



JOHNS HOPKINS
MEDICINE
CYSTIC FIBROSIS CENTER

News from the Cystic Fibrosis Center
at Johns Hopkins
Fall 2008

Partners IN DISCOVERY

Translating Theory into Therapy

NACFC Highlights

The 22nd North American Cystic Fibrosis Conference was held in Orlando, FL, October 23-25, 2008

VX-770

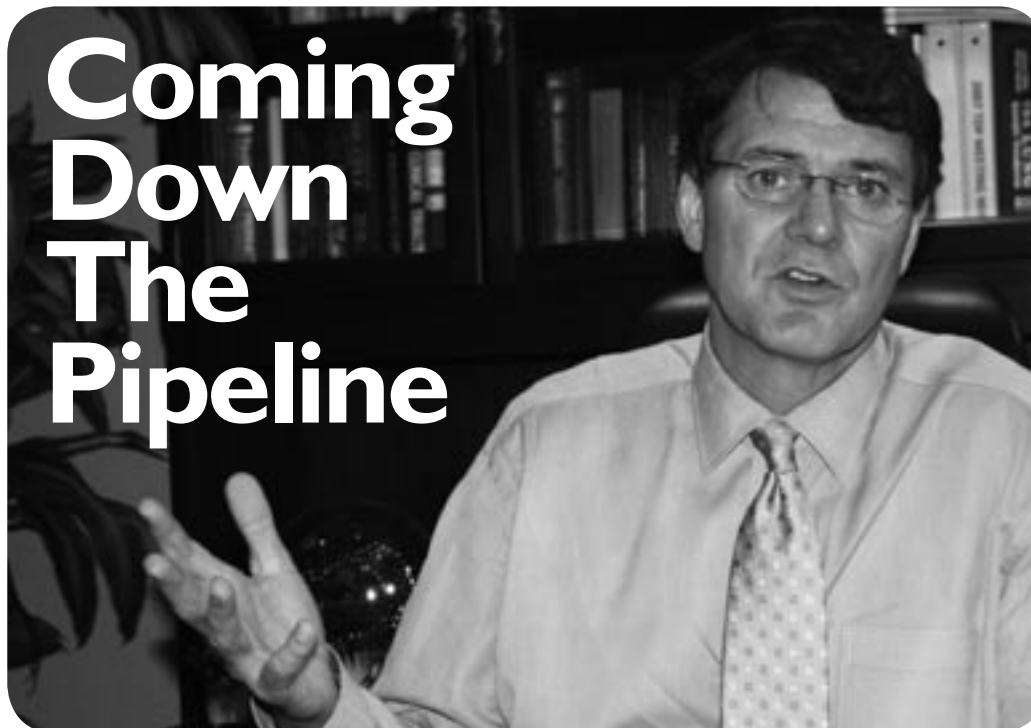
Two trials testing the safety of VX-770 (Vertex Pharmaceuticals) were presented at NACFC. VX-770 has the potential to treat the basic defect in cystic fibrosis, CFTR dysfunction. VX-770 is designed to activate or "potentiate" abnormal CFTR that is located on the cell surface. Patients with certain mutations, such as G551D, produce CFTR that gets to the cell surface but it does not function properly. Thirty-nine patients with one or two G551D mutations participated in these 14 and 28 day trials, which were conducted at Johns Hopkins and other sites around the country. Chloride transport improved in patients who received VX-770 in both studies. The exciting aspect of these studies is that not only did the nasal potential difference (NPD) improve, the average sweat chloride fell to levels found in patients without CF. There were improvements in lung function as well, but the small number of patients studied makes these results difficult to interpret. There were no serious safety concerns raised, and the results are very encouraging. Hopkins researchers will be participating in VX-770 studies next year.

PTC-124

PTC-124 (PTC Therapeutics) also treats the basic CFTR defect present in CF. It is designed to treat patients with stop codon mutations (those that end with an X, for example W1282X). Previous short-term studies have shown promising results suggesting that PTC-124 can improve chloride transport in patients. Analysis of nasal cells from patients treated with PTC-124 showed evidence of increased CFTR gene expression as well. There was also modest improvement in lung function. Dr. Eitan Kerem presented

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Coming Down The Pipeline



Preston Campbell, M.D.

