



NACFC Highlights

The 20th annual North American Cystic Fibrosis Conference (NACFC) was held in Denver, Colorado, November 2-5, 2006.

MOLI-1901 BACK IN THE NEWS

Moli-1901 (Lantibio, Chapel Hill, NC) is an inhaled drug that activates an alternative chloride channel within the lung. Moli-1901 is one of several drugs in development that may bypass the defect in chloride transport that is the cause of cystic fibrosis. Results from a recent European study showed an improvement in lung function with 5 days of treatment. The improvement persisted for several weeks after the drug was stopped. This is an exciting development for a drug which had early studies conducted at Johns Hopkins under the direction of Dr. Pamela Zeitlin.

STOP CODON MUTATIONS

PTC-124 (PTC Therapeutics, South Plainfield, NJ) is designed to treat patients who have CF caused by a "stop" mutation. These mutations end in the letter X, such as W1282X or G542X. PTC-124 causes cells to skip over the stop signal and make a functional cystic fibrosis transmembrane conductance regulator (CFTR) protein. Two multi-center trials, one in the US and another in Israel, studied the effect of oral administration of PTC-124 on chloride transport. The Israeli study showed a significant improvement in chloride transport measured by nasal potential difference (NPD). For unclear reasons the results of the US study were not as significant. The reason for this difference in outcome is unclear, but it may relate to differences in the types of mutations that cause CF in the two countries. These results are promising enough that PTC Therapeutics is proceeding to develop this drug in Phase 2 and 3 trials.

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Advancing the Knowledge

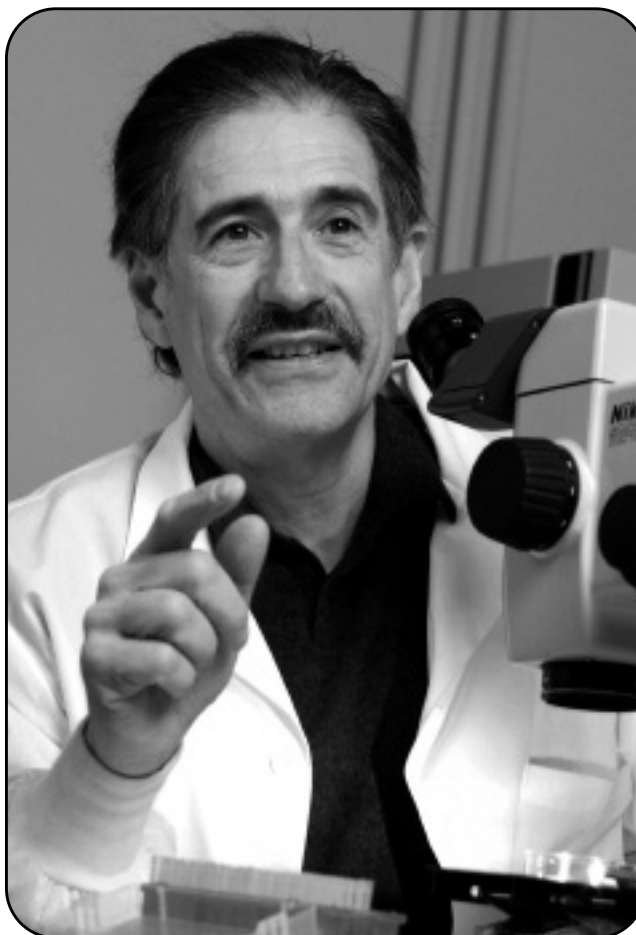
A distinct advantage to being a patient of The Johns Hopkins Cystic Fibrosis Center is that the doctors you see regularly are contributing significantly to the understanding and management of cystic fibrosis worldwide.

Over the years, Hopkins basic scientists and clinical investigators have established genetic counseling for children and the standard "sweat test" used to diagnose CF, defined the course of disease for cystic fibrosis, identified mutations in the CF gene, and developed genetic and drug therapies used to keep symptoms under control.

The result? A three-fold increase in the average lifespan for cystic fibrosis patients. Thirty years ago, says Beryl Rosenstein, M.D., professor of pediatrics and former director of the CF clinic, most patients only lived until they were 8 or 10 years old. Today, the average lifespan is 36.

