and how the mutation creates problems for these signals.

Also it was determined what mutations cause defects in the ability of the channels to pass bicarbonates through as well as how this mutation can cause CF and the methods by which treatments can be created to allow for this problem to be addressed.

Amount Funded: \$75,000.00

4) Daniel J. Hassett, Ph.D. Principle Investigator- University of Cincinnati

“Molecular Basis Underlying Killing of Mucoic Pseudomonas aeruginosa by Nitrite”

The pathogen Pseudomonas aeruginosa which is associated with CF exists within the CF airways that are already filled with mucus with reduced oxygen tension. Here these pathogens grow and develop because of the ideal conditions present there. However as they develop they form into a highly organized yet antibiotic and phagocyte-resistant communities known as biofilms. The most resilient form is called the mucoid form which overproduces a thick exopolysaccharide called alginate that is growing under anaerobic conditions (without oxygen). However to destroy these colonies there could be used nitrites to kill the mucoid the most resistant and as a result stop the potential to create more mucus. This would help CF patients breathe better and create targeted treatments.

Amount Funded: \$75,000.00

Elizabeth Nash Memorial Fellowship Program

1) Susan Lynch, Ph.D., Principal Investigator - University of California San Francisco and Weidong Kong, Ph.D., Post Doctoral Fellow

“Clinical and Basic Research Studies of CF Airway Gland Secretions.”

CF involves a defect in a protein (CFTR) present in the airway glands. Airway glands secrete mucus onto the airway surface. Gland mucus is an important component of the defense mechanism against environmental agents (e.g. bacteria) that we inhale. Gland mucus secretion is controlled by local nerve cells in the airways; the local nerve cells are controlled by local stimuli and by central nerves arising from the brain.

The central nerves are stimulated in response to strong irritation, such as inhalation of fluid or food in the airway. They then stimulate glands to secrete through a non-cystic fibrosis protein. This causes the glands to secrete large amount of fluids and also provokes coughing as a defense mechanism to clear the airways. This kind of gland secretion is still strong in cystic fibrosis patients.

In contrast, the local nerves are also weakly stimulated by mild irritating agents, such as Inhalation of bacteria or viruses during normal breathing. We hypothesize that the response to mild local stimulation is mediated mainly or entirely by gland secretion that requires CFTR. This 24x7 gland secretion through CFTR allows normal airways to remove inhaled bacteria; thus airways are usually sterile.

In the absence of functioning CFTR, the glands no longer respond to these local stimuli, so bacteria are able to reside in the mucus for much longer times unless they are killed and cleared with inhaled antibiotics and mechanisms to mobilize the intact gland secretion system. Our research seeks to gain control of CF glands so that their residual function can be used to help fight against airways infections.

Amount Funded: \$40,000.00

2) Bruce Hammock, Ph.D., Principle Investigator - University of California Davis, Jun Yang Ph.D., Post Doctoral Fellow

“A New Therapeutic Strategy Focusing on Anti-Inflammatory Therapies for Cystic Fibrosis-Related Lung Disease: Preliminary Data Towards Consideration of Therapy with Soluble Epoxide Hydrolase Inhibitor (sEHI).”

Majority of Cystic Fibrosis patients must contend with the high amounts of mucus production that is within their lungs. This results from the frequent lung infections and huge inflammation that plagues CF patients. However, it is becoming more important to not only understand the inflammatory response but also to develop therapies to aid in the inflammation that results in the mucus present in CF patients.

To understand the inflammation process, researchers had to first determine the cellular components as well as the specific chemicals involved with the inflammation process. They also had to determine the pathways that the chemicals go through to generate an inflammation response of the lungs. It was determined that oxylipids such as prostaglandins and leukotrienes (which are eicosanoid lipid mediators derived largely from phospholipase released arachidonic acid) are important molecules of the inflammation process. However to tract the inflammation process it was important to mark arachidonic acids, w-3 fatty acids and linoleic acids cascades which are present in the cyclooxygenase (COX) and lipoxygenase 5 (5-Lox) pathways and use this to

determine the progression of the inflammation process. All of this would allow researchers an opportunity to see the process of inflammation and what can be done to hinder the inflammation process.

Later on, after figuring out the pathway as well as chemicals involved, work was started on figuring out anti-inflammatory drugs that could be given to hinder the inflammation response and thus reduce the amount of mucus production within the lung. This is seen by the transformation of lipidepoxyde which in an anti-inflammatory agent that transforms into lipid diol a proinflammatory agent through the introduction of sEH, to allow for the transformation. However with the sEHI that acts as an inhibitor of the chemical sEH that halts lipid diol pro inflammatory agent to be created. This would be administered by testing a new anti-inflammatory therapy by co-administration 5-LOX inhibitor with sEHI that would aid in forcing the body to use its own natural system to prevent inflammation. All of these elements would allow for the CF patients to be able to lessen inflammation and aid them in breathing.

Amount Funded: \$40,000.00

3) Paul Quinton, Ph.D. Principle Investigator - University of California San Diego, Ning Yang M.D., Ph.D. Post Doctoral Fellow

“Can Bicarbonate Help Mucus Release in Cystic Fibrosis”

CF patients must contend with mucus creation within various exocrine organ systems such as respiration, digestion and reproduction. Here CF patients, who have mutations within a gene that codes for the cystic fibrosis transmembrane regulator (CFTR) which controls Cl⁻ and HCO₃⁻ conductance through the cell and thus through allows for mucus creation. This research discovered the link between CFTR dysfunction and CF mucoviscidosis which results in figuring out the clues for treating the mucus production within CF patients. Therefore as a result the HCO₃⁻ might be used to prevent the dense formation of mucus thus helping the CF patients breath.

Amount Funded: \$40,000.00

4) Dennis Nielson, M.D., Ph.D. Principle Investigator - University of California San Francisco, Nico Derich, M.D. Post Doctoral Fellow

“Ex Vivo surrogate Assays to Assess Efficacy of Ion Channel-Targeted CF drugs”

The method by which most transport occurs in the cell is via ion-channels through which all the chemicals from the cell can be transported outside of the cell and vice a versa. However specifically for CF patients, they have a faulty ion channels that transport the necessary Cl⁻ across the member that triggers the cell to respond a certain method. This particular research modified the ion transport proprieties of CF cells to be like non CF cell transport. The change of this ion channel would have to be by creating a method to fix the CFTR gene (Cystic fibrosis transmember regulator) that is responsible for controlling the ion channel and thus forcing an inflammatory response therefore creating mucus. However this would aid patients in allowing them the opportunity to create a method to have health transport channels thus allow for proper cell communication.

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