



JOHNS HOPKINS
MEDICINE
CYSTIC FIBROSIS CENTER

News from the Cystic Fibrosis
Center at Johns Hopkins

Winter 2008

Partners IN DISCOVERY

Translating Theory into Therapy

NACFC Highlights

The 21st Annual North American Cystic Fibrosis Conference (NACFC) was held in Anaheim, CA, October 4-6, 2007

UNITED KINGDOM CF GENE THERAPY CONSORTIUM

Several CF research centers in the United Kingdom are embarking on an exciting endeavor to attempt to cure CF. These Centers have combined forces to conduct a multicenter trial of gene therapy using inhaled liposomes containing a normal copy of the CFTR gene. The study will involve 200 patients who will be followed for one year to identify an optimal group of 100 patients to participate in a placebo-controlled gene therapy trial. This study will provide very important information on the viability of this form of gene therapy.

AZITHROMYCIN FOR PATIENTS WITHOUT PSEUDOMONAS AERUGINOSA INFECTION

Azithromycin is an antibiotic that also has anti-inflammatory properties. It is prescribed to cystic fibrosis patients who are colonized with *Pseudomonas aeruginosa* to prevent exacerbations and preserve lung function. A multicenter trial known as AZ004 is now underway at CF Centers throughout the United States to determine if azithromycin is helpful in children and adults who are not colonized with *P. aeruginosa*. To date, 80 of the 350 patients needed for this year-long trial have been enrolled.

TIGER TRIALS

The phase 3 trial of Denufosal (INS 37217 Respiratory) known as TIGER-1 has completed enrollment of the required 350 patients. This year-long trial, which is being performed at Hopkins as well as over 20 other CF Centers, will test the

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Johns Hopkins geneticist Garry Cutting

The Jigsaw Puzzle of CF Lung Disease Severity

What is it in the genes and environment that really makes a difference? Why does one cystic fibrosis patient have only mild lung disease while another patient—with the same CFTR mutations—suffers severe lung disease? Are genes other than CFTR responsible for these variations? Or is the environment the cause?

That question, raised two years ago in this newsletter by Johns Hopkins geneticist **Garry Cutting**, led to an unprecedented nationwide study focusing on twins and siblings with CF, an ideal group for studying CF disease variation because they share genetic make-ups and similar environments. The so-called CF Twin and Sibling Study came up with some surprising early results: Identical twins with CF have remarkably similar degrees of lung disease when living

together compared to those who live apart. The conclusion? Environment—not modifier genes, as originally suspected—has a major influence on the severity of CF lung disease, the primary cause of morbidity and mortality in patients.

“We were thinking that genes were going to dictate the whole story,” says Cutting.

But now an offshoot twins study by Johns Hopkins pediatric pulmonary fellow **Lori Vanscoy** has arrived at a different con-

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Research Briefs

TDN EXPANSION

Before a drug can get from the lab to your medicine cabinet it must go through a rigorous set of clinical trials. To facilitate these studies the CF Foundation created the Therapeutics Development Network or TDN. Johns Hopkins was one of the original 12 centers that established this network. Since then the TDN has expanded to 18 sites. However, the success of drug development for CF has created a need for more CF patients to participate in an expanding number of drug trials. To satisfy this need the CF Foundation will be expanding the TDN in the next few years. Fifty Facilitation Grants were awarded last year to enable CF Centers around the country to build the infrastructure needed to participate in clinical trials. Eventually, all the CF Centers in the United States will be part of an expanded TDN, allowing all CF patients an opportunity to participate in clinical research.

WHY DO WE LIMIT WHO CAN BE IN A DRUG TRIAL?

Some people can be either too healthy or too sick to participate in a clinical trial. Measures of lung function are typically used to determine if a drug is useful in treating CF patients. The forced expiratory volume in one second, or FEV1, is the most widely used test in clinical trials. However, it may be difficult to see a response to a drug if an individual's lung function is too good. Even a drug that works may not be able to improve normal lung function during a short research study. On the other hand, if the FEV1 is very low then there may be too much lung damage, which cannot be altered by any drug. For these reasons, drugs are typically initially tested in CF patients with mild to moderate lung disease.

