



NACFC Highlights

The 23rd North American Cystic Fibrosis Conference was held in Minneapolis, MN, October 15-17, 2009.

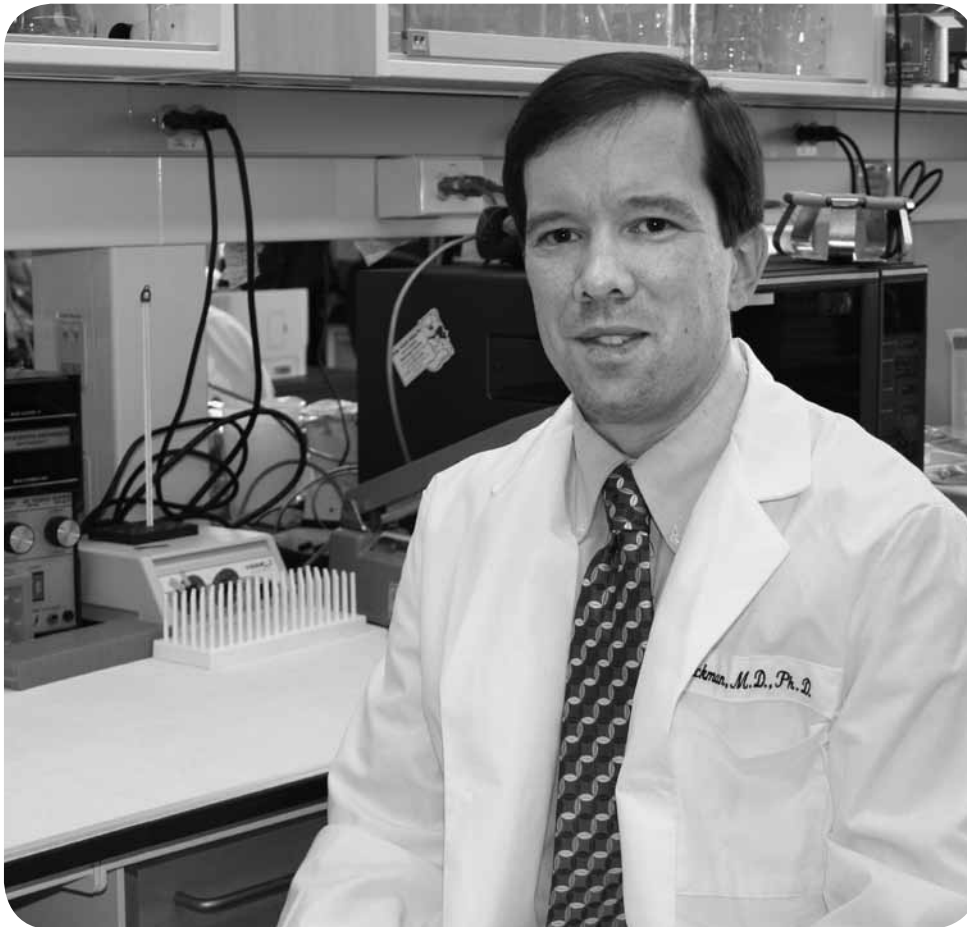
HYDRATING MUCUS

Bronchitol® (Pharmaxis) is an inhaled version of the sugar mannitol that is designed to pull water into airway secretions. When given to cystic fibrosis (CF) patients this drug makes secretions less thick and sticky. This dry powder medication is inhaled twice daily using a small portable inhaler. The results of a phase 3 international trial that enrolled 295 adults and children with CF demonstrated that patients receiving Bronchitol® had a 6.5 percent increase in lung function (FEV1) compared to those that received placebo. The effect was present regardless of whether or not patients received rhDNase (Pulmozyme®). The patients receiving Bronchitol® also had a reduced frequency of exacerbations, but this finding was not statically significant. Johns Hopkins researchers are currently participating in a similar United States multicenter trial.

VX-770

Hopkins researcher **Michael Boyle** presented a new analysis of the trials of VX-770 (Vertex Pharmaceuticals) conducted in CF patients with at least one G551D mutation in the CFTR gene. Thirty-nine adults with mild-to-moderate lung disease participated in two separate phase 2 studies lasting 14-28 days. VX-770, an oral drug, was well tolerated. Patients who received VX-770 had a significant improvement in lung function after 14 days. Approximately half of the treated patients had at least a 10 percent improvement in FEV1. There is a suggestion that those patients who received VX-770 had improvement in quality of life measurements as well. Johns Hopkins researchers are participating in a phase 3 trial of this exciting new therapy.