CFTR-targeted drugs lead a diverse pack of therapies to improve quality of life, extend survival and find a cure for CF patients.

In recent years, Robert Beall, president of the Cystic Fibrosis Foundation (CFF), noticed a significant amount of science being generated around the defective CF protein itself, Cystic Fibrosis Transmembrane Regulator, or CFTR. But what he didn't see was a robust translation of that research into new therapies. Consequently, Beall conceived and developed a therapeutic development program that would both open up and speed up discovery by the pharmaceutical industry of new CF therapies targeting CFTR. *The key?* High-throughput screening of a large chemical library and use of a cell-based assay to determine if a compound placed on a CF cell corrects the CFTR function. *The result?* Researchers have moved from testing one or two compounds a day to thousands a day.

"This brute-force approach to drug discovery has allowed the Foundation's drug development pipeline to grow dramatically in recent years, with a significant increase in therapies in Phase II and Phase III trials for patients," says Preston Campbell, CFF's vice president for medical affairs.

While there has been a shift in focus from treating the symptoms of CF to finding a possible cure through correcting CFTR, Campbell notes, the Foundation's current pipeline of therapies in development for patients is both broad and robust, ranging from novel anti-inflammatories and antibiotics to nutritional supplements and transplant drugs. Diversity is key, he explains, because failure is expected in any drug discovery program. Only 20 percent of Phase I clinical trials are successful, 50 percent of Phase II, and 80 percent of Phase III trials. "We have so many programs in the pipeline because they increase our success by increasing our shots on goal," says Campbell.

Noting that CF patients' survival is now in the 37-year plus range and going up each year, he adds, "Our hope is that through these new therapies and improved care CF patients will live with the disease and die from other causes. While our bull's eye is centered around restoring the CFTR function, we are diversified across all CF therapeutic targets."

Regarding the CFTR focus, Campbell explains that while proteins produced from

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Upcoming Clinical Trials

TIGER-2

Johns Hopkins will be participating in an 18-month Phase III study of Denufosal™ (Inspire Pharmaceuticals), called TIGER-2, beginning in spring 2009. This drug activates an "alternative" chloride channel in the airway epithelial cells to bypass the defective CFTR that causes CF. Data from the previous year-long TIGER-1 study, which was conducted at Johns Hopkins and 61 other CF centers, was presented at the 2008 North American CF Conference. This study investigated the effect of inhaled Denufosal™ in 352 CF patients with mild lung disease compared to placebo after 24 weeks of treatment. Many of the patients then continued in another 24-week extension in which everyone received Denufosal™. Lung function (FEV1) had a significant improvement of 45ml. Additionally, those patients who continued to take Denufosal™ for an additional 24 weeks continued to have an improvement in lung function. This is an important finding because it suggests that it may take a longer time to get a maximal benefit from this drug. Based on these results, the TIGER-2 trial will last 18 months. There was no difference in the number of exacerbations or quality of life measurements. In general the drug was well tolerated.

RESEARCH TO AID YOUNG CHILDREN

Newborn screening for CF gives us the potential to treat asymptomatic children to prevent lung disease and maximize nutritional status. Currently, 47 states in the United States have CF newborn screening programs, which present a unique opportunity to determine what therapies are effective in young children. In a study beginning this winter, researchers at Johns Hopkins will be studying the effect of hypertonic saline in children less

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A New Era of CF Research

"You are the key" is the slogan of the CF Foundation's campaign to increase participation in clinical research trials. This slogan is absolutely correct. We all play a critical part in the successful development of new therapies for CF. Researchers, clinicians, patients and parents all play vital roles in getting new therapies to market. Last year, 3,000 CF patients participated in clinical research studies. The CF Foundation estimates that the number of research subjects needed will double by 2009. This fact is a testimony to the success of the drug development programs for CF. Each year there are more drugs entering clinical trials. Also, as drugs move closer to market, the number of patients needed for each trial increases. Typically a Phase III trial requires hundreds of patients to determine if a drug is truly effective.

As a founding member of the CF Therapeutics Development Network (TDN), Johns Hopkins plays a vital role in the drug development process.

