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Making Strides in Cystic Fibrosis

As recently as 1980, children with cystic fibrosis (CF) survived only into their teens or early 20s. However, with continued advances made in treatment therapies, their prognosis has improved considerably. Today the predicted median age of survival is about 38, thanks in part to the ongoing clinical research conducted at the more than 100 Cystic Fibrosis Centers across the country accredited by the Cystic Fibrosis Foundation. NewYork-Presbyterian/Columbia University Medical Center, one of the designated centers, also is among 77 centers to participate in the Foundation's Cystic Fibrosis Therapeutics Development Network (TDN), the largest cystic fibrosis clinical trials network in the world.

"About half of the patients in the country with CF are adults over the age of 18, and in fact, we follow nearly 200 adults," says Emily A. DiMango, MD, pulmonologist and Director of the Gunnar Esiason Adult Cystic Fibrosis and Lung Program at NewYork-Presbyterian/Columbia. The program's multidisciplinary team includes physicians, a nurse trained in CF, as well as a social worker, physical therapist, and dietitian.

"Our social worker serves as a patient advocate and addresses the psychological issues that go along with chronic disease," adds Dr. DiMango. "We have a physical therapist who helps patients with exercise and clearing the thick mucus from their lungs. Weight gain is also a battle in this disease because it affects the digestive tract as well. So we have a dietitian who provides our patients primarily with strategies to gain weight."

> **"We've developed a model program for transitioning patients from pediatric care to the adult team here."**
>
> **— Dr. Emily A. DiMango**

The Gunnar Esiason Adult Cystic Fibrosis and Lung Program, which works closely with NewYork-Presbyterian/Columbia's nationally regarded lung transplant program – one of the oldest in the United States – also collaborates with the Sarah E. Nash Children's Lung Center and the

(continued on page 2)

Studying Chronic Lung Disease in HIV-Positive Smokers

As a lung specialist for more than 25 years, Robert J. Kaner, MD, has observed dramatic changes in HIV-related lung diseases. "During the initial part of the outbreak we were focused on diagnosing and treating infectious diseases of the lung," says Dr. Kaner, a pulmonologist in the Division of Pulmonary and Critical Care Medicine at NewYork-Presbyterian/Weill Cornell Medical Center. "Since the advent of highly active antiretroviral therapy, HIV can be controlled with medications. However, the spectrum of HIV-related lung diseases has changed, and now we are looking at more chronic complications in the lung because people are surviving so much longer. These other problems are now becoming more important in determining morbidity and mortality in the HIV-positive population."

Lung complications related to HIV have been the subject of intense study by Dr. Kaner, whose research focuses on the application of innovative molecular techniques to advance the understanding of pathophysiology and further improve the diagnosis and treatment of lung disease. He has served as principal investigator of National Institutes of Health-sponsored basic research in mechanisms of vascular permeability in the lung and the interactions of human alveolar macrophages with HIV-1 and was the project leader of an NIH-sponsored study of the molecular basis of accelerated emphysema development in HIV-1 positive smokers. This effort was part of a Specialized Center of Clinically Oriented Research for chronic obstructive pulmonary disease (COPD)

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Making Strides in Cystic Fibrosis (continued from page 1)

Sue and John L. Weinberg Cystic Fibrosis Center at NewYork-Presbyterian/Morgan Stanley Children's Hospital. "We've developed a model program for transitioning patients from pediatric care to the adult team here," says Dr. DiMango.

Dr. Emily A. DiMango

Ongoing Research Efforts

As part of the TDN, NewYork-Presbyterian/Columbia is conducting a number of clinical trials in CF. "Over the last five years some very promising disease-modifying compounds have been developed," says Dr. DiMango. "Until now most of the treatments for CF have just addressed the symptoms. Our clinical trials help test these new compounds and allow us to offer our patients the latest medications available."

Dr. DiMango notes that the majority of Americans with CF have one specific gene mutation for which a targeted drug has not yet been found. One drug approved by the FDA in 2012, ivacaftor, is being used for the treatment of a rare form of CF in patients ages 6 and older who have the specific G551D mutation in the cystic fibrosis transmembrane regulator gene. "However, only about 5 percent of people have this particular form of CF," says Dr. DiMango. "While we expect the drug will prolong life, and certainly we've already seen it improve lung function and quality of life, we don't know yet about longevity."