"We didn't just improve survival but also quality of life," Rosenstein says. "Patients are so much more active, and better able to participate in school, work and life."

Some of the specific milestones in CF history originated here in Hopkins' laboratories. William Guggino, Ph.D., director of the CF research development program, helped identify the role of the cystic fibrosis transmembrane regulator (CFTR) protein in causing CF. Shortly after, pulmonologist Pamela Zeitlin, M.D., Ph.D., CF Center Co-director, developed antibodies to the CF protein, and created for laboratory studies a line of cells from the airway surface of a CF patient. These materials have been widely requested by CF researchers around the



"The next milestone in research would be a complete understanding of the CFTR protein." – William Guggino, Ph.D.

world.

In other historical advances, geneticist Gary Cutting, Ph.D., has identified some genetic mutations involved in the development of CF, and Guggino and Zeitlin were the first to test adeno-associated virus as a potential gene therapy to restore functional CFTR in patients.

"The next milestone in research," says Guggino, "would be a complete understanding of the CFTR protein." That could happen, he estimates, within the next 20 years or so.

Guggino likens the still-unknown structure of CFTR to the gate of a picket fence.

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Upcoming Clinical Trials

DENUFOSOL: PHASE III

Researchers at Johns Hopkins are participating in the definitive Phase III trial to determine if denufosol (INS37217 respiratory) is effective. This drug, manufactured by Inspire Pharmaceuticals, works by activating an alternate chloride channel in the CF lung. Previous studies have suggested that denufosol can improve lung function. During this trial, which will last one year, patients will inhale either nebulized drug or placebo three times daily.

EPIC ENROLLMENT

The observational portion of the Early Pseudomonas Infection Control (EPIC) trial has reached its enrollment goal of 1400 children. This study will document the natural history of Pseudomonas aeruginosa (Pa) colonization in younger CF patients around the country. However, the interventional part of the study, which continues to enroll children that become infected with Pa, will test the effectiveness of oral ciprofloxacin in combination with inhaled tobramycin. Although, children are typically treated when Pa is first isolated, the optimal therapy to eradicate this bacterium is unclear. The EPIC trial should provide valuable insight into the best treatment for initial Pa infection. During this 18 month study all children will receive treatment for Pa. After the initial treatment, patients will be randomized to one of four treatment protocols using either scheduled therapy every 3 months or therapy given only when Pa is detected.

TIOTROPIUM SAFETY TRIAL

Tiotropium bromide (SPIRIVA®) is typically used to treat patients with chronic obstructive pulmonary disease (COPD). Tiotropium is a powdered drug that relaxes the airways. It also decreases the amount of mucus that produced in the lungs. This medication is inhaled once-a-

Newborn Screening Comes to Maryland



Although children are born with cystic fibrosis, many are not diagnosed until they present with significant symptoms, some-

times months or even years later. Effective therapies cannot be started until the diagnosis is made, a delay that can lead to significant nutritional and pulmonary problems. But a new newborn screening program, started in Maryland earlier this year, aims to change all that and the way we care for the newly diagnosed.

The new screen measures the blood level of a protein known as immunoreactive trypsinogen, or IRT. If the IRT level is elevated, the infant may have CF and be referred to a CF center for a sweat test. Although most children with a positive newborn screen do not in fact have CF, those children with CF will start treatment before they have developed any symptoms. The importance of preventive therapies, even in these smallest patients, cannot be over estimated. Optimizing nutrition as early as possible helps the lungs grow and stay healthy, thereby improving the lives of these children.

As a compliment to this new newborn screening program, we've established a Monday afternoon CF clinic tailored to these young patients. Our mission? To develop a comprehensive approach to the care of newly diagnosed children and to educate their families about CF. For more information, see the story on the opposite page. And enjoy this issue. Thank you.

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

CF Center (continued from page 1)

"If the hinges are a little bit bent, the gate will not work well. But if you can bend it a little bit or put something in it, you could potentially get it to work," he says. "Right now we don't know what the fence looks like, just that something is not working. All we know is that stuff is not getting through the barrier, across this fence."

