



## Research Briefs

### VX-770 LEADS TO IMPROVED LUNG FUNCTION

Vertex Pharmaceuticals announced positive results from the Phase 3 STRIVE trial of VX-770, which is designed to activate or “potentiate” abnormal CFTR that is located on the cell surface. Patients with a G551D CFTR mutation had a 10.6 percent improvement in lung function as measured by FEV1, after 24 weeks of treatment with VX-770. This improvement corresponded with a decrease in exacerbations and improvement in sweat chloride.

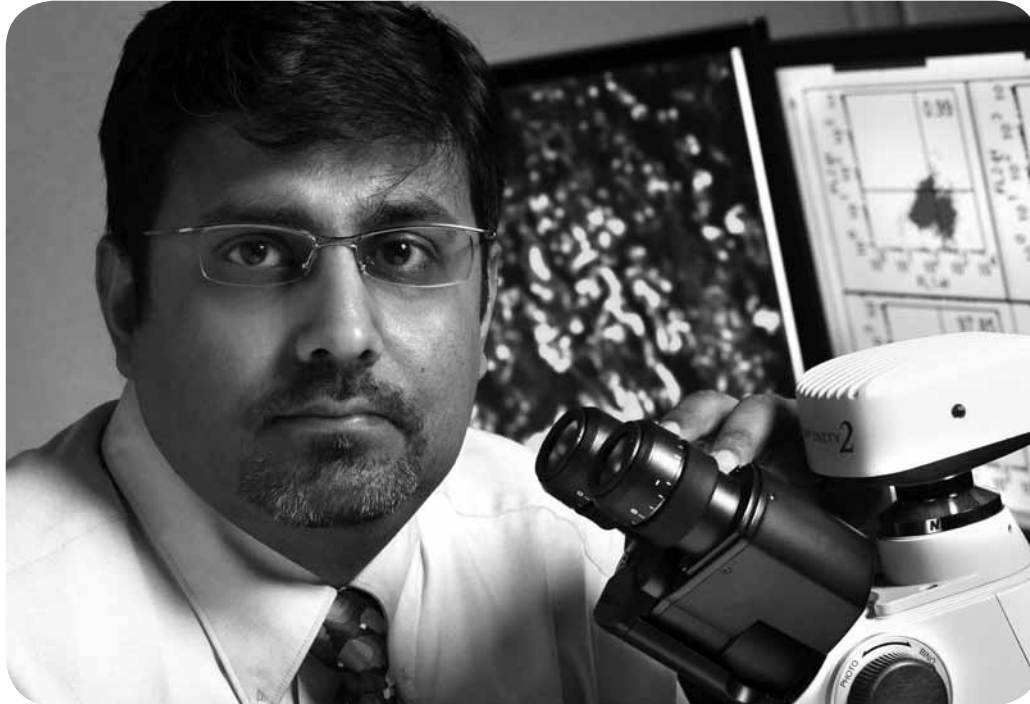
### DISAPPOINTING DENUFOSOL RESULTS

Inspire Pharmaceuticals announced disappointing results from the TIGER-2 study of Denufosal. The top-line results from this second Phase 3 clinical trial of Denufosal did not demonstrate a statistically significant improvement in lung function compared to the placebo after 48 weeks. Denufosal is an inhaled drug that activates an “alternative” chloride channel on the airway surface in hopes of bypassing the defective CFTR that causes CF.

### FUNGAL INFECTION IS MORE COMMON

Pulmonologist Michael Boyle and his colleagues in the Johns Hopkins CF Program have found that the incidence of fungal infection in CF patients has increased 10 fold over the past decade. In a paper published in the *Journal of Cystic Fibrosis* (2010;9(2):110-116), these researchers found that fungal infection was more common in older patients and those that used antibiotics

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Searching for signs of inflammation in cystic fibrosis and other chronic lung diseases, pulmonary researcher Neeraj Vij in the lab.

## Understanding Inflammation

Pulmonary researcher Neeraj Vij uncovers new clues regarding airway inflammation in cystic fibrosis and other obstructive lung diseases.

**N**eeraj Vij, Ph.D., is a man in search of signals – specifically signals that lead to a greater understanding of inflammation in obstructive lung diseases like cystic fibrosis (CF). What better condition to study airway inflammation, asks the pulmonary researcher, noting that inflammation plays a pivotal role in the pathogenesis of lung disease in CF, and that the inflammatory response in CF is more intense than in other airway diseases.

