

Research Briefs

A PIG WITH CF?

That is exactly what a group of researchers at the University of Iowa, led by Dr. Michael Welsh, is trying to create. Traditionally, animal models have been used to better understand diseases and to test new treatments, however, no animals get CF naturally. Several mouse models of CF have been created, but they do not have significant lung problems. Therefore, creating a different animal model of CF that has lung problems is vitally important. Attempts have been made in the past to use primates, sheep and ferrets as models of CF, but none has been successful. Dr. Welsh presented encouraging results from his group's efforts at the annual CF Foundation research conference in June. If these animals do indeed develop lung disease that is similar to the problems seen in patients, it will be a tremendous advance for CF research.

NEW INHALED ANTIBIOTICS

Fighting *Pseudomonas aeruginosa* (*Pa*) infections in the lung is critically important to the health of CF patients. Unfortunately, most of the antibiotics that are effective against *Pa* must be given intravenously. Additionally, *Pa* is often resistant to many of these antibiotics. The use of inhaled antibiotics allows the drug to reach the place where it is needed most, at very high concentrations that can overcome resistance with few side effects. Only one antibiotic, tobramycin or TOBI®, is currently approved for inhalation in the United States. However, there are several new inhaled antibiotics that are effective against *Pa* in the pipeline.

Aztreonam is an intravenous antibiotic that is being developed by Gilead Sciences for inhalation. This antibiotic will be administered using a new nebulizer called an

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Studying the Science of Resistance



“You scratch your head and ask, ‘What are we going to use to treat them?’”

—NOAH LECHTZIN, M.D.

Pseudomonas aeruginosa is a nasty bug, infecting nearly 80 percent of all CF patients. And its success lies in part to its reputation for resisting many common antibiotics thrown at it. In fact, although immediate treatment with antibiotics can clear the infection, in many cases the bacteria adapt and establish permanent colonies in the lungs, increasing sputum production and decreasing lung function. In many cases, rather than cure the infection, antibiotics can only reduce the amount of chronic infection.

“You scratch your head and ask, ‘What are we going to use to treat them?’” says pulmonologist **Noah Lechtzin** of the Johns Hopkins Cystic Fibrosis Center. “At the end of the line we may have no good antibiotic to treat them, which translates into a deep downhill course.”

But through studying various strains of *P. aeruginosa* and other bacterial infections, Lechtzin is learning more and more about this enemy called antibiotic resistance and how to

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Upcoming Clinical Trials

HYPERTONIC SALINE

Inhaling a concentrated salt solution, known as hypertonic saline, leads to improved lung function and fewer pulmonary infections in older children and adults with CF. However, it is unknown if hypertonic saline works in younger children with normal lung function. Aerosol researcher **Beth Laube** is studying the effect of hypertonic saline on the clearance of mucus from the lungs of 8-12 year olds with normal lung function. Results from this study will determine if this therapy is effective in school-aged children. In another hypertonic saline study, Johns Hopkins will be participating in a multi-center trial of hypertonic saline therapy in infants with CF. This study, beginning in early 2008, will test the effect of six months of hypertonic saline on the lung function of children less than 2 years old. Lung function will be measured using infant pulmonary function testing. This type of sedated testing provides values similar to those obtained from older children and adults.

TIGER TRIAL

The TIGER (Transport of Ions to Generate Epithelial Rehydration) is a phase III study of inhaled Denufosal (INS37217 Respiratory), manufactured by Inspire Pharmaceuticals. Johns Hopkins is currently recruiting patients for this study, which hopes to enroll 350 CF patients nationwide. Denufosal, which is inhaled three times daily, activates an alternative chloride channel, thereby bypassing the defective CFTR channel in CF. Previous studies have shown that Denufosal is well tolerated and may improve lung function. The TIGER

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What Causes CF Lung Disease?

You might think this is an easy question to answer. Obviously, CF is caused by mutations in the CFTR gene. These mutations prevent a chloride channel—also called CFTR—from being formed and inserted into the surface of cells. This leads to abnormal salt transport into and out of cells creating thick sticky mucus, which blocks small airways in the lungs and traps bacteria.

What causes the lung disease? Is it the fact that the mucus is too thick and sticky from the lack of chloride transport, or is it the infection with bacteria such as *Pseudomonas aeruginosa*?