Researchers are continuing the search for clues today. Cutting has started a national study of twins and siblings with CF to tease out how environmental factors may play a role in modifying CF. "Understanding the environmental factors will give us the tools to help CF patients protect themselves," says Cutting. Mike Boyle, M.D., director of the adult CF program, is investigating the expression of known genes in CF patients with both mild and severe lung disease in hopes of identifying differences between these two groups. Pharmacist Carlton Lee, Pharm.D., is studying the way CF patients metabolize commonly used drugs such as antibiotics.

Research also is ongoing to unravel barriers to

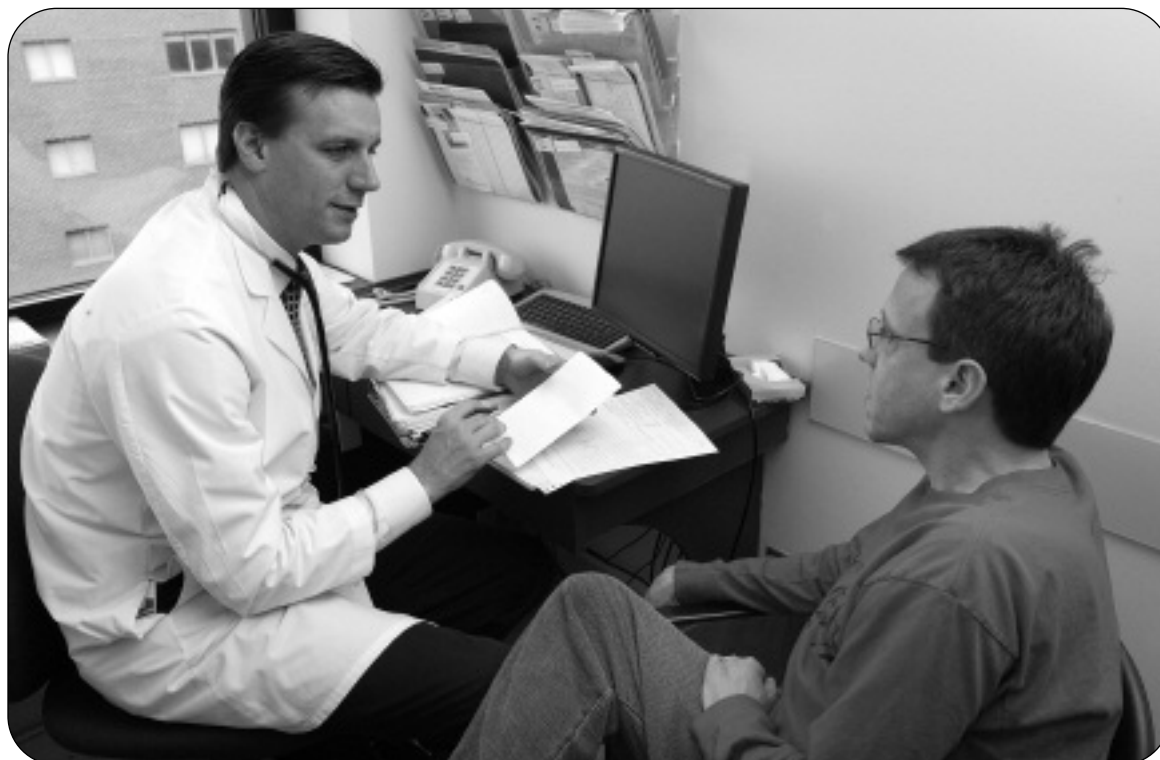
gene therapy, study resistant bacteria and their effect on lung function and further tease out the role of CFTR and how it is regulated.

Meanwhile, in the clinics, there has been a large focus on quality improvement, says Rosenstein, including reviewing patient satisfaction surveys: "There are more standard treatment protocols, and we have more involvement with patients and their families through support groups, the CF Center Web site and patient advisory groups."

There also has been a greater emphasis on a multidisciplinary team approach to managing CF, he says, going beyond a patient's physician to incorporate nursing care, respiratory care, social work and pharmacy services.

And just this year, Hopkins started a clinic for newborns diagnosed with CF shortly after birth by newborn screening. Early diagnosis means that more infants can be put on preventive therapies before lung damage occurs.

"Essentially, over the past 30 years we've gone from hopelessness to hope, from pessimism to optimism," Rosenstein says. "You can see a much brighter future for patients today."