In an effort to enlarge the pool of potential research participants, the TDN will be expanded from the current 18 centers to 50 centers in 2009 and then to all the CF centers in the United States over the subsequent few years. The goal is to have all CF centers in this country actively involved in clinical research by the end of the decade.

We are fortunate to have a robust basic science and clinical CF research program at Johns Hopkins. However, we need your help to continue to expand our clinical research program. What can you do to help? **LEARN** about CF clinical trials. Our website, www.hopkinscf.org, has information about clinical research and a listing of ongoing studies. Additional information about clinical research can be obtained from the CF Foundation at www.cff.org. **ASK** us about clinical trials. Ask members of the care team about what research studies might be right for you or your child. Our research coordinators are actively recruiting patients to join a variety of clinical trials. **JOIN** a clinical trial. Participation can be as simple as filling out a questionnaire or having blood drawn or could involve testing a new drug. There are many options to participate in research at Johns Hopkins. Join us to be part of developing new therapies for CF...You are the key.

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



CF Research Nurse Manager Karen Callahan



Hopkins CF patients, notes new research nurse manager Karen Callahan, "are very smart about their illness and medications."

It's a great time to be active in cystic fibrosis (CF) research, says Karen Callahan, the Cystic Fibrosis Center's new research nurse manager. Exciting new therapies are in development, raising researchers' faith in finding a cure.

"One of the most impressive aspects of working here is the doctors' enthusiasm for their research and genuine belief that there will be a cure for CF in their lifetime," says Callahan, whose new job is managing all the adult and pediatric CF trials and related research at Johns Hopkins.

A pediatric nurse, Callahan began her research career at Hopkins School of Medicine in 1999 while finishing her Master's degree in developmental psychology at Johns Hopkins University. Joining forces with Hopkins pediatric allergist Peyton Eggleston in his newly founded Center for Childhood Asthma in an Urban Environment, she brought with her years of experience taking care of pediatric asthma patients in a clinical setting. Callahan, also a mother of two children diagnosed with asthma, understood the effects of a chronic respiratory disease on the lives of children and families. Also drawing upon an earlier degree in community health education, she helped Eggleston develop an educational intervention aimed at reducing indoor allergen exposure for families of children with asthma, and developed methods for sharing indoor findings with them.

"At that time, investigators didn't have systems in place to share study results with participants," she says. "What we were doing was groundbreaking in this regard."

When Eggleston retired in 2006, she moved to the Johns Hopkins Bloomberg School of Public Health to work for pediatric infectious disease

specialist Ruth Karron, testing live-attenuated avian flu vaccines in healthy adults. Findings from two of the avian trials are about to be published.

"I loved that job," she says, of the opportunities to get to know the participants, aged 18-50, and to work closely with them on an isolation unit at Johns Hopkins Bayview Medical Center.

In joining the Johns Hopkins Cystic Fibrosis Center and the Division of Pediatric Pulmonology in July 2008, Callahan returns to the treatment-based studies that first drew her to research, and enjoys "the best of both worlds" by working with both pediatric and adult patients. Pulmonologist Michael Boyle, Callahan and the CF research team recently completed a clinical trial testing VX-770, a selective CF Transmembrane Conductance Regulator (CFTR) potentiator, which increases chloride ion transport properties (see page 1, "Coming Down the Pipeline"). They plan to test a CFTR corrector medication in early 2009. Several other studies are underway to test medications that have not yet been approved for use in the CF population such as denufosol, mannitol, digitoxin, hypertonic saline and tiotropium bromide.

Callahan exudes excitement as a member of the CF world, a world that fast-tracks research findings into treatment. "This is a dynamic field of study within an extraordinarily dedicated and collegial community," she says. "Our patients are very smart about their illness and medications. CF families and adult patients are well integrated into the Cystic Fibrosis Foundation, which is actively working with physicians and pharmaceutical companies to develop better medications and therapies to improve outcomes and ultimately find a cure." ■

Pulmonologist J. Michael Collaco

Unraveling the genetic and environmental components of cystic fibrosis.

When he arrived at Johns Hopkins in July 2005, pulmonologist J. Michael Collaco found himself surrounded by research opportunities. But the one that piqued his curiosity the most was a project with geneticist-pediatrician Garry Cutting, who was exploring the relationship between environmental factors and lung disease.