There are other possibilities as well. The CF lung has an exaggerated inflammatory response that may be responsible for much of

the actual lung damage that occurs. Also, transport of several other compounds in the CF airway—including water, sodium, bicarbonate, glutathione and cyclic AMP—is abnormal. And the abnormal transport of one or more of these compounds may actually be more important than problems with chloride transport. Investigators have also found problems in the airway defense mechanisms and in lipid metabolism in CF patients.

So, what needs to be done to cure CF? Is it enough to just fix chloride transport, or do we also need to improve bicarbonate transport and slow sodium transport? What about blocking inflammation and correcting the lipid abnormalities? How many of these problems do we have to correct to improve the lives of CF patients? We don't really know, which is why our approach has been to study and find therapies for all of these problems. ■

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

Nutrition Update

Pediatric Clinical Dietitian Amanda Leonard on Two New Studies



Amanda Leonard, MPH, RD/LD

What are these new studies about?

Leonard: Basically, two new products involving antioxidants and pancreatic enzymes. The antioxidant product, called Aquadek, is actually a vitamin supplement rich in antioxidants, which researchers believe CF patients need more of because they tend to suffer more oxidative stress than people without CF.

Oxidative stress?

Leonard: Yes. As you breathe your cells constantly interact with oxygen, producing highly reactive molecules called free radicals, which can damage genes, membranes and proteins. The body produces antioxidants to neutralize these free radicals and counter this oxidative stress.

And what did the researchers in the study find?

Leonard: They found that Aquadek increased levels of important fat-soluble nutrients and antioxidants like carotenoids, tocopherols and coenzyme Q(10). They also learned that improvements in antioxidant plasma levels were associated with reductions in airway inflammation in CF patients. (See "A pilot study on the safety and efficacy of a novel antioxidant rich formulation in patients with cystic fibrosis," *Journal of Cystic Fibrosis*, June 12, 2007.)

Is Aquadek available now?

Leonard: Yes, it is on the market, which could be a good thing because these antioxidants were missing in our previously available vitamin formulations and may be helpful.

What's the other study about?

Leonard: A new, non-porcine replacement enzyme called ALTU-135, which is currently in a CF Foundation phase III trial for patients over age 18. The results aren't in yet, but hopefully this enzyme will be more stable and work better than the pig enzymes currently available.

Why would it work better?

Leonard: The downside of porcine enzymes is that too much acid makes them less effective. Many people with CF have a lot of acid in their gastrointestinal system. But a man-made enzyme may work well regardless of acid levels in the stomach. Also, this enzyme may be available as a liquid formulation, which would be much easier for patients to take. Parents would no longer have to open the capsule and put the beads in applesauce.

Any other issues on your radar screen?

Leonard: We continue to look at bone health and the increased incidence of osteoporosis in people with CF, which adds to their stress. While there are some treatments for adults, there are none for kids under age 18 because of the potential effect of the therapies on bone growth. So, in a prevention approach we're doing more vitamin D supplementation to maximize their bone health. Also, with more and more CF patients being appropriately nourished, we're looking at the fats they're getting. Beyond calories it's important that they get enough fats, but we want to make sure they're healthy fats like the Omega 3 fatty acids and the monounsaturated fats found in olive oil and avocados. We think CF patients should be getting some "healthy" fat in addition to "junk food" fat. ■

For more information, email Amanda Leonard at amleonar@jhmi.edu.

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e-flow, which shortens the delivery time. Aztreonam for inhalation, or AI, is currently in phase III trials. The company anticipates submitting an application for approval of AI to the Food and Drug Administration (FDA) later this year.

Tobramycin Inhalation Powder, or TIP, a dry powder version of TOBI® manufactured by Novartis Pharmaceuticals, is currently in a large phase III trial in the United States. The drug is packaged in capsules that are inhaled using a small dry powder inhaler. This formulation should decrease the time to administer tobramycin dramatically. Bayer Healthcare is developing a dry powder form of Cipro® as well.

Arikace™, manufactured by Transave, is an inhaled form of amikacin, an antibiotic related to tobramycin. In this formulation the amikacin is encapsulated in lipid spheres, allowing it to penetrate mucus better and hopefully remain in the lung longer than other inhaled drugs. Arikace™ will also be delivered by the e-flow nebulizer. This drug is currently

undergoing phase I safety trials. Johns Hopkins will be participating in a trial of Arikace™ later this year.