Caption

NACFC Highlights

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CORRECTORS AND POTENTIATORS

Drugs developed to treat patients with CF caused by at least one CFTR "processing" mutation are classified as either correctors or potentiators. Cells from CF patients with processing mutations, such as $\Delta F508$, make a defective form of CFTR that gets trapped on its way to the cell surface and is destroyed. Correctors help the $\Delta F508$ -CFTR escape destruction and get to the cell surface where it will function, although not as well as normal CFTR. That is where potentiators come in. This class of drugs enhances the function of $\Delta F508$ -CFTR that reaches the cell surface. Vertex Pharmaceuticals (Cambridge, MA) has identified a potentiator called VX-770 through a high-throughput screening approach. This drug has been tested for safety in small Phase 1 trials. A larger Phase 2 trial will begin later in 2007 at Johns Hopkins and other centers around the country. Development of a promising corrector is also ongoing.

GENE STUDIES CONTINUE

Researchers in the United Kingdom have come together to focus their efforts on perfecting lipid-mediated gene therapy using a drug called Lipid 67 to enable a new copy of CFTR to be inserted into airway cells of CF patients. Recently, these scientists have made great strides in re-engineering the vector that contains the new gene. This new DNA vector has been less irritating to the lung and has produced a higher level of gene expression for a longer period of time in animal models. A different approach for gene therapy, using a compacted form of DNA called a Nanoparticle, has been developed by Copernicus Therapeutics and Case Western Reserve University (Cleveland, OH). This technology not only gets the normal CFTR gene into the cell but helps it to reach the nucleus. Getting the CFTR gene to the nucleus is critical for it to function. This therapy is being optimized and should be in human trials soon.

A New Clinic for the Newly Diagnosed

About 70 percent of individuals with cystic fibrosis are diagnosed by 1 year of age, about 20 percent by age 10, and the other 10 percent after age 10. Sometimes family history or an intestinal obstruction related to meconium ileus will tip off the pediatrician early on, but most often it's coupling the classic symptoms of a chronic cough and failure to thrive that drives the diagnosis. But by then, says Hopkins pediatrician Beryl Rosenstein, serious damage may have already been done.

"We have some patients who unfortunately were not diagnosed until age 3, 4, 6 or 10 and who had evidence of significant lung disease," says Rosenstein. "Catch these kids early and you can favorably impact the clinical course and maybe even survival."

A new newborn screening program, starting in Maryland in July, will help pediatricians detect the disease and intervene in early infancy. Before newborns are discharged from the hospital, their dried blood – spot-collected for newborn screening – will be used to measure levels of a pancreatic enzyme called trypsinogen, which is usually substantially elevated in newborns with CF. A positive result can be followed up with a diagnostic sweat test. This means 90 percent of individuals with CF will be di-



A newborn screening test for CF means patients will be diagnosed and treated earlier, reducing their risk for pulmonary damage and malnutrition

agnosed before 1 month of age. They will form a different group of patients for pediatricians like Rosenstein—CF patients who have no signs of pulmonary damage or malnutrition.

"They will have somewhat unique needs," says Rosenstein. "The focus will be on education and counseling for families, and monitoring patients for problems early on as they develop."

In conjunction with the screening, the Children's Center has developed a new clinic for these newly diagnosed newborns. Families will learn nutritional strategies and airway clearance techniques early on, while Rosenstein and his colleagues stay on the lookout for organisms like *Pseudomonas aeruginosa*. Once colonized in a young CF patient's airways, *P. aeruginosa* can quickly become a permanent resident and lead to significant lung damage. Patients with the organism are known to suffer steeper declines in pulmonary function and infections requiring IV antibiotics and hospital stays.

"It's been shown in recent years that if you can pick up *Pseudomonas* by airway cultures as soon as it starts to colonize, there's a window of opportunity to eradicate the organism with intensive oral and aerosolized antibiotic therapy," says Rosenstein. "We have a treatment protocol to fight it."

The clinic also has the capability to measure pulmonary function in infants, and to intervene early with any signs of decline. Knowing there's an association between poor nutrition in the first year of life and susceptibility to respiratory infections, clinic staff are raising the bar on nutritional status for these patients, too. Counseling will be offered to parents who may be shocked to learn their seemingly healthy newborn has CF.

