



JOHNS HOPKINS
M E D I C I N E

News from the Cystic Fibrosis Center
at Johns Hopkins

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Partners IN DISCOVERY

Translating Theory into Therapy

Research Briefs

DO YOU USE COMPLEMENTARY OR ALTERNATIVE THERAPIES?

Patients often use therapies beyond what their doctor prescribes for medical problems, many times without informing their doctor. These so-called complementary or alternative therapies might take the form of herbal remedies, vitamins and other treatments. Kara Brazzie, Pharm.D., and Carlton Lee, Pharm.D., are spearheading a study on the use of complementary and alternative therapies in the Johns Hopkins CF Center, asking patients and parents whether they use them, and whether their physician is aware of it. The potential for harmful medication interactions will be studied as well. The results of this trial will be available early next year.

LAST PATIENT ENROLLED IN INFANT LUNG FUNCTION STUDY

Johns Hopkins is one of 10 centers around the country participating in a three-year study of infant pulmonary function testing (iPFT). This study investigates whether the lung function of children younger than 2 can be accurately measured using recently developed technology. Although the final patients were enrolled in April, researchers will continue to collect iPFT data over the next eight months. The information will provide the basis for the use of iPFT in young children enrolled in clinical drug trials.

ADENO-ASSOCIATED VIRUS (AAV) GENE THERAPY VECTOR FAILS TO IMPROVE LUNG FUNCTION

Unfortunately, a large trial testing the repeat dosing of aerosolized AAV failed to show any improvement in lung function in CF patients. The first human trials of this vector were conducted at Johns Hopkins. Although

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Piloting the Enterprise



Lois Brass examines CF patient Charles Hawkins.

Master multi-taskers, clinical research program manager Lois Brass and colleagues keep clinical trials running smoothly

To the casual observer, the multi-colored tangle of handwriting covering every inch of the wall-sized whiteboard in Lois Brass's office looks hopelessly complex. And it is. The board tracks in meticulous detail the various stages of the 11 clinical studies currently underway at the Johns Hopkins CF Center.

Brass smiles, because she sees something different: a recently hospitalized patient to whom she wants to send a get-well card; a young woman who used to be afraid of procedures, but who now calls at the end of the school year to see what clinical trials she might enroll in over the summer break; her oldest patient, a senior citizen who participates in research because she sees herself as a living testament to its importance.

"These are my patients," she says with a sweep of her arm. "This is what it's all about."

Brass is the clinical research program manager at the Hopkins CF Center. Taking responsibility for that daunting whiteboard, Brass and colleagues—Angela Gronlund, RN; senior lab technician Karen McKenzie;

and administrative assistant Shawnice Foster—literally run the clinical research enterprise at the Center. It's not a job for the faint-hearted, nor the organizationally challenged.

At the Hopkins CF Center, clinical trials start with an idea – for a new drug, a different dosage, an improved therapy, etc. The idea could be a continuation of Hopkins research, or it could come from the outside – through the pharmaceutical industry, for example, or through the Therapeutics Development Network (TDN). Johns Hopkins University is a founding member of the TDN, a consortium of 14 CF research centers and the Cystic Fibrosis Foundation, whose goal is to concentrate resources and brainpower, exchange information, and ultimately bring therapies from bench to bedside faster.

The first task for the research coordinators is to determine whether the clinical trial is appropriate for Hopkins, and to try to predict enrollment.

"We see if we can do it logistically – do we have the clinic space and resources to ac-

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Upcoming Clinical Trials

CURCUMIN STUDY STARTS

There was much excitement last year when Marie Egan, M.D., a Johns Hopkins alumna currently working at Yale University, discovered that curcumin improved survival in mice with CF. Johns Hopkins and Yale will continue this research, conducting a study to determine the safety of curcumin, a component of the Indian spice turmeric, in adults with CF. In addition to safety measures, CFTR function will be measured through sweat testing and nasal potential differences in eight patients receiving escalating doses of curcumin.