PATIENT REPORTED OUTCOMES

The FDA has mandated that applications for new drugs evaluate their effectiveness in improving patient reported outcomes (PRO). These are problems that only patients can describe, such as amount of coughing or inability to do activities because of breathing problems. This type of outcome has been measured in the past by "Quality of Life" questionnaires. Several well-studied questionnaires for CF patients are now in use. However, to obtain more detailed and sensitive views of patient symptoms, new questionnaires and symptom tracking scores are being developed for CF patients. These instruments will be incorporated into most future studies of new drugs. ■

Carlton Lee, PharmD, MPH CF Center Pharmacist is Hawaii's Loss, Hopkins' Gain

Carlton Lee had no qualms about growing up in Honolulu, Hawaii. Who would? But when he decided he wanted to study hospital pharmacology and apply for a residency, he discovered there was no such program in the islands. He looked east and found Johns Hopkins, where he completed his pharmacy residency. But then he stayed and, despite his intentions, one year turned into 22.

"The initial plan was to come here, do the training, and then head back west to become a hospital pharmacist somewhere," says the soft-spoken Lee. "But something made me stick around."

That something, Lee says, was an extremely stimulating environment filled with cutting-edge clinicians and world-renowned researchers. During his residency, he got increasingly curious about research studies, started asking himself questions. At the same time, hospital pharmacists were increasingly getting involved in ambulatory care to help manage chronic conditions like asthma and cystic fibrosis on an outpatient basis. Lee saw the planets aligning for hospital pharmacists like him to have a much greater impact on treating these patients with chronic medications. But when he searched for opportunities focusing on asthma, none was available. However, the world of CF pharmacology was wide open.

"To me, the next best clinical thing was CF," says Lee. "In 1992, I dove in."

Initially he counseled patients at the Hopkins CF Center regarding their medication use. Because the typical CF patient may be taking a dozen or more drugs, medication compliance and reconciliation are critical issues.

"It's a matter of developing strategies, keeping track, making sure that kids at school have access to their medications," says Lee. "CF patients eliminate antibiotics much quicker, so you have to make dosage adjustments to account for that."



For Lee, the clinical experience stimulated the research questions and studies into just how fast children with CF clear antibiotics from their bodies. That led him deeper into the fields of pharmacodynamics, the study of drug mechanisms and their physiologic effects, and pharmacokinetics, or what the body does to the drug through processes like medication metabolism and excretion. Today, like pulmonologist **Noah Lechtzin** (see page 1), Lee is looking at antibiotic-resistant bacterial infections in CF patients, and the potential impact of antibiotics, especially the inhaled therapies.

"So far, we've seen that we can't totally eradicate the persistent colonization of bacteria because the lung disease pathology in CF patients is so different," says Lee, "But we can keep the bacteria at bay."

The big answers for CF patients, Lee says, lie in

"It's a matter of developing strategies, keeping track, making sure that kids at school have access to their medications."

—CARLTON LEE, PHARM D.

eliminating the causative links to that disease pathology through gene therapy. Effective and safe drug delivery is still the key challenge in genetic therapies, Lee says, but once that door is unlocked, treatments and outcomes will improve dramatically.

"If those efforts prove out and you can correct the gene that triggers the cascade of symptoms, you'd stop them from occurring from the get-go," says Lee. "Instead of putting out fires, we'd be going for the jugular."

Until then, Lee continues to focus on the development of new classes of antimicrobial agents for CF patients. So, we asked him, is he going back to Honolulu anytime soon?

"Only if I hit the lottery," he laughs.

For more information about Carlton Lee's work, please e-mail him at cleea@jhmi.edu. ■

Studying the Science

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combat it. For example, through sending several resistant *Pseudomonas* strains to Columbia University for synergy testing of different antibiotic combinations, he's discovering some new joint weapons: "Even though a single antibiotic may not be effective, combining two antibiotics may have a synergistic effect." In fact, the standard therapy at Hopkins for many resistant strains of *P. aeruginosa* is a combination of two antibiotics.

Concerned that less common CF infections like *Staphylococcus aureus* are becoming more resistant to antibiotics, Lechtzin is looking beyond *P. aeruginosa*, too. One culprit that has been a concern since the 1980's is *Burkholderia cepacia*, which can be transmitted from one patient to another, typically resulting in a rapid decline for the patient, but emerging resistant organisms may not cause such complications. One such bacterium, *Stenotrophomonas maltophilia*, is growing in resistance but not playing out in dramatically worse outcomes in lung function and life expectancy.