Dr. DiMango's own research recently has focused on the effect of proton pump inhibitors for patients with gastroesophageal reflux disease (GERD). "We conducted a prospective randomized pilot study to see if reducing acid reflux would actually improve the pulmonary health of patients with CF," says Dr. DiMango. "While our study was small, surprisingly it showed a trend in increased infections in people taking those agents compared to people taking placebo."

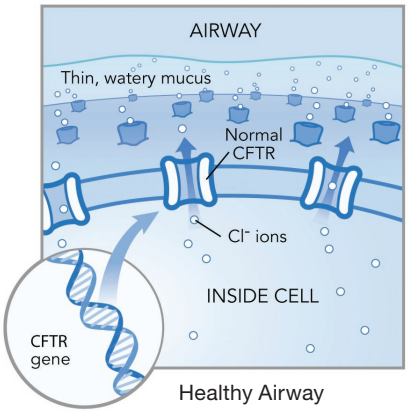
GERD is common in cystic fibrosis and may contribute to lung disease. Approximately 50 percent of patients with cystic fibrosis are being treated with proton pump inhibitors (PPIs). In a randomized controlled double-blind trial study of adults, Dr. DiMango and her colleagues compared treatment with esomeprazole 40 mg twice daily versus a placebo in patients with CF and frequent respiratory exacerbations. They conducted their study over a 36-week treatment period to determine effect on time to first exacerbation and other health-related outcomes. Seventeen patients without symptoms of GERD were randomized and 15 completed the study. At the end of the trial, the researchers saw a trend to earlier exacerbation and more frequent exacerbations in subjects randomized to esomeprazole compared with the placebo.

"Based on our study, we think that prospective studies are needed to test the safety and effectiveness of these agents in CF," says Dr. DiMango. "While PPIs are effective for relieving reflux symptoms, they probably should not be used indefinitely and should be reevaluated in six weeks to see if they are helping."

> **"Based on our study, we think that prospective studies are needed to test the safety and effectiveness of proton pump inhibitors in CF."**
> **— Dr. Emily A. DiMango**

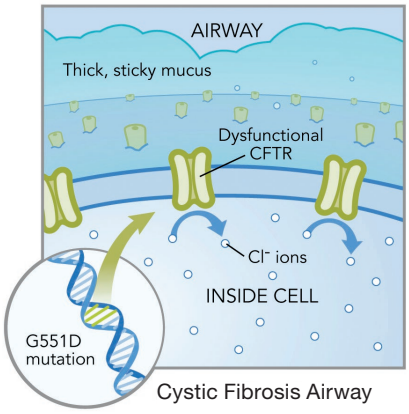
At NewYork-Presbyterian/Columbia many of the current studies focus on disease-modifying drugs, and studies of inhaled antibiotics and anti-inflammatory agents are ongoing. "We have about 30 patients enrolled in clinical trials of disease-modifying drugs right now and we are in the process of collecting data to understand if the drugs work," says Dr. DiMango. "An advantage of these new therapies is that they are in pill form and less of a treatment burden for patients to take."

Gene Mutations in Cystic Fibrosis



Healthy Airway

A normal cystic fibrosis transmembrane conductance regulator (CFTR) gene produces a normal CFTR protein. This protein works like a channel to allow chloride (Cl^-) ions to move into or out of cells and maintain a thin, watery layer of mucus.



Cystic Fibrosis Airway

Mutations in the CFTR gene can create abnormal or too few CFTR proteins, resulting in little to no Cl^- ions passing into or out of cells and thick, sticky mucus. The G551D mutation creates CFTR proteins that reach the cell surface but do not work correctly. This mutation is the most common gating defect and is present in a subset of people with CF.

(Courtesy of Vertex)

Reference Article
DiMango E, Walker P, Keating C, Berdella M, Robinson N, Langfelder-Schwind E, Levy D, Liu X. Effect of esomeprazole versus placebo on pulmonary exacerbations in cystic fibrosis. *BMC Pulmonary Medicine*. 2014 Feb 15;14:21.