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The Key to 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 3 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

Psychologist Kristin Riekert on Adherence



In her recent study of young CF patients’ adherence with taking medications to reduce the risk of lung infections, Johns Hopkins CF Center psychologist Kristin Riekert was surprised to see only a 47 percent adherence rate for 19- to 25-year olds. Not only that, but she saw a disappointing trend—as CF patients age from children to adolescents and young adults, the less likely they’ll take their prescribed therapies. Here she talks about some of the factors influencing this dim picture, and what doctors and patients can do to improve adherence.

How did you first get involved with studying adherence?

Within a month of starting graduate school a colleague asked me to help transcribe interviews with parents of children with CF. Right away I realized how worried parents were about what would happen with adherence as their child became a teenager. Adherence goes down in adolescence for many normal developmental reasons. That’s when kids are really developing a sense of who they are, trying out new roles and challenging authority (see opposite page).

So, adherence does decline with age?

Yes. In our study looking at TOBI prescription refills, children had 78 percent adherence, adolescents 60 percent and young adults 41 percent. This was the pattern with every medicine. This supports some of Garry Cutting’s twins study data that shows when you leave home, your health declines (see cover story). It’s a behavioral story – when Mom’s not around you’re less likely to take your meds. And being in college or starting a career is not conducive to taking good care of yourself. Frankly there’s not a lot of discussion

about how to manage the transition from adolescence to adulthood when a chronic illness is involved.

What else are you learning from the study of adherence?

That adherence is around 50 to 60 percent across many illnesses. For example, for HIV patient who are less than 50 percent adherent, there’s some data suggesting you get no benefit from the medicine. On the other hand if you’re in that 50 to 90 percent adherence group, you’re at risk of becoming resistant to the drug and you’ll get less benefit. So, HIV patients have to be extremely adherent. Unfortunately, we don’t really know how much medicine a patient with CF needs to get most of the benefit.

So what’s the answer?

Personalizing medicine, or having a more informed conversation with patients regarding a particular drug and the patient’s particular health status, would help. With more information about the patient, the physician can say, “To benefit from this medication you need to be this adher-

ent.” That’s more effective than saying to all patients “you need to be 100 percent adherent all the time to every medicine” because it is a high expectation. I think patients would appreciate having that conversation with their physician.

What’s the focus of your work now?

We continue to look at predictors of non-adherence and how non-adherence affects clinical outcomes, but we also need to improve communication and, through studies, develop interventions that will change behaviors.

What kinds of interventions are we talking about?

I’m on the verge of getting NIH funding for an intervention study for that high-risk group, patients 16 and older. Half of the group will receive regular CF education, and the other half an adherence-promoting intervention called motivational interviewing. This is a therapeutic technique very popular in the addiction field, one in which you help patients build an internal sense of how adherence will help them achieve their goals and then make a plan to change. A kid’s goal might be to play basketball, but no physician would say the goal of therapy is to play basketball. So, making the goals really relevant to the patient, and less about the long term and more about the here and now, can shift adherence.

Does disease severity affect adherence?

In general, adherence is confounded by the severity of the illness. Sicker people tend to take more of their medicine because they’re not feeling well. But if you’re doing well, it doesn’t necessarily mean it’s because you’re taking your medicine. Or if you’re doing poorly, it’s not necessarily because you didn’t take your medicine. Many physicians like to hold on to the philosophy that, of course, my CF patients take their medications because otherwise they would die. That’s why I like motivational interviewing, because it’s a patient-centered way of exploring options that fit in with real expectations.

Still, adherence is hard to change.

Yes, it’s very difficult – behavior in general is difficult to change. We all have something we know we should be doing, avoiding certain foods, getting enough sleep, but do we? It’s no different for CF patients, and they often don’t fit the stereotype of being non-adherent. They’re organized and tend to know what drugs they’re taking and what they’re supposed to do because they spend a lot of time in hospitals and health-care settings. But still, as we’ve seen, many patients are not adherent with their medicines. That’s why their relationship with their CF team is very important.

How are CF centers managing this problem?

Good CF teams are really in tune to the problem but they’re frustrated and not clear what they can do about it. Some physicians may not feel confident about getting the patient to do anything different and so don’t spend a lot of time counseling on non-adherence. Through interventions like motivational interviewing we’re changing physician behaviors at care centers, and we’re seeing benefit. But there’s still much work to be done to help patients be adherent enough to get benefit from the treatment and still have a life. ■

Adherence in Adolescence an Even Bigger Challenge

Poor adherence, says University of Miami health psychologist Alexandra Quittner, is the number-one reason for treatment failure across pediatric and adult chronic illnesses. And because of the complexity and time-consuming nature of treatments for cystic fibrosis, adherence to that particular chronic condition is particularly challenging. Now, consider adolescence and its accompanying developmental issues, and adherence becomes an even bigger challenge.