EARLY INTERVENTION TRIAL FOR PSEUDOMONAS AERUGINOSA ACQUISITION

Two concurrent trials investigating the effect and treatment of *Pseudomonas aeruginosa* (Pa) in younger CF patients are underway at Johns Hopkins and other CF centers. The Early *Pseudomonas* Infection Control (EPIC) trials will study the natural history of Pa colonization in 1,400 children around the country with the goal of providing insight into the best treatment for initial Pa infection. Although children are typically treated when Pa is isolated, the optimal therapy to eradicate this bacterium is unclear. Children who become infected with Pa will have the opportunity to enroll in an interventional trial to test the effectiveness of oral ciprofloxacin in combination with inhaled tobramycin. They will be randomized to one of four treatment protocols using either scheduled therapy every three months or therapy given only when Pa is detected.

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Summer Vacation



Some students want to get more out of their summer vacation than a great tan... they want to learn about CF research. Every summer several college students spend their vacations

learning what research is all about in the CF labs at Johns Hopkins. These undergraduates learn how to design experiments as well as collect, analyze and present data. This exposure has helped many decide on careers in medicine or biomedical research.

Johns Hopkins has a rich tradition of training students, residents and fellows who have gone on to become leaders in cystic fibrosis care and research. Most patients and families have come into contact with many clinical trainees at Johns Hopkins. However, many more students and post-doctoral fellows work behind the scenes in basic science laboratories. Training physicians, biomedical researchers and other health-care providers who will discover and administer new therapies for cystic fibrosis is a vital mission of the Johns Hopkins CF Center.

The summer research program exposes students to the exciting potential of basic science research, but this is just the tip of the iceberg. The CF Foundation has partnered with Johns Hopkins to fund the training of the next generation of CF researchers by providing grants to support fellows and junior faculty. In addition, the Johns Hopkins CF Research and Development Center directed by Dr. William Guggino strives to develop the careers of young researchers. The vast potential for teaching and training is one of the great assets of the Johns Hopkins CF Center.

If you or someone you know is interested in learning more about the summer research program, please give us a call at 410-955-2795.

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

Lois Brass, RN, CCRP Clinical Research Program Manager

How can interested patients learn more about the various clinical trials underway at Johns Hopkins CF Center?

By reading *Partners in Discovery* for one thing! Also, in the near future we will be launching a website for patients which will have a lot of information about CF research and a listing of current clinical trials. They can also visit the National Institutes of Health website at www.clinicaltrials.gov and the Cystic Fibrosis Foundation website at www.cff.org/research/clinical_trials/. And, of course, they can always ask one of us during their clinic visits, or call our office at 410-955-1167.

Why is it important to participate in clinical research?

To move the science forward, one step at a time, toward a cure. Along the way, research enables us to develop new therapies that help patients today, and will make someone's life better tomorrow.

How does the CF Center ensure the safety of clinical research?

First, by law, all research studies at Johns Hopkins and other academic medical centers must be stringently reviewed and approved by independent institutional review boards to be sure they are medically sound, ethical and appropriate. Also, independent clinicians who are members of the institution's Data Safety Monitoring Board monitor patient safety as the trial is running. And lastly, every one of us is committed to providing the best possible care for

our patients, and safety is always at the top of our minds.

How long has CF clinical research at Johns Hopkins been going on?

Johns Hopkins was among the first hospitals doing CF gene therapy research. I've been here since our original gene therapy work began in 1996. Back then, the studies involved an 18-day inpatient stay.

Our first gene therapy patient is now well into her 40s, healthy, and I'm still in touch with her. Looking back over time, I can see how far we've come in developing therapies.

Why are you involved in CF research?

People say the heart or the mind is the center of the body. To me, breath is centering. Breathing is a subtle and gentle motion. But in CF, it can be a true effort to move

air in and out of one's body. I know what we do at the CF Research Center makes a difference for people living with this disease. I am confident that through participation in research, we will find effective treatments and one day soon, find a cure.

What's the one thing you want CF patients to know?

There's reason to be hopeful. We respect our patients and families and hold them in the highest esteem. It is their participation in CF research that helps us find treatments for longer, healthier lives. ■



Coordinating Trials

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usually conduct the study? But more importantly, we ask ourselves, 'Does this study fit the culture of our patients?'" Brass says. "After working with a group of people for so long, we have a good understanding of who they are as people. Is this study something they'll be interested in, want to participate in?"