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In the lab, pediatric endocrinologist Scott Blackman.

CF and Diabetes

Researcher Scott Blackman's search for modifier genes to tailor treatments.

On a mid-May morning last year, pediatric endocrinologist **Scott Blackman** raised a number of questions regarding the relationship of diabetes and cystic fibrosis. Are CF patients susceptible to diabetes? If so, how? Do treatments for CF put them more at risk for diabetes? And do treatments for diabetes affect the status of their CF? Does diabetes increase the severity of lung disease in CF patients?

The questions seemed endless and critically important, Blackman suggested, noting that 25 percent of CF patients ages 10-19—and 40 percent of CF patients over age 40—have diabetes. But the answers may have more to do with so-called modifier genes—genes other than the CF gene,

CFTR—that may affect how the body responds to conditions that develop as the result of the defective CFTR. That ground, Blackman added, has been broken by Johns Hopkins geneticist **Garry Cutting**, who showed in twin and sibling studies that modifier genes, rather than CFTR, are responsible for most of the variability in severity of lung disease in CF patients. Building on those findings, Blackman is seeking out modifier genes related to diabetes in CF patients.

“By studying twins and siblings with cystic fibrosis, we are able to test which features of CF are influenced by modifier genes and which are not,” Blackman reported last May. “Identifying and understanding modifier genes will help us

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Upcoming Clinical Trials

INFANT STUDY OF INHALED SALINE (ISIS)

Researchers at Johns Hopkins are studying the effect of hypertonic saline in children less than 5 years old this summer. Hypertonic saline is often prescribed for older children and adults. However, it is unknown if this therapy will help younger children who have good lung function. This 18-month study will investigate whether pulmonary exacerbations can be prevented by hypertonic saline inhaled twice daily. The ISIS trial is the first of several studies that will be testing drugs in younger children with CF. The goal of these trials is to intervene early to prevent permanent lung damage.

ATALUREN® (PTC124) TRIAL IS UNDERWAY AT HOPKINS

Ataluren® is an oral medication designed to help patients with nonsense CFTR mutations (those mutations that end with an “X” in its name, such as G542X, W1282X, or R553X). This study, which is being carried out at 38 international sites, will enroll a total of 208 subjects. Hopkins will be enrolling five children and/or adults with cystic fibrosis (CF) who have a nonsense mutation and who meet eligibility criteria. The study will last one year.

PREDICTION BY ULTRASOUND OF THE RISK OF HEPATIC CIRRHOSIS IN CYSTIC FIBROSIS (PUSH)

The purpose of the PUSH study is to learn more about liver disease in people with CF using a test called a liver ultrasound. Liver disease is a common complication in CF. However, it is hard to predict which people with CF are at greater risk for liver disease. It is also hard to identify liver disease in the early stages. The liver ultrasound test may help to diagnose and treat liver

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Continuing a Legacy of Milestones

Over the past half-century we have made tremendous strides in our understanding of cystic fibrosis (CF). Diagnosis of CF was revolutionized by the development of the sweat test at Johns Hopkins by Drs. Gibson and Cooke in 1959. Today it is still the gold standard for the diagnosis of CF. The discovery that immunoreactive trypsinogen, or IRT, is elevated in infants with CF was made in 1979, a finding that made possible universal newborn screening for CF. The modern era of our understanding of CF began in 1989 when mutations in the CFTR gene were discovered as the cause of CF. This led to a new era of therapeutics, one in which we are now exploring the use of drugs that can alter the basic defect that causes CF.



As one decade closes and another begins, we continue this legacy of achieving milestones in our understanding and treatment of CF. Today we're helping to develop new drugs that will slow the progression of CF lung disease. Researchers at Johns Hopkins have participated in 25 clinical trials in the past two years, and phase 3 trials are currently underway for Denufosal, Ataluren®

(PTC124) and inhaled mannitol (Bronchitol®). Earlier phase trials of VX-770 and VX-809 continue. This remarkable achievement would not have been possible without the commitment of the CF patients cared for at Johns Hopkins. Patient participation in clinical trials assures that new therapies continue to move as quickly as possible through the pipeline towards Food and Drug Administration approval.

