

THE HARTWELL FOUNDATION

2013 Individual Biomedical Research Award

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**Inhibition of Mucus Hypersecretion as a Therapeutic Approach
for Respiratory Disease**



In normal breathing, the function of mucus is to protect airway passages from injury and infection. Mucus is the first line of defense, trapping dust, bacteria, fungi and viruses that might otherwise enter the lungs, while humidifying inspired air to keep airways moist. . However, excessive production of mucus (hypersecretion) combined with inflammation and narrowing of the airways (bronchial constriction) leads to severe breathing difficulty chronic wheezing, and increasing susceptibility to infections. The result often produces irreversible changes in airway structure. Babies born prematurely with undeveloped lungs, newborns that require prolonged mechanical ventilation support and young children with small airways are particularly vulnerable. Common diseases characterized by airway mucus hypersecretion include asthma and chronic obstructive pulmonary disease. In addition, mucous hypersecretion occurs in cystic fibrosis, where mucous production is unusually thick and sticky. In these children mucus clogs not only the respiratory passages, but the intestine, liver, and pancreas, causing a host of painful and deleterious symptoms. To mitigate the consequences of early and irreversible damage to lung airways and other organ systems, early and effective treatment is extremely important. While anti-inflammatory drugs can reduce airway inflammation, bronchodilators can reduce airway constriction, and expectorants can help loosen and clear the mucus from the airways, there are unfortunately no drugs to treat the problem of airway mucus hypersecretion. To address this unmet need, Jennifer proposes to use high throughput screening of a large library of small, drug-like molecules to identify those compounds that will interfere directly with known enzymes involved in the biosynthesis of mucus. Target drugs will be then carried forward into cell-based assays to identify those that demonstrate the ability to selectively interfere with mucus production in cultured cells. If she is successful in developing a means to directly decrease the hypersecretion of mucous, a new therapeutic strategy will be available for diseases where excessive mucus formation is an important part of pathology. Effective intervention to control mucus formation in asthma and chronic obstructive pulmonary disease, as well as in cystic fibrosis, will improve the clinical management of these respiratory-related diseases by reducing morbidity and mortality in growing children, enhancing their quality of life, and reducing the economic burden on affected families.