“We’ve found that the most powerful predictor of poor adherence is conflict between parents and the teen,” says Quittner. “Adolescence is a time when teens are testing the limits and rules, and arguing with parents about their medical regimen. Parents are worried and tend to nag them about doing their treatments.” What are

disciplinary teams has reinforced an approach in which the physician ‘tells’ the patient what to do, and assumes that the patient will go off and do it,” says Quittner. “Better results occur when the physician and teen make a collaborative decision about which therapies are most important. That allows the team to target those treatments that are most important for that patient, which makes it easier to provide suggestions for fitting them into their daily life.”

Quittner adds, however, that CF teams are only now receiving the training they need to help patients improve their adherence. The CF Foundation, for example, is funding quality improvement projects aimed at improving adherence communication, and Dr. Quittner has two grants from NIH to evaluate adherence interventions.

“Better results occur when the physician and teen make a collaborative decision about which therapies are most important.”

ALEXANDRA QUITTNER, Ph.D.

parents, patients and CF teams to do?

Improving communication skills is essential, says Quittner. For parents, that means a shift from bugging their teen about taking enzymes and doing airway clearance to a negotiation in which the responsibility for these therapies is gradually transferred to the adolescent. Parents can agree to get off the adolescent’s back, and the adolescent, in turn, agrees to be more responsible about his/her treatments and provide some documentation that the treatments have been done. This gives the teen more control and the parent more peace of mind. In one family Quittner worked with, for example, the teen posted a chart on his bedroom door with a checkmark for each completed airway clearance session. Rewards for adherence were given, including free video rentals, later bedtimes and special time spent with one of the parents.

“Spending an hour or two with mom or dad on a Saturday, doing something the teen finds fun was one of the most popular rewards in our intervention study,” says Quittner. “This is a great way to improve the parent-teen relationship and to decrease arguments and conflict.”

For CF team members working with adolescents, negotiation also comes into play. Rather than requiring patients to adhere 100 percent to all prescribed therapies, Quittner suggests that team members may achieve better adherence by negotiating with patients and helping them prioritize their treatment regimen.

“Unfortunately, the medical model in multi-

Her most recent intervention trial is testing a program that is implemented in clinic during a routine visit. In this intervention, the nurse assesses knowledge of disease management and ensures that patients and families have the skills to do their treatments correctly. Any gaps in knowledge, like not knowing the best time to take enzymes or the correct way to use a flutter for airway clearance, are taught in brief, one-on-one education sessions with the nurse or respiratory therapist. Next, a behavioral interventionist (a social worker or counselor) identifies the key barriers for the patient/family and then problem-solves the ways in which this barrier can be overcome. For example, an adolescent may be willing to do an aerosol treatment before a basketball game if it is done in the car with a power adaptor, rather than in the locker room in front of peers.

Perhaps more appealing to adolescent patients is a new project aimed at developing a web-enabled cell phone that Quittner and Lisa Saiman of Columbia University are working on. This cell phone will provide reminders to teens to do their treatments, a Web site to share information and suggestions and profiles of successful teens and young adults. This technology will enable adolescents to connect with other CF teens without the risk of patient-to-patient transmission of infections.

“We hope it will be a safe place for them to develop relationships,” says Quittner, “and obtain support for managing their disease.” ■

NACFC Highlights

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effectiveness of Denufosal inhaled three times daily compared to a placebo. This drug activates an alternative chloride channel to bypass the defective CFTR. Patients will receive either Denufosal or placebo for the first six months and then all the patients will receive the active drug for the remaining six months of the trial. A similar sized international trial named TIGER-2 will be started shortly to confirm the results of the TIGER-1 study.