“One thing led to another,” says Collaco, “and we started to do some work with secondhand smoke and other environmental factors that might modify lung disease.”

That initial work was a retrospective study of 817 cystic fibrosis patients, which provided definitive evidence that secondhand smoke reduces or is associated with reduced lung function. No surprise. But the intriguing news that came out of the study, Collaco says,

was the potential influence of environmental factors on so-called modifier genes, which in turn influence pulmonary outcomes. How well a patient does, he explains, is not determined solely by the particular mutations in his or her CF gene.

“Two people can have identical mutations in their CF gene but have wildly different outcomes – one has normal lung function and the other is close to transplant,” Collaco says. “It’s the interaction between genes and the environment that causes the disease.”

Indeed, Collaco found that patients did especially poorly if they lived in a home with secondhand smoke, and had a certain variant of the TGF-beta gene. But Collaco believes he and his colleagues have only begun to unravel the genetic and environmental compo-

nents of cystic fibrosis. Other genes and other environmental factors, such as climate and air pollution, also probably affect disease severity. But how much variation in disease severity is due to environmental factors – and how much to genetic factors – will influence future research and how quickly discoveries are translated into therapies.

“If most of the variation is caused by environmental factors, then it makes sense to spend your research time and effort on looking at environmental factors,” Collaco says. “On the flip side, if it’s mostly related to genetic factors, then it makes sense to study modifier genes.”

But preliminary findings, he concludes, point toward a combination of both environmental and genetic factors with no particular predominance of one over the other.



J. Michael Collaco, M.D.

But by characterizing CF patients by environmental influences and gene mutations, Collaco concludes, pulmonologists will be better able to provide more personalized care for their CF patients: “We’ll be able to provide targeted medications and interventions rather than prescribe everyone the same therapies.” ■

Coming Down The Pipeline

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normal cells create channels in their membranes that, like gates, enable ions to come and go, the gate in the defective CF protein is either missing or impaired, preventing chloride from moving out. The result is the characteristic thick mucus produced in CF patients’ lungs. Restoring the CF protein function, Campbell notes, may produce benefits ranging from improved airway clearance to reduced infections in the lungs.

Among the therapies targeting CFTR is VX-770, which has been shown to open up chloride channels and lower sweat chloride values, a diagnostic measure of CF. The results from a Phase I trial of 16 patients over two weeks in March, Campbell explains, show for the first time that a drug could actually fix the biochemical flaw in some CF patients.

“There was a significant reduction in the concentration of salt in the sweat, reflecting restoration of CF protein function,” says Campbell. “Lung function went up 10 percent, too,” he adds, noting that results of a Phase II dosing trial of the drug will be coming soon.

While VX-770 appears to be safe, Campbell says, it benefited only a small number of CF patients because the majority of patients have a mutation that prevents CFTR from getting to the membrane where it’s supposed to operate. These patients are predicted to benefit from another compound in the pipeline, a corrector known as VX-809. Campbell sees promise in combining the use of both therapies. “You get the protein to the working part of the CF cell with 809 and then boost the effect with 770,” says Campbell.

Another “very promising” CFTR-targeted therapy, says Campbell, is PTC-124, a compound that also allows the protein to be made. This will help patients with premature stop mutations, which result in only part of the protein being made. A small trial of the drug in Israel and Europe has shown through nasal potential difference tests an increase in transport of chloride across cell membranes, as well as some improvement in lung function. A larger international trial is being organized.

Restoring Airways

Therapies in the pipeline to hydrate thick CF mucus in the lungs by correcting the amount of sodium and chloride along the cell surface include hypertonic saline, which showed improved lung health in a Phase III trial in Australia. Because CF airways lack salt and water,

researchers believe hypertonic saline, an extra-salty water that is germ free, would help clear the thick mucus from the lungs. The CFF is now funding a year-long clinical trial of 300 infants to determine if hypertonic saline compared to normal saline reduces pulmonary exacerbations and improves lung function. “If it works and it’s safe,” says Campbell, “we would recommend that patients begin hypertonic saline treatment when they’re diagnosed as infants to keep the lungs healthy.”