Citing a recent study by University of Washington researcher Chris Goss [*Am. J. Respir. Crit. Care Med.* 2002;166:356-61], Lechtzin says, "It's fairly reassuring that though *S. maltophilia* is resistant, we don't have to worry about it as much as bacteria like *Burkholderia cepacia*."

In one of his own studies, Lechtzin explored whether *P. aeruginosa* behave more like *S. maltophilia* or *B. cepacia*. He looked at three groups of Hopkins CF patients—one with persistently resistant *P. aeruginosa*, another with transiently resistant *P. aeruginosa*, and a third group with susceptible strains of *P. aeruginosa*. As suspected, Lechtzin notes, those patients who had resistant strains had more advanced disease: "They tended to be a little older, had received more courses of antibiotics at baseline, had lower lung function and had more hospitalizations."

However, the differences in lung function and hospitalizations, Lechtzin explains, were not dramatic. Using the same methodology for a larger, national

"Even though a single antibiotic may not be effective, combining two antibiotics may have a synergistic effect."

—NOAH LECHTZIN, M.D.

sample of patients, Lechtzin and other researchers in a CF Foundation study found similar results.

Of course, in the war against resistance, there is always the risk of producing more resistance through greater exposure to antibiotics. In fact, some CF clinics will withhold certain antibiotics unless they're forced to treat. In general, says Lechtzin, those places tend to have worse outcomes. Hopkins CF Center clinicians use antibiotics aggressively when patients suffer exacerbations. They've added chronically inhaled Tobramycin and Colistin to their arsenal to get higher levels of the drug in the lungs to improve the odds of overcoming

resistance. Additional inhaled antibiotics may soon be available to clinicians (see *Research Briefs*).

By and large, Lechtzin concludes, Hopkins CF Center clinicians have found that aggressive use of antibiotics has improved lung function and survival, and decreased hospitalizations. Any price they've paid in encouraging resistance has been clearly offset.

"Even if the bacterium is resistant to the antibiotic, it may still work. What you see in a Petri dish in the lab doesn't necessarily correlate with what you see in a patient," Lechtzin says. "So, developing resistant bacteria is not the end of the world." ■



Research Coordinator Carolyn Chapman with a parent and patient at the pediatric clinic in the Johns Hopkins Cystic Fibrosis Center.

A New Face in CF Research

Carolyn G. Chapman, RN, joined the Hopkins CF team as a research coordinator in October 2006. Before moving to Baltimore last summer, she worked as a nurse at a busy medical/surgery unit at St. Vincent Regional Medical Center in Santa Fe, New Mexico. Nursing, however, is Carolyn's second career. For close to 10 years, she worked in New York City in science education jobs at non-profit organizations, including the American Institute of Physics and Ventures In Education. More recently in Santa Fe, she worked for six years at *The American Naturalist*, a monthly scientific journal published by The University of Chicago Press, where she served as managing editor. Carolyn will be in both the adult and pediatric CF clinics to discuss clinical research opportunities with patients and families. You can reach her at 410-955-9782. ■

Upcoming Clinical Trials

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trial will compare the effectiveness of six months of Denufosol to placebo. This is followed by an additional six months when all patients will get Denufosol.

A POTENTIATOR

Johns Hopkins is one of 11 sites participating in a phase IIa clinical trial to assess the safety and pharmacokinetics of the CFTR potentiator compound, VX-770. This drug was created by Vertex Pharmaceuticals by high-throughput screening of tens of thousands of compounds. VX-770 activates dysfunctional CFTR that is at the cell surface. Therefore, this trial will enroll patients with G551D, R117H and 2789 + 5 G to A mutations in the CFTR gene because these patients have some CFTR at the cell surface.

Mark Your Calendar October 20 Family Education Day

Don't forget to mark your calendar for the CF Center's Annual Family Education Day, this year on Saturday, Oct. 20 in the Turner Auditorium on The Johns Hopkins Hospital East Baltimore campus. In past Family Education Day events, subjects have ranged from patient-to-patient transmission of bacterial infections to reproductive issues for CF patients and new airway clearance techniques. The keynote speaker this year will be Alexandra Quittner, Ph.D., professor of psychology at the University of Miami, who will talk about motivating adherence in children with CF. For more information, call 410-955-2795. ■

Partners IN DISCOVERY

Cystic Fibrosis Center

200 N. Wolfe Street
Baltimore, MD 21287
410-955-2795

www.hopkinscf.org

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

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