To answer this all-important question, Brass and her team draw on the relationships they've built with their patients over the years – the faces she sees on the whiteboard, if you will. To Brass, the primary, most important part of her job is building therapeutic relationships with her patients, educating them, following their care, watching them grow and live their lives. She and her team take great pride in knowing what will, and what will not, be a good fit for their patients.

If the answer is "yes" the next step is regulatory agency approval. All human research studies at Johns Hopkins must be thoroughly reviewed and approved by an independent institutional review board (IRB). This important process protects patient safety and ensures that research studies are both medically sound and ethical.

This is the paperwork and logistics phase. In addition to submitting the study to the appropriate regulatory bodies, Brass prepares the study's consent form, which all participating patients must sign, and

orients the clinic staff to the study. In the case of multi-center or sponsored studies, her team coordinates visits from the sponsor to initiate the CF Center into the study, and enters into contract negotiations. Because many CF studies are part of multi-center trials, to protect the integrity of the data, Brass says, "We have to make sure that researchers at all centers are on the same page, that everyone's doing the study the same way."

Next is the task of recruiting patients to participate, a process that can pose challenges. Brass says it's a bit easier at the CF Center, which she attributes to an "amazing, altruistic group of patients."

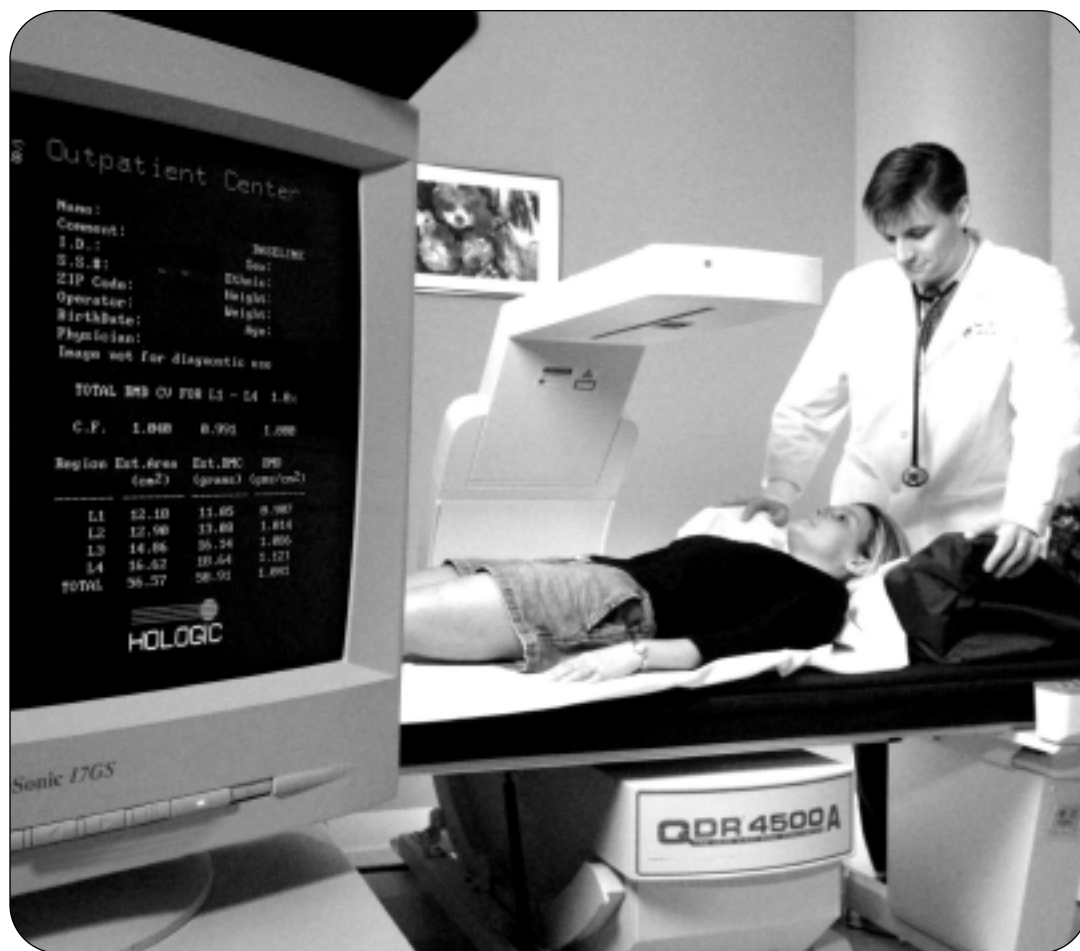
"They live with a chronic disease, and many of them have seen their siblings die of the disease. They know the limitations of their own lives, and want to do something to benefit others. They are really amazing people," she says.