"In the past, the child wasn't thriving and the parents weren't getting an answer," says Rosenstein. "With newborn screening, we should detect CF before there's any damage." For more information, call 410-955-5816, or visit www.hopkinscf.org.

Profile

Shruti Paranjape: Still Pursuing Peptides

Shruti Paranjape, M.D., first became interested in lung research as an undergraduate at the University of Pennsylvania, when she landed a summer job in a physiology lab. But she didn't think about it again until it was time to get another summer job, this time after starting medical school at the University of Pittsburgh. She soon found herself working in a lung physiology lab.

There in Pittsburgh, during a pediatric pulmonology fellowship at Children's Hospital, Paranjape started an investigation that would earn her national attention as a promising researcher. She developed a laboratory model that mimics how bacteria adhere to cells lining the airways in cystic fibrosis patients. Next, using small, engineered compound proteins called cationic antimicrobial peptides, Paranjape was able to kill off the bacteria. The work earned her a James Sutherland Award for outstanding research by a young investigator.

Then Paranjape faced a tough decision. Her research was going well and she was assistant director of the CF center. But her husband had taken a position as a professor of physics at Georgetown University in Washington, and urged her to move closer. Fortunately for Johns Hopkins, one of Paranjape's scientific mentors introduced her to Pamela Zeitlin, M.D., Ph.D., co-director of the



Johns Hopkins CF Center. Paranjape joined the staff in December 2005 as an assistant professor of pediatrics, splitting her time between seeing patients and continuing her studies.

"My research was blossoming and it would have been a tragedy to let it go," she says. "This was a place where I could continue and foster my work. Hopkins has a very collegial atmosphere, and the people here have been welcoming and wonderful!"

At the bench, Paranjape next hopes to develop a model of infection in mice and get a better understanding of how molecules in the airways work to protect the body from predators: "I want to figure out more of how a patient with cystic fibrosis fights off infection and try to develop new antibiotics."

She also plans to continue studying the peptides that put her on the map: "We know that peptides are effective against virulent strains of bacteria, but not how toxic they are to normal cells."

On the clinical side, Paranjape says she enjoys working with such "extraordinarily courageous" patients.

"Living with a chronic disease is by definition challenging, unfair and difficult," she says. "To be able to provide longitudinal care for a patient -- in some cases from infancy to adulthood -- is truly a privilege. I learn as much about CF from working directly with patients and families as they might learn from me. Over time, we all learn more together."

Taming the Beast

A team led by scientists at the Johns Hopkins CF Center has identified and tamed an overactive protein called VCP that plays a key role in the development of cystic fibrosis. The work could lead the way toward development of new drugs that restore normal cell function to prevent CF.

Using a tool called RNA interference, which inhibits gene expression, a scientific team led by CF Center Co-director **Pamela Zeitlin, M.D., Ph.D.**, blocked the production of VCP, restoring injured lung cells to normal. Their report was published in the *Journal of Biological Chemistry* (June 23, 2006).

VCP, or valosin containing protein, binds to the defective chloride transporter in the cells in a majority of CF patients, leading to a dangerous buildup of thick, sticky mucous in the lungs and other organs. But quieting the protein restores the cells' ability to transport chloride, researchers found.

Cells have a built-in quality-control machinery called ERAD (endoplasmic reticulum-associated degradation), which chemically marks defective proteins for destruction and sends them to the cell's waste-disposal complex. In CF patients, defects in genes for a protein called CFTR (cystic fibrosis transmembrane conductance regulator) interrupt the transport chemistry, but researchers hadn't identified the precise search-and-destroy proteins that ERAD deploys to seek out the mutant CFTR until this study.