“These patients do have very severe lung disease and are prone to very severe lung infections,” Vij says.

So, why is that? Central to the pathogenesis of CF is the absence or impairment of the protein CFTR (cystic fibrosis transmembrane conductance regulator) due to genetic mutations. Without CFTR, chloride cannot be transported in and out of cells, resulting in mucus buildup in the airways, lung infections and breathing problems.

But in casting his net for inflammatory signals, Vij has snared the role CFTR plays as

a critical regulator of inflammatory signaling. In his most recent study, he’s learned that decreases in CFTR also correspond to increased buildup in the lung cells of a fatty molecule called ceramide, a well-known trigger of inflammation and cell death. Thus, by regulating ceramide’s inflammation-causing activity, CFTR appears to be a watchdog for inflammation and cell death (*The Journal of Immunology*, December 2010).

“Our findings suggest that CFTR is a multitasker protein that is not only involved in chloride transport but also in regulating cell death and inflammation by keeping in check the rampant and dangerous accumulation of ceramide,” says Vij.

But Vij’s findings also indicate that CFTR is involved in immune regulation and immune response on a far wider scale. His research — conducted in mice and using lung tissue from people with and without emphysema — shows that those with lung damage from emphysema had less CFTR on the cell surface and that

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## Ongoing Clinical Trials

### DIGITOXIN

Can Digitoxin, a drug used in Europe to treat heart failure and known to decrease inflammation in airway cells, decrease inflammation in the airways of CF patients? This study aims to find out. CF patients over 18 years of age are eligible to participate.

### ATALUREN (PTC124)

Ataluren, formerly known as PTC124, 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 one-year study, which is being carried out at 38 international sites, will enroll 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.

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

The purpose of this research study is to learn more about liver disease in people with cystic fibrosis (CF) using a test called a liver ultrasound. CF is an inherited disease that involves the lungs and the digestive system, including the liver. 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 in people with CF. The liver ultrasound test may help to diagnose and treat liver disease in people with CF. In this five-year study, participants will have labwork and complete questionnaires once a year and have a liver ultrasound test every two years. ■

## A Bright Future for CF Drug Development

The success of the phase 3 trial of VX-770 (see “Research Briefs” page 1) is a milestone in the treatment of cystic fibrosis (CF). The increased lung function, in combination with a decrease in sweat chloride concentration, in patients receiving VX-770 compared with placebo demonstrate that it is possible to fix a defective CFTR channel. There are several more hurdles that this drug must overcome before being approved by the Food and Drug Administration. However, I am optimistic that this drug will eventually be approved for use by CF patients. VX-770 is just

one of three drugs designed to treat the basic defect in CF, which are now in phase 3 trials.

Hundreds of CF patients, including many at Johns Hopkins, participated in studies of VX-770. More drugs are in the pipeline and continued participation by our patients is the key to bringing new therapies to the market.

But we know that not all novel approaches to treat CF will be successful. Although initial studies of Denufosol seemed promising, a large phase 3 trial (TIGER-2) failed to show a benefit of Denufosol over placebo. These disappointing results led Inspire Pharmaceuticals to cease development of this drug.

But the future for CF drug development is bright, as illustrated in this issue of *Partners in Discovery*. Studies of inflammatory pathways by pulmonary researcher **Neeraj Vij** are helping us to identify new targets for therapeutic development (see story page 1). Pulmonologists like **Natalie West** and **Noah Lechtzin**, along with health psychologist **Michelle Eakin**, nutritionist **Meredith Harter** and physical therapist **Holly Loosen**, are showing us new ways to improve clinical outcomes with tools we already have at hand.

New therapies will not be able to reverse lung damage that has already occurred. Therefore, developing optimal approaches to caring for patients using currently available drugs is vitally important so that patients can receive that maximum benefit from new therapies on the horizon.

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



## Battling Barriers to Adolescents' Adherence

As if being born with cystic fibrosis (CF) wasn't enough, nature plays somewhat of a cruel joke on CF patients' ability to adhere to their lifelong medications. Generally, the younger you are, the less your needs for medications and the easier to maintain them. Conversely, the older you get, the greater your medication needs but the less capable you are of sticking with your regimen, especially if you're an adolescent.