In a Phase III trial of Denufosal – described by Campbell as a “bypass drug” that stimulates and opens up other chloride channels to move chloride into the airways – patients’ lung function improved after six months. A second, slightly longer Phase III trial just underway, says Campbell, “hopefully will add more evidence that by restoring normal airway concentration of salt and water you can keep the CF lung healthier.”

Anti-Inflammatories

In the obstructed airways of CF patients, Campbell explains, white blood cells come in like kamikaze cells in

“This brute-force approach to drug discovery has allowed the Foundation’s drug development pipeline to grow dramatically in recent years.”

– PRESTON CAMPBELL, M.D.

an attempt to gobble up any bacteria. When these cells die they release proteolytic enzymes that can damage the airway itself, resulting in an overly aggressive inflammatory response. The job of anti-inflammatories in the pipeline, Campbell says, “is to reduce that response so we can slow down the rate of decline of lung function.” A single-center trial of the antioxidant N-acetylcysteine started to do just that, he notes, showing a very significant reduction in inflammatory cells in the airway and positive indications of changes in lung function.

“The response was similar to what we see in an IV antibiotic course for pulmonary exacerbation, so it’s a very strong signal,” says Campbell. He adds that a multi-center Phase II trial is underway to test the treat-

ment with a larger patient population before researchers move on to a Phase III trial.

Other anti-inflammatories include inhaled glutathione, currently in a Phase II trial in Germany, and HE-3286, a novel compound designed to both fight inflammation and infections by restoring the normal immune response. “If that works,” says Campbell, “it will be quite exciting.”

Anti-Infective Agents

Among antibiotics in the pipeline, inhaled agents like AZLI (the aerosolized form of the antibiotic aztreonam), TIP (Tobramycin Inhaled Powder) and SLIT-amikacin are following the path of TOBI (Tobramycin Inhalation Solution), which is currently being used by more than 15,000 patients worldwide whose lungs contain the bacteria *Pseudomonas aeruginosa*. Another inhaled antibiotic, GS 9310/11, a combination of both fosfomycin and tobramycin, has completed Phase I testing in Australia.

“GS 9310/11 has different antibiotic spectrums, which our patients have not yet seen,” says Campbell.

Transplantation and Nutrition

Like other organ transplant patients, CF patients who undergo lung transplant are at risk of organ rejection and death – 50 percent of CF patients die within five years of transplant. But in a single-center trial of inhaled cyclosporine, CF lung transplant patients showed a significant decrease in the number of deaths and the development of chronic rejections. “This has the potential of doubling the survival of CF patients after lung transplant,” says Campbell, noting that a larger Phase III trial is now underway.

On the nutritional front, the Foundation has been working with the Food and Drug Administration and makers of pancreatic enzyme products to reformulate those products to provide more precise dosing. Also, a non-animal enzyme in the pipeline, Trizytek, may mean patients will have to take only one or two capsules, instead of four or six, with each meal. Trizytek, which has gone through Phase II and Phase III trials, may also be taken in liquid form, possibly improving digestion in children. ■

For more on the CFF therapeutic pipeline, visit <http://www.cff.org/research/DrugDevelopmentPipeline/>

A Prescription for Exercise?

Pediatric pulmonologist Shruti Paranjape recalls a mother some years ago questioning what kind of exercise would benefit her two children with CF: “She said ‘Every month I come here to clinic and we talk about nutrition and you have a dietician tell me exactly how many calories my kids need. But when it comes to exercise, all you do is tell me to have my kids run around the back yard. There’s nothing being

“For all we know about CF and lung disease, there is still no exercise prescription.”

— SHRUTI PARANJAPE, M.D.

measured, so how can you tell me it’s really effective?” The point was well made, says Paranjape of the Johns Hopkins Cystic Fibrosis Center, noting that the experience spurred her to look into the issues surrounding exercise and CF. No one, she stresses, disputes that exercise translates into benefits for CF patients, including increased bone and muscle strength, strengthened heart and lungs, and improved well-being and ability to carry out normal activities. But neither has anyone, she adds, come up with an exercise formula for CF patients – a way to correlate their exercise needs with an exercise program, and when and how to administer it.

“For all we know about CF and lung disease, there is still no exercise prescription,” says Paranjape. “We’re pretty vague when it comes to exercise.”