Brass also attributes patients' willingness to participate in research to the extensive education she and her staff provide. An integral part of every clinic visit, research education is complementary to the clinical care patients receive.

"We see the big picture for that individual," she says. "We keep track of the clinical care, know what trials they've been part of, what works and what

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Rethinking Vitamin D Repletion



Pulmonologist Michael Boyle measures bone density in CF patient Kathy Shank.

Current guidelines for vitamin D replacement in adult CF patients are ineffective in improving bone health, and may need to be revised, Johns Hopkins CF Center researchers report.

Their study, published in the July, 2005 issue of the *American Journal of Respiratory and Critical Care Medicine*, also found that most adults with CF have a vitamin D deficiency.

In the study, five of 66 adult CF patients (eight percent) who took the recommended 50,000 IU of vitamin D per week for eight weeks had their serum vitamin D levels return to recommended levels. Of 49 CF patients who started a second eight-week vitamin D repletion

course, none showed a correction in their vitamin D deficiency.

The vitamin D regimen tested in this study may need to be revised.

Bone health is an important issue for adult CF patients. Vitamin D is necessary for the body to absorb calcium and build bone; a deficiency leads to abnormal bone growth and impaired ability to heal after injury. Approximately 20 to 25 percent of adults with CF have osteoporosis, according to the study's lead author, Mike Boyle, M.D., direc-

tor of the adult CF program at Johns Hopkins.

The vitamin D regimen tested in this study was recommended by a consensus panel of the Cystic Fibrosis Foundation and is meant to maximize calcium absorption and therefore improve bone density in adult CF patients. The study's authors conclude that these guidelines may need to be revised to increase the dosage of vitamin D.

Boyle reports early success in vitamin D repletion in approximately 20 Hopkins patients who recently began taking 50,000 IU daily for 30 days. He says further study is needed to establish the ideal serum levels of vitamin D for maximizing calcium absorption and bone health in people with CF. ■

Literature Check

THE FOLLOWING STUDIES, PUBLISHED IN 2005 BY RESEARCHERS AT THE JOHNS HOPKINS CF CENTER, CAN BE ACCESSED ONLINE AT WWW.NCBI.NLM.NIH.GOV/ENTREZ OR BY CALLING THE CENTER AT 410-955-2795.

Cutting GR.

Modifier Genetics: Cystic Fibrosis.

American Review of Genomics and Human Genetics, 2005 Feb 15; 6:237-60.

While CFTR, the gene responsible for CF, was identified 15 years ago, research suggests that other factors, such as environment and "modifier" genes influence disease severity and progression. Author Garry Cutting, M.D., Ph.D., discusses the role of "modifier" genes in pulmonary and intestinal aspects of CF.

Boyle MP, Noschese ML, Watts SL, Davis ME, Stenner SE, Lechtzin N.

Failure of High-Dose Ergocalciferol to Correct Vitamin D Deficiency in Adults with Cystic Fibrosis.

American Journal of Respiratory and Critical Care Medicine, 2005 April 28; 172(2):212-7.

(See article "Rethinking Vitamin D Repletion" above.)

Wang X, Kim J, McWilliams R, Cutting GR.

Increased Prevalence of Chronic Rhinosinusitis in Carriers of a Cystic Fibrosis Mutation.

Archives of Otolaryngology-Head and Neck Surgery, 2005 Mar; 131(3) :237-40

In search of a genetic basis for chronic rhinosinusitis (CRS), a condition that affects approximately 14 percent of Americans and tends to cluster in families, researchers studied parents of patients with CF. They found that carriers of a single CF mutation have a higher prevalence of CRS than the general population.