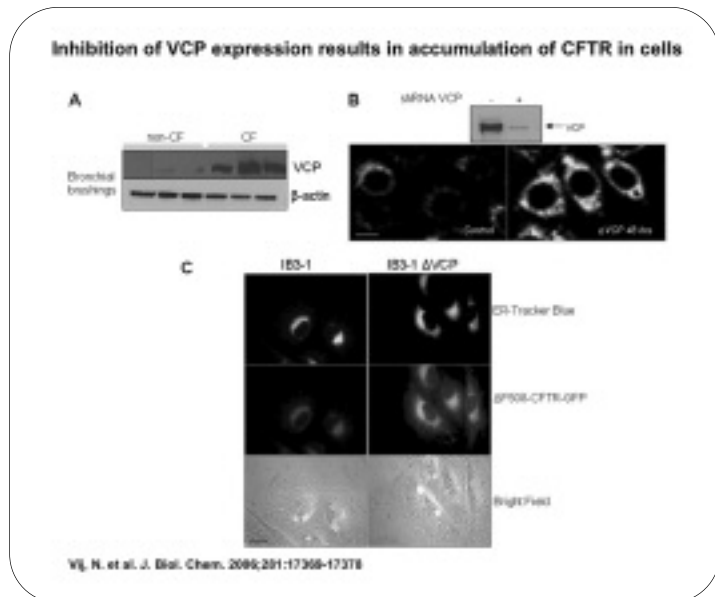
Zeitlin and colleagues compared cells from air passages in the lungs of CF and non-CF patients,

finding the VCP protein was strikingly high in the samples from CF patients. When the researchers inhibited VCP, it no longer destroyed CFTR.

"We were able to confirm that cells deploy VCP protein, which latches onto damaged CFTR and sends it to the trash can," Zeitlin says. "By honing in on VCP and blocking its production, we enabled the defective CFTR to sneak past this quality control and race up to the cell surface."

Zeitlin is now applying for grant funding from the Cystic Fibrosis Foundation to screen large libraries of chemicals, hoping to find one that will selectively lower VCP and be safe for children and adults.

"Our goal," adds Zeitlin, "is to develop small molecules, much like tiny guided missiles, that can take out portions of this rampant VCP protein before it latches onto CFTR."



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A Web Forum for CF Families

A new interactive Web site developed at the Johns Hopkins Children's Center provides extensive medical resources and a community for children, teens and adults with cystic fibrosis, and their families. Pediatric pulmonologist Peter Mogayzel, director of the Johns Hopkins Cystic Fibrosis Center, led the development of the site, made possible by the Herbert Bearman Foundation. Designed to provide an online meeting place for patients and their families, the site allows for the exchange of insights and experiences in managing and coping with CF. Because of the risk of patient-to-patient transmission of respiratory infections, patients and families often must keep their distance from each other. But a special "member families" section on the site links Hopkins CF patients and families with one another and with their Hopkins caretakers via e-mail and electronic chats. To visit the site, go to www.hopkinscf.org.

Researchers In the News

GUGGINO NAMED DIRECTOR OF PHYSIOLOGY

William B. Guggino, Ph.D., who has dedicated more than two decades of his professional life to studying cystic fibrosis, has been named the Director of the Department of Physiology. He has served since 1996 as vice chairman of research in the Department of Pediatrics and since 1989 as director of the Cystic Fibrosis Development Program. In 1992, Dr. Guggino, along with Peter Agre, M.D., authored a seminal paper in *Science*, detailing the discovery of the very first water channel protein. That line of research, 11 years later, won Agre the Nobel Prize in Chemistry. Dr. Guggino's work on CF was recognized last year when he won the prestigious Doris F. Tulcin Cystic Fibrosis Research Award, an honor that marked not only his research achievements but also his role in the training of a significant number of clinician scientists dedicated to unraveling CF's mysteries and bringing new treatments to patients quickly.

ZEITLIN NAMED INNOVATOR OF THE YEAR

Pamela L. Zeitlin, M.D., Ph.D. was named an "Innovator of the Year" by the Baltimore business newspaper, *The Daily Record*. The award recognizes

Partners IN DISCOVERY

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Runover - Upcoming Clinical Trials

day using a device called a Handi-Haler®. The proposed trial to begin this winter will test the safety of this drug in adults and children older than 5 years who are treated for up to 28 days.

Runover - Researchers in the News

Maryland organizations and individuals who have demonstrated the spirit of innovation by creating products, services or programs that benefit their businesses, industries or communities. Dr. Zeitlin's research is pointing the way for what she hopes is an eventual cure for CF. She and her team have identified the protein that eliminates the mutant cystic fibrosis gene, a finding that may help pave the way not only for a treatment for cystic fibrosis but also for cures of a host of protein deficiency diseases.