“It’s been proven that exercise is beneficial to patients with CF,” adds Karen von Berg, a physical therapist at the Hopkins CF Center. “There are lot of variables surrounding what is appropriate exercise, depending on their age and severity of disease.”

To get at those variables, Paranjape and von Berg asked 125 patients in clinic, age 6 to 16, to self-report their daily activity level through the Habitual Activity Estimation Scale. They also used pulmonary function tests to measure patients’ lung function, and BMI measurements to assess their nutritional status. While the findings from 85 respondents showed boys and girls reporting similar activities during weekdays and weekends, they also revealed a greater decline in pulmonary function and nutritional status in girls after age 12, than in boys.

“So these are the groups we want to target earlier in incorporating exercise into their daily regimen,” says Paranjape. “If we can increase their activity, we may be able to bump these numbers up.”

But what type of activity? Aerobic exercises that raise the heart rate and make breathing harder provide the most benefit for improving airway clearance and lung function, considered a high clinical priority for CF pa-



Exercise has been shown to be beneficial for young CF patients, notes physical therapist Karen von Berg.

tients. And while it may be beneficial to suggest a CF patient do such activities as cycling or running 30 minutes each day for 7 days a week, adherence to such a strict regimen is an issue. Individualizing an exercise program with activities the patient enjoys doing and can fit into his or her schedule, von Berg says, improves adherence, as do activities the whole family can do together.

“Good airway clearance is what you need to keep your lungs healthy, and exercise is a very good adjunct to that,” Paranjape concludes. “On top of that, we want to use this opportunity to teach our patients and families the importance of exercise so that it will improve their physical health and overall well-being.” ■

For more information, call 410-955-2795.

Upcoming Clinical Trials

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than 5 years old. This 18-month study will investigate if exacerbations can be prevented by inhaled hypertonic saline twice daily.

ANTIBODIES AGAINST PSEUDOMONAS AERUGINOSA

The immune system uses antibodies to protect the body from infection. KaloBios is attempting to do the same thing by manufacturing an antibody that can bind to *Pseudomonas aeruginosa*. A trial to determine if this drug can be safely administered to CF patients will start this fall at Johns Hopkins and other centers.

TIOTROPIUM

Inhaled tiotropium (Spiriva™, Boehringer Ingelheim) is a medication that is already approved for use in Chronic Obstructive Pulmonary Disease (COPD). Tiotropium, inhaled once daily, relaxes the muscle that surrounds the airways to increase their diameter and also decreases mucus secretion in COPD patients. Johns Hopkins is participating in a large international study to determine if this medication is effective in the treatment of CF. Patient enrollment for this trial will begin in the next few months. ■

NACFC Highlights (continued from page 1)

data from a 3-month trial of PTC-124 conducted in 19 CF patients. As expected, PTC-124 led to a significant improvement in chloride transport as measured by NPD. An unexpected finding was that chloride transport continued to improve over the entire three months. Additionally, some patients who did not respond in the first month did respond by the third

month. There was a suggestion that lung function improved and the frequency of coughing decreased with PTC-124 treatment. A year-long double-blind, placebo-controlled trial to determine if this improved chloride transport translates into improved lung function is slated to begin in the spring of 2009. Hopkins researchers will be participating in this study.

INHALED AMIKACIN

Arikase™ (Transave Inhalational Biotherapeutics) is an inhaled version of the antibiotic amikacin encapsulated in a lipid coating called a liposome. A 28-day treatment with once-daily Arikase™ in 64 patients demonstrated a 15 percent improvement in FEV1 in those patients who received the antibiotic. A longer trial of this antibiotic

will be beginning at Johns Hopkins this winter. Promising results from studies of several other inhaled antibiotics in development were also presented at NACFC.

BLOCKING SODIUM

Preliminary data from studies of two drugs that block sodium transport out of the airway were presented at NACFC. QAU-145 (Novartis) and

PS-643 (Parion Sciences) act by different mechanisms to block sodium absorption. A phase I trial of QAU-145 showed that it can decrease sodium transport measured by NPD. PS-643 appears to be very effective in blocking sodium transport in cell and animal models of CF. These early studies are promising, but time will tell if this approach can improve lung function in CF patients. ■

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