ELITE AND EPIC

It is vitally important to determine the best way to treat children when *Pseudomonas aeruginosa* is first found. If this bacteria can be eradicated, then colonization can be prevented. The Johns Hopkins CF Center and many other centers in this country are participating in the EPIC (Early *Pseudomonas* Infection Control) trial. This five-year study will determine the best approach to preventing colonization after *P. aeruginosa* is first detected. European CF Centers are conducting the ELITE (EarLy Inhaled Tobramycin for Eradication) trial to determine if 28 or 56 days of inhaled tobramycin is the best therapy to treat the initial *P. aeruginosa* infection. This trial has completed enrollment and the two-year follow-up will be completed in November 2009. The information obtained from these two trials should determine the best approach for treating initial *P. aeruginosa* infection.

AZTREONAM LYSINE FOR INHALATION

Gilead Sciences has submitted an application to the Food and Drug Administration (FDA) for permission to market aztreonam lysine for inhalation to treat *P. aeruginosa* in CF patients. This new antibiotic is administered three times daily using an e-flow nebulizer which can deliver the medication very rapidly. Gilead, in three large phase 3 trials, has shown that aztreonam improved lung function and quality of life for CF patients. Inhaled aztreonam is administered in 28-day on/off cycles either alone or in combination with another inhaled antibiotic during the "off" cycle. This drug should be available to patients in late 2008. ■

Jigsaw Puzzle of CF

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clusion—a significant portion of variability in CF lung disease is due to modifier genes, those genes that affect the clinical manifestation of disease (*Am J Respir Crit Care Med*, 175:1036-1043, 2007). Assessing lung function and environmental data from identical and fraternal CF twins and siblings through some 70 CF centers around the United States, Vanscoy found substantial genetic control of variation in CF lung disease, independent of

“Most of our understanding of when a patient does better or worse in relationship to genes and the environment is an incomplete jigsaw puzzle.”

GARRY CUTTING, Ph.D.

CFTR genotype. In other words, modifier genes are back on the table and should be further sought out and explored to open the door to new therapies.

“What Lori Vanscoy’s study told us is that the genes identical twins share dictate how sick they become,” says Cutting. “That’s important because what we’re trying to do is alter the genes that dictate how sick kids get.”

In the study the relationship of all measures of lung function for identical twins was high, but not 100 percent, suggesting a role for environmental factors in CF lung disease severity, too. Numerous studies have linked environmental factors like smoke exposure, bacterial infection and socioeconomic status with reduced pulmonary function. And both Cutting and Vanscoy are exploring future studies to investigate the influence of such environmental factors – and their modifier genes – on lung disease severity. All in all, Cutting concludes, it is a complex picture.

“Most of our understanding of when a patient does better or worse in relationship to genes and the environment is an incomplete jigsaw puzzle,” says Cutting. “We don’t know how the pieces fit together, but we are filling them in.” ■

Research Briefs

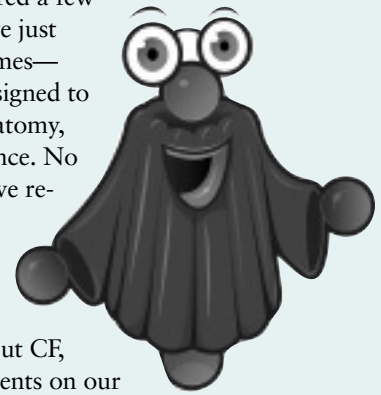
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FIRST PATIENT ENROLLED IN VX-770 TRIAL

The first Johns Hopkins CF patient has been enrolled into the Phase 2 trial of VX-770 manufactured by Vertex Pharmaceuticals. VX-770 was discovered by the CF Foundation’s high throughput screening program. The possibility of a drug that acts directly on the defective CFTR gene is a very exciting development. This oral drug enhances or potentiates the function of any CFTR that has made it to the cell surface. Therefore, VX-770 is being tested in patients with certain CFTR mutations such as G551D. This trial will enroll 36 patients at 11 CF Centers in the US. ■

Let the Games Begin

Well, you didn't think we were going to create a Web site for children and adolescents without a game room, did you? We figured the odds of keeping you interested in our site, launched in 2006, would go way up if we offered a few electronic pursuits. So, we've just added some educational games—starring CFTR Charlie—designed to teach children about CF anatomy, nutrition and airway clearance. No codes to break, no alternative reality games, and no sinister story lines, but we think patients will enjoy the games we've developed. We think they'll learn more about CF, too! And in other developments on our password-protected site, a message board has been added as a means for patients and families to communicate with one another. Also, there are separate message boards for children, teens and adults. So check out the site, the Game Room and Message Board at www.hopkinscf.org/. ■



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