“As children get older life's demands take on more and more time,” explains **Michelle Eakin, Ph.D.**, a health psychologist with the Johns Hopkins CF Center. “Teenagers have school and after-school activities, perhaps a part-time job, and at the same time they're getting busier their treatment demands are increasing as well.”

Yet complying with strict regimens of CF therapies is critical for patients to reduce their risk of pulmonary exacerbations and lung infections, frequent ED visits and hospital stays, a poorer quality of life and shortened lifespan. So Eakin's job is to help all CF patients, particularly adolescents, find ways to adhere. But what works best, Eakin says, is parents and practitioners educating young patients about their disease and the consequences of non-compliance before they reach adolescence.

“You wouldn't ask a 6-year-old to set up a nebulizer by himself but there are steps he can learn to gain self efficacy and build confidence,” Eakin says. “Our research shows that children who know more about their medications and what they do, and who feel more confident in doing certain steps of the treatment, are going to be more likely to take their medications when they get older.”

But there is still the problem of how to fit lengthy CF therapies—in some cases adding up to three or four hours daily—into a busy adolescent's day. In her study with colleague **Kristin Riekert, Ph.D.**, of the Johns Hopkins Adherence Research Center, Eakin found self-reported

adherence to airway clearance poor – ranging between 41 and 54 percent of adolescent and adult patients. Barriers identified included the burden of the treatment, social and work demands, forgetfulness, no perceived health benefit, fatigue and embarrassment related to performing treatments in public (*Journal of Cystic Fibrosis*, December 2010;9;6;425-432).

Another potential barrier is how the adolescent and parents address adherence. Often times the parent, who is generally more aware than the teen about health implications of not taking medications, is more motivated than the patient. The teenager isn't thinking 10 minutes ahead, let alone 10 years, notes Eakin. So often the issue becomes one more source of conflict between the parents and the adolescent. What can be done? One thing is certain, Eakin says—nagging doesn't help.

“Every family needs to assess how they spend their day and when is the best time for therapy,” says Eakin, “but parents who have a collaborative working relationship with their teenager are going to have more success than those who are more dogmatic and force the issue. Yelling and screaming are not going to work.”

Eakin recommends that parents and teens write a contract with consequences—like no Facebook time or the family car Friday night—if the teen doesn't comply. And parents promise not to nag.

“But often it will be the parent who sabotages the agreement,” notes Eakin. “They're not willing to enforce the consequence or stop the nagging, so the teenager gets more and more frustrated and acts out more and more.”

Other factors supporting adherence among patients, Eakin found, included regular visits to their CF clinic and feedback from physicians. Patients reported feeling “amped up” to do their therapies after each clinic visit, she says, and perceived their time in the CF clinic as a “positive experience that reinforced their efforts to stay on track.” ■



Working with a young patient, health psychologist Michelle Eakin.

# Spirometer: Don't Go Home Without It

In the Cystic Fibrosis Center at Johns Hopkins, pulmonologists Noah Lechtzin and Natalie West closely watch a young patient exhale into a spirometer. They then check the reading on the device that represents this patient's current peak expiratory flow in one second, or FEV1, a number that for CF patients means so much more than just a number.

"That's the number we pay most attention to, how fast air can be blown out of the lungs after inhalation," says Lechtzin. "It's very predictive of how people are going to do over the long term."

Indeed, FEV1 is a very telling measurement that can signal a decline in lung function or a pending exacerbation, or send a message to the patient's pulmonologist that aggressive treatments with airway clearance, mucolytics and antibiotics may be needed immediately if not sooner. In CF, the thinking goes, the earlier the detection and treatment of a problem the better the outcome.

But spirometry tests that can send such warning signs

tend to be conducted in CF clinics and not patients' living rooms. More often than not, CF exacerbations are typically detected only when patients are sick enough to seek care.

"Too often they run into problems they're not even aware of, or haven't bothered them enough where they feel they need to call us," says Lechtzin.

Lechtzin and West are trying to turn such scenarios around through the use of spirometry in a different venue—the patient's home. And it seems to be working. In their six-month pilot study, each of 10 young adult patients was given a hand-held spirometry device and asked to measure their FEV1 twice daily and to

record their symptoms daily. The results? There were 28 exacerbations detected through home monitoring, but only eight of these were reported by patients to their physicians and treated with antibiotics. Also, of the 28 exacerbations detected, 16 were detected by FEV1 alone, and 12 by both FEV1 and symptoms. Home monitoring detected exacerbations an average of 16 days before patients contacted their care center because of symptoms (*Pediatric Pulmonology* 2009;44(S32):343-44.)