Although the potential of these drugs is very exciting, none of these therapies will reverse lung damage. Several recent studies have shown changes in the lungs of CF children occur at a very early age. That's why we're focusing more on our youngest patients through studies of drugs such as hypertonic saline in the ISIS trial. We are also introducing therapies such as azithromycin at a younger age to more children with CF.

The Johns Hopkins CF Center continues to develop new research and clinical programs to improve the lives of our patients. This issue of *Partners in Discovery* at Johns Hopkins introduces you to researchers exploring diabetes and lung transplantation – areas that are becoming increasingly important as CF patients are living longer and healthier lives. Thank you for your support, and enjoy this issue.

Peter J. Mogayzel Jr., M.D., Ph.D.
Director, Cystic Fibrosis Center
at Johns Hopkins

Lung Transplantation

Pulmonologist Christian Merlo explores the unique issues for CF patients considering transplant.

Pulmonologist **Christian Merlo** knew for years that lung transplant patients did not fare as well as heart, kidney or liver transplant patients. What he didn't know was how well the people he treated—CF patients with end-stage lung disease—did after lung transplantation. Were there predictive factors, like the patient's age, that influenced outcomes following transplant? And was there value in knowing such predictive factors?

The questions were important one, Merlo notes, because lung transplants for CF patients, due in part to a change in the organ allocation system by the United Network for Organ Sharing (UNOS) in 2005, increased significantly over the past decade—from 120 patients per year in 1999 to more than 200 patients in 2009. Consequently, wait-list times are dramatically shorter, too. But lung transplantation, while a viable option for patients with severe end-stage CF, is not without complications. And who the best CF candidates are for lung transplant could be better answered with a fresh review.

So Merlo, cardiac surgeon **Eric Weiss** and other co-investigators at Johns Hopkins dug deep into the UNOS organ transplant registry from 1999 to 2007. Surprisingly, they found that CF lung-transplant patients 35 and older had a higher five-year survival rate—62 percent—compared with 43 percent for CF lung-transplant patients ages 7 to 20 years (“Lung Transplantation in Older Patients with Cystic Fibrosis: Analysis of UNOS Data,” *The Journal of Heart and Lung Transplantation*, February 2009). Also, the researchers found that increasing age was strongly associated with decreases in early post-operative



Christian Merlo, M.D.

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—CHRISTIAN MERLO, M.D.

infections, the development of bronchiolitis obliterans – inflammation of the small airways in the lungs – and hospitalizations for rejection. Why?

“We can speculate but we don't know why that is,” says Merlo. “Maybe someone who is older is more responsible, more compliant with their medications. Or maybe there's a difference in social support. All these questions deserve future investigations.”

Interestingly, Merlo also found that CF lung-transplant patients tend to do better than lung-transplant patients with other lung conditions, including chronic obstructive pulmonary disease,

pulmonary fibrosis and pulmonary hypertension. But there are also unique issues for the CF patient considering lung transplant, including the risk of diabetes, osteoporosis and distal obstructive intestinal syndrome (DIOS)—all of which increase with the administration of immune suppressants following organ transplantation. Another issue for CF patients, Merlo notes, is pancreatic insufficiency, or the inability to maintain proper nutrition.

“Patients have to be supplemented with pancreatic enzymes, which is something a CF clinic is used to dealing with,” says Merlo. “But a transplant clinic may not be used to managing issues like this.”

There are many important factors that go into the organ allocation score developed by UNOS, Merlo adds, but, as his research reveals, there are other predictive factors unique to the CF patient undergoing transplant. Noting that he and Johns Hopkins pulmonologist **Noah Lechtzin** are analyzing lung-transplant outcomes for CF patients with multiple antibiotic resistant *Pseudomonas aeruginosa*, as well as looking at outcomes at medical centers that perform more lung transplants in CF patients, Merlo concludes, “The thread for us are the factors that may predict post-transplant outcomes, that will help us risk stratify and guide CF patients considering lung transplantation. Also, these studies have given us some insight into how we can improve our treatment and delivery of care, so that patients and their outcomes will get better.” ■

Mutation-Specific Therapy in CF

Focusing on Class I CFTR mutations, world-renowned CF researcher Eitan Kerem reports some surprising results.