For More Information
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Studying Chronic Lung Disease in HIV-Positive Smokers *(continued from page 1)*

directed by Ronald G. Crystal, MD, a pulmonary disease specialist and Chairman of Genetic Medicine at Weill Cornell Medical College.

"Something that is not very well publicized is that people with HIV who smoke have an increased incidence of emphysema that occurs at an earlier age and with a lower number of packs-years compared to HIV-negative smokers," says Dr. Kaner. "We've been trying for nearly a decade to understand the molecular mechanisms that explain why HIV-positive people are more susceptible to developing emphysema if they smoke."

Dr. Kaner's work has focused on matrix metalloproteinases (MMP), a group of molecules that as a family has the capacity to degrade all of the structural components of the lung and the process that underlies the development of emphysema. With co-principal investigator Marshall J. Glesby, MD, PhD, Associate Chief of the Division of Infectious Diseases at NewYork-Presbyterian/Weill Cornell, and Director of the Cornell HIV Clinical Trials Unit, Dr. Kaner is about to embark on a pilot study to determine if the antibiotic doxycycline, which also has MMP inhibitor properties, can be used to slow down this process.

In this study, funded by the National Heart, Lung and Blood Institute, the researchers seek to recruit 30 individuals who are HIV-positive, smokers or ex-smokers, who have COPD and/or emphysema. "They will have a baseline bronchoscopy to determine their epithelial lining fluid MMP activity and then be treated for three months with doxycycline or placebo," says Dr. Kaner. "At the end of three months we'll do another bronchoscopy and measure their MMP activity in epithelial lining fluid to see if doxycycline has had a measurable effect on reducing the amount of MMP activity in their lungs."

As it is a pilot study, Dr. Kaner believes that it is too early to have any idea whether the strategy will be effective in blocking MMP activity, and if it is effective, whether that will result in a clinically meaningful change in the course of the disease. However, if the study is successful, he and his colleagues plan to design a much larger Phase II or Phase III trial with clinical endpoints to see if this strategy of inhibiting matrix metalloproteinases can slow the progression of COPD and/or emphysema in HIV-positive people who are smokers or ex-smokers.

"We also speculate that there may be a role for testing this mechanism in HIV-negative people who have COPD and emphysema," says Dr. Kaner. "If this proof of concept is demonstrated, it might have applications down the road to a much larger population of patients."

Dr. Robert J. Kaner

Physicians who may have potentially qualified patients interested in participating in this study, as well as other studies on the pathogenesis of lung disease in HIV-positive people, should contact Dr. Kaner. "We're particularly interested in recruiting subjects who have either newly diagnosed or uncontrolled HIV infection because they seem to have the most rapid decline in lung function and seem to be at the highest risk for developing emphysema. We are very interested in studying the effect of HIV infection in its early stage on lung function and lung biology."

Pathogenesis of Chronic Obstructive Pulmonary Disease: Potential Opportunities for Interactions with HIV

Independent influx of CD8+ lymphocytes

Increased number of activated macrophages
Increased expression of matrix metalloproteinase-9, a destructive enzyme

Oxidant-antioxidant imbalance
Increased oxidant stress from direct viral effects of HIV
Decreased levels of antioxidants in the lung, including glutathione

HIV protein induction of apoptosis of lung endothelial cells

Antiretroviral effects
Direct effects
Immune reconstitution inflammatory syndrome (IRIS)-type response to organisms in the lung

Increased susceptibility to bacterial pulmonary infection

Increased susceptibility to *Pneumocystis* colonization after *Pneumocystis* infection
Primates with SHIV infection with *Pneumocystis* colonization develop airway obstruction over time
Humans with HIV infection with *Pneumocystis* colonization show increased rates of airway obstruction after controlling for smoking

Source: *Clinical Infectious Diseases*, 2013 Jul;57(2):275-82.

Reference Articles

Shirley DK, Kaner RJ, Glesby MJ. Effects of smoking on non-AIDS-related morbidity in HIV-infected patients. *Clinical Infectious Diseases*. 2013 Jul;57(2):275-82.

Kaner RJ, Santiago F, Crystal RG. Up-regulation of alveolar macrophage matrix metalloproteinases in HIV1(+) smokers with early emphysema. *Journal of Leukocyte Biology*. 2009 Oct;86(4):913-22.

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