"Looking at the data on lung function before and after," Lechtzin says, "it turns out they did a little bit better during the time they were using the meter at home, and



Pulmonologists Natalie West and Noah Lechtzin provide some patient education on using a spirometer in the home.

they required fewer courses of antibiotics."

Lechtzin and West are now parlaying what they've learned in a randomized study of adolescents, a group of patients particularly challenged by adherence. After patients record their FEV1 measurements, they will answer a series of multiple choice questions presented on a digital menu on the device itself. Among the questions: Have you changed your medication? Have you noticed more coughing? They will then send their answers

via modem to Lechtzin and West, who will compare their data with that of patients receiving standard therapy.

"By getting feedback on the meters and keeping tabs on how well they're doing, they're more likely to use their prescribed therapies and stay healthy," says West.

Lechtzin adds, "The goal is to catch problems early so we can intervene, keep them healthier without having to see them all the time, and without having them become very sick and hospitalized." ■

## Fighting Weight Loss

Typically, a CF patient's weight begins to decline soon after admission. Let's face it, hospital food isn't all that great and as accessible as at home.

"A lot of kids who come into the hospital don't eat and their weight begins to plummet, but CF patients can't afford to have weight loss," says nutritionist Meredith Harter, noting that failure to maintain a healthy body mass index (BMI) is associated with lower pulmonary function because the body is not absorbing the nutrients needed to build up strong respiratory muscles. She adds, "We want to keep them building instead of taking steps back because they're in the hospital."

So, how do you do that? Through a comprehensive and ongoing nutrition initiative emphasizing an array of approaches, from educating parents and patients about appetite stimulants and oral supplements to meticulously tracking pancreatic enzymes and patients' growth charts. Patient education for inpatients begins early in the morning with a discussion about oral supplements and the benefits of trying different supplements during their hospital stay, something they're less able to do at home. Next on the list—food options during their admission.

"Patients need to know that they can choose two entrees with their meals and that we have

these after-hour specials like Baja Fresh, hot pockets and lunchables," says Harter. "We want to make sure they're aware of all of their options so they increase their intake."

Keeping an eye on pancreatic enzymes is especially important for absorption, digestion and weight gain, so nutritionists spend a good amount of time counseling patients when and how to take the enzymes. Slightly higher doses of enzymes may be necessary with high-fat and processed foods. Also, some foods and drinks do not require enzymes because they contain only simple, easily digestible carbohydrates.

Nutritionists like Harter are also renewing their efforts to educate patients and families about all aspects of tube feeding. Also, with outpatients CF nutritionists are making sure their nutritional needs are being consistently evaluated—at least annually—and that there's more communication between inpatient and outpatient staff.

"If I have an inpatient with poor nutritional status, I could remind the outpatient nutritionist to check on him," says Harter. "We hold weekly meetings to discuss each patient, decide whether social work needs to see the patient about other things interfering with nutrition."

Harter concludes, "The mentality of the team is more weight gain and greater BMI correlates with better lung function and better PFTs." ■

## Inflammation

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changes in the level of CFTR corresponded directly to disease severity.

Also, in comparing lung tissue from mice with "virgin" lungs never exposed to smoke to tissue from the lungs of mice exposed to cigarette smoke, Vij found the lungs of smoke-exposed mice had decreased CFTR expression and increased ceramide levels. The heavier the smoking, the greater the lung damage, the lower the CFTR expression and the higher the ceramide accumulation, Vij notes, clearly linking CFTR and ceramide levels to smoking history and disease severity.

So, just how does CFTR cause ceramide to trigger lung-damaging inflammation? To find the answer, Vij analyzed lung cells from people and mice lacking CFTR in their cell membrane. Using a microscope and a technique called flow cytometry that captures changes in inflammatory and protein markers, Vij noticed increased clustering of ceramide molecules on sections of the cell membrane called lipid rafts, known to be hot spots where inflammatory signaling proteins congregate. This clustering, Vij explains, leads to increased inflammatory signaling, greater inflammation and cell damage in the absence of normal CFTR. Apparently, when functioning properly, CFTR keeps a lid on the signaling activity of inflammatory receptors by preventing them from clustering, thus warding off inflammation and lung damage.