Imagine driving down a road and then suddenly seeing a stop sign obscured by an overhanging tree branch. You slam on the brakes but are unable to avoid a crash before reaching your true destination. Your response, world-renowned Israeli CF researcher Eitan Kerem recently explained to parents of Hopkins CF patients, is not unlike that of the molecular mechanism of a Class I mutation and its impact on CFTR protein production. The CFTR, like your car, is already en route to its destination—the cell membrane. But a premature stop codon characteristic of this Class I mutation screeches the protein to a halt, resulting in a sort of genetic fender bender.



“The CFTR has already been processed to find its way to the cell membrane,” Kerem said. “But if by mistake there is a premature stop sign, unstable mRNA is produced and the protein is not functional.”

Preventing that sudden stop and restoring the functionality of the CFTR protein has been the latest quest of Kerem, director of the Cystic Fibrosis Center at Hadassah Medical Center in Jerusalem. The principal investigator of many international clinical trials and author of key publications in the field, Kerem’s interests span all aspects of CF research, from the association between phenotype and genotype to prognostic factors for disease severity. Now his eye is on the development of new mutation-specific pharmacologic therapies to correct the basic defects in CFTR, or in his words “to see if we could impair the premature reading of the stop sign and produce a functioning CFTR.”

The good news, he reported, is that aminoglycoside antibiotics have been shown to suppress the premature termination codon by allowing the incorporation of an amino acid and, thus, normal translation of the CFTR. In one study patients were asked to take nose drops of the most potent of these aminoglycosides—gentamicin—or placebo. According to nasal potential difference measure-

ments, gentamicin improved chloride transport, which surprised Kerem: “Having a high negative value is characteristic of CF. We usually don’t see chloride transport.”

Finding the appearance of CFTR in scraped nasal cells of patients who took gentamicin, Kerem was about to continue with these studies when PTC Therapeutics asked him to collaborate in an Israel/U.S. trial of PTC 124, also known as Ataluren®, over two weeks. (In studies with CF mouse models, PTC 124 has been shown to prompt the appearance of functional CFTR in the apical cell membrane.) While not an aminoglycoside antibiotic, PTC 124 also targets premature stop signals—or so-called nonsense mutations—in the genetic code that disrupt protein production. Here the findings were mixed, with PTC 124 normalizing nasal potential difference and improving pulmonary function in the Israel patients but showing no effect in patients in the U.S. arm of the study. A third PTC 124 study in Belgium and France, Kerem added, showed improvement with PTC 124.

“We do not want patients to take drugs to show improvement in the nasal electrical gradient in the nose, we want them to feel better.”

—EITAN KEREM, M.D.

“We don’t know why the results in America were so negative while the results in Israel, Belgium and France were partially positive,” Kerem said.

To get at the answer, Kerem conducted a longer, three-month trial of the Israeli patients who had participated in the two-week PTC 124 trial. The results? Patients who received PTC 124 showed continued significant improvement in nasal potential difference but only slight improvement in pulmonary function. Kerem is now beginning a year-long PTC 124 trial with the goal of giving patients something more than normal nasal potential difference.

“We do not want patients to take drugs to show improvement in the nasal electrical gradient in the nose, we want them to feel better,” said Kerem. “We know PTC 124 does something, but how significant this is we do not yet know. This study may give us the answer.” ■

To view the video of Dr. Kerem’s presentation on PTC 124 at the Johns Hopkins Cystic Fibrosis Center, visit www.hopkinscf.org

CF and Diabetes

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identify new pathways and more effective treatments for CF-related diabetes.”

With Cutting and other collaborators in the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins, Blackman has found that modifier genes do indeed play a substantial role in diabetes complicating cystic fibrosis (*Journal of Clinical Endocrinology Metabolism*, April 2009). The first such example, Blackman said, is a variant in TCF7L2, a susceptibility gene for type 2 diabetes in people who do not have CF, which has a significant effect on diabetes risk in CF patients (see *Diabetologia*, September 2009).