Cheng J, Wang H, Guggino WB.

Regulation of Cystic Fibrosis Transmembrane Regulator Trafficking and Protein Expression by a Rho Family Small GTPase TC10.

Journal of Biological Chemistry, 2005 Feb 4; 280(5) :3731-9

This basic science study demonstrates how a Rho family small GTPase TC10 serves as a molecular switch, regulating CFTR protein levels in cells.

Coordinating Trials

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doesn't work for them, what they'll want to try, what they won't. There are so many opportunities over time to educate them, to help them understand the importance of the research.

"They realize that the reason they have the benefit of a certain treatment is because someone before them was involved in a clinical trial."

Once patients express an interest in participating, the team begins discussions to explain the medical jargon, the purpose of the trial, what happens at each visit, safety measures, potential side effects and any compensation that might be offered. In a nutshell, they help patients weigh the risks and benefits of participating, so they can make an informed decision.

It's a dynamic process that can take months, Brass explains, and she sees it as the focus of her work. This is the role of research coordinator as patient advocate, educating, answering questions, supporting a person's life-altering decisions with knowledge and compassion.

With a signed consent form, the research coordinators shift their focus to

stewarding a patient through the trial, from scheduling the first clinic visit to sending a follow-up letter with results of the study. For each of the Center's 450 patients, the schedules of up to 12 care providers must be coordinated for every visit. Exam rooms must be reserved, equipment and supplies ordered, patient notes entered into medical records. Along the way, Brass says, she and her colleagues are "globally available" to answer questions and give updates to patients.

Finally, following the last clinic visit, Brass and her team follow up with patients to thank them for participating and to assure them they will receive more information about the findings once the data is collated and analyzed, and the results published. This step is important, she says, because it demonstrates their genuine respect for their patients, and is yet another opportunity to educate them about living well with CF. ■

Upcoming Clinical Trials

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PHASE II STUDY OF DENUFOSOL (INS37217 RESPIRATORY)

Researchers at Johns Hopkins are participating in a Phase II safety study of denufosol (INS37217 respiratory), which activates an alternate chloride channel in cells. Researchers hope to confirm the safety of this drug in CF patients and demonstrate some efficacy so that the drug can move into a Phase III clinical trial to definitively determine efficacy. The study, involving approximately 100 CF patients around the country, will examine the effects of 28 days of treatment with inhaled denufosol (INS37217 respiratory) on lung function and patient safety.

INFLAMMATION IN THE CF LUNG

Inflammation is thought to contribute a great deal to the lung disease seen in CF patients. This summer, the Hopkins CF Center started a study to measure inflammatory compounds or "mediators" in the lungs of CF patients and the effects of anti-inflammatory therapies such as ibuprofen. By measuring changes in these mediators, investigators hope to determine if new therapies are effective in controlling inflammation and thereby preventing lung damage.

CLINICAL TRIALS WEBSITES

Did you know that both the National Institutes of Health and the Cystic Fibrosis Foundation have web sites that list clinical trials underway at medical centers throughout the United States? Check them out at

www.clinicaltrials.gov or
www.cff.org/research/clinical_trials/

Research Briefs

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this AAV vector does not appear to improve lung function, its development and testing have provided many insights into gene therapy, both its potential and its limitations. Gene therapy studies continue, and Johns Hopkins researchers are developing newer, more efficient AAV vectors (*Partners in Discovery*, August 2004). A newer AAV vector, termed AAV5, is 100 times more effective at introducing a normal CFTR gene into CF cells grown in the laboratory. Safety studies of AAV5 may begin early next year. ■

MARK YOUR CALENDAR

The Cystic Fibrosis Center at Johns Hopkins will host its annual family education day on November 5. Our featured speaker will be Bruce Marshall, M.D., director of quality improvement initiatives at the Cystic Fibrosis Foundation.

More details are coming soon. We hope you'll join us to hear how the CF Center at Johns Hopkins is striving to improve patient care. ■



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MEDICINE

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