"We anticipate," Vij says, "that membrane CFTR and ceramide may turn out to be useful predictors of susceptibility to lung damage from smoking and infections and may be tailored for drug therapy to alter disease course." ■

## Pancakes at 9, Physical Therapy at 10

**A**s a cystic fibrosis patient you've likely had this hospital experience. You wake up and your no-longer hot breakfast is sitting on your bedside hospital tray as both a physical therapist and a respiratory therapist enter the room for your daily therapies. At the same time a nurse comes in to notify you she'll need to place an IV line. Rather than health care being delivered in a seamless way, your room suddenly looks more like a beltway backup.

"They feel bombarded with the physical therapist and respiratory therapist and the nurse team rounding all at once when breakfast is served," says respiratory therapist **Andrea Honesto**.

Prompted by substandard patient satisfaction surveys, a new quality improvement initiative is striving to eliminate such tangled scenarios for CF patients at Hopkins Children's by increasing coordination between nutritionists and physical and respiratory therapists. The result is a daily schedule alerting patients within 30-minute windows when meals and therapists will arrive at their bedside.

"Now the patient isn't always waiting and wondering what's happening next," says physical therapist **Holly Loosen** of the initiative underway since November 2010. "Getting everybody on board is probably our biggest challenge because PT and RT staff is so extensive, but communication between all the therapists has increased."

"This is especially helpful for a first-time parent and patient in the hospital," adds nutritionist **Meredith Harter**. "It's more comforting to know who's who and what's going on."

But smooth scheduling is only one



**Physical therapist Holly Loosen works with patients in the hospital to improve their breathing and adherence to therapies at home.**

component of quality improvement for CF patients at Hopkins Children's. For inpatients, respiratory therapists are increasing airway clearance sessions from three to four times a day to improve patients' pulmonary function test results. Also, in coordination with physical therapists, they're observing whether certain exercises may be an adjunct to clearance.

On their end, physical therapists are initiating endurance testing for patients upon admission and discharge to measure the impact of the airway clearance measures. Also, they're focusing more on postural interventions to counter the hunched-over posture CF patients are

prone to from constantly coughing up mucus. PT is also doing more staff and patient education to improve patients' breathing and adherence to therapies when they return home.

"Now it's not just the clinic therapist who knows about vest settings for high-frequency chest wall oscillation," says Loosen.

"We're trying to improve quality of care not just from the standpoint that it looks nice and feels good but that patients are getting better medically," concludes Honesto. "We want to make sure they're getting the best treatment possible from their health-care team." ■

### Research Briefs

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chronically. How this increase in fungal infection affects lung function is unknown.

#### GARRY CUTTING HONORED

Johns Hopkins researcher Garry Cutting's leadership in CF research was recognized at the North American CF Conference held in November. Dr. Cutting received the Paul di Sant'Anges Distinguished Scientific Award from the CF Foundation. Dr. Cutting has been at the forefront of identifying CFTR mutations that cause CF. He has created a worldwide study of twins and siblings with CF that has resulted in a greater understanding of the effects of modifier genes and environmental factors on CF lung disease.

#### LIPROTAMASE NOT RECOMMENDED

An advisory panel of the U.S. Food & Drug Administration said it did not have sufficient clinical trial data to recommend approval of liprotamase, a non-porcine pancreatic enzyme therapy for the treatment of CF. The panel also had questions about the degree of efficacy of the drug. Additional studies may be required before this drug can be approved.

Visit the Johns Hopkins Cystic Fibrosis Center website at [www.hopkinscf.org](http://www.hopkinscf.org)

## Partners IN DISCOVERY

**Johns Hopkins Cystic Fibrosis Center**  
200 N. Wolfe Street  
Baltimore, MD 21287  
410-955-2795  
[www.hopkinscf.org](http://www.hopkinscf.org)

Adult CF Program  
1830 East Monument Street, 5th Floor  
Baltimore, MD 21205  
410-502-7044

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Kim Martin, *Director*  
Gary Logan, *Editor*  
Peter Mogayzel, M.D., Ph.D., *Medical Editor*  
Ekaterina Pesheva, *Contributing Writer*  
Max Boam, David Dilworth, *Design*  
Gary Logan, Keith Weller, *Photography*

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