“Although non-genetic factors contribute to risk of worse outcomes,” Blackman said, “genetic modifiers are the primary cause of diabetes in CF.”

In time, such findings should translate into improved health and survival and quality of life for CF patients with diabetes, as outcomes studies show they have worse lung function and shorter survival than CF patients who do not have diabetes. What modifier genes reveal will also likely influence when and how to treat—or not treat—CF patients with diabetes.

“Maybe we want to give insulin to patients we normally wouldn’t give insulin? Or maybe there’s a benefit in treating diabetes in the CF patient earlier?” Blackman concluded. “By identifying new pathways and increasing our understanding of the relationship between diabetes and CF, we can better identify at-risk patients and individualize therapy.” ■

Upcoming Clinical Trials

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disease. During this 5-year study, participants will have blood tests and complete questionnaires once a year and have a liver ultrasound test every two years. ■

Research Coordinator Erin Felling Mixes Science and Patient Care

As a child growing up in Pennsylvania, Erin Felling figured she'd end up doing something in medicine. After all, her mom was a nurse, and Erin sensed she had the same passion for taking care of people. But there was also the scientist in her, she'd later discover – someone who bonded with biology and microbiology. So after obtaining her Bachelor of Science Degree in Nursing from Pennsylvania State University and working as a staff nurse in the pediatric intensive care unit (PICU) at Hershey Medical Center, it was only natural that she found herself coordinating clinical research trials in endocrinology and gastroenterology there.

“For me, health care and science was a good combination, and I enjoyed working with kids,” says Felling. “Working in the PICU was difficult but rewarding in seeing kids bounce back.”

Serendipity and her husband's pediatrics residency took her to Philadelphia, where she took on the role of clinical research manager for a private medical device firm. She found writing research protocols stimulating, but missed the patient care piece, which led her to the Johns Hopkins Cystic Fibrosis Center. Here she enjoys the challenges of coordinating clinical research trials – enrolling and educating patients about the research—and also connecting with patients and families, many persistently upbeat despite the struggles of managing a chronic condition.



“You see patients who have been doing all these strict regimens for years, and they’re still positive.”

—ERIN FELLING

“You see patients who have been doing all these strict regimens for years, and they’re still positive,” says Felling.

Much of the research Felling is coordinating has to do with getting CFTR to the cell surface through compounds like VX-809. Other trials involve ge-

netic modifiers and molecular phenotypes in CF lung disease. Regardless of the study at hand, she's finding patients and parents eager to participate to help improve survival and quality of life for CF patients: “Families know what's out there, and they want to participate in these trials because they want their children to live long lives.”

And where does her role as research coordinator at the CF Center leave this researcher clinician?

“Lately in the lab I'm pipetting solutions for a research study. I enjoy that,” Felling says. “But I get the patient piece of it, too,” she laughs, “so it's a win-win experience.” ■

NACFC Highlights

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AZITHROMYCIN HELPS

Azithromycin is an antibiotic that is currently used chronically to treat CF patients who are colonized with *Pseudomonas aeruginosa*. A multicenter trial of 203 children aged 6-18 years who were not infected with *Pseudomonas aeruginosa* has been completed. This therapy did not improve lung function in these children. However, the children who received azithromycin had a 51 percent reduction in exacerbations compared to the children receiving placebo. The children who received azithromycin also had better weight gain. This finding has prompted Hopkins physicians to begin prescribing this therapy to children who are not colonized with *Pseudomonas aeruginosa*.

ERADICATING PSEUDOMONAS AERUGINOSA

The EPIC study enrolled 304 patients at CF centers across the country, including Johns Hopkins, to determine the most effective method to eradicate *Pseudomonas aeruginosa* when it is first detected in children with CF. The results of this 5-year study showed that inhaled tobramycin treatment led to the eradication of *Pseudomonas aeruginosa* in the majority of children. Additionally, researchers found that there was no difference in outcome if patients were treated with inhaled tobramycin only when *P. aeruginosa* was identified from a culture or if they took this drug on a routine basis every three months. Additionally, the use of the oral antibiotic ciprofloxacin did not add additional benefit. These results suggest that less may in fact be more in the treatment of early *P. aeruginosa* infection. ■

Partners IN DISCOVERY

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