What if you could replace the faulty gene that causes cystic fibrosis with a complementary version of that gene that restores its function? Delivered via a harmless virus, the new gene would get to work providing the instructions for restoring the function of the native protein that regulates the production of mucous, sweat, saliva and digestive enzymes—all the things that cystic fibrosis dangerously disrupts.

Liudmila Cebotaru, whose research at Johns Hopkins includes engineering that gene and the virus to carry it to its destination, never loses sight of her goal. "We’re looking for a cure for cystic fibrosis," she says.

Cebotaru says that Americans are living longer with cystic fibrosis. Antibiotics and physical therapy are helping manage the pulmonary problems that plague patients. But eventually, cystic fibrosis takes a dramatic toll on the lungs, pancreas, the liver and the intestines. Blocking ducts and poorly managing the body’s water system, the disorder creates enormous—and ultimately fatal—inflammation and infection. "It’s a genetic defect," says Cebotaru, "so the only way to cure it is by fixing that gene."

Because cystic fibrosis stems from a mutation in a single gene, Cebotaru calls it a good candidate for gene therapy. She and her Johns Hopkins lab team have spent the past 10 years engineering a new gene to correct the mutation that causes roughly 70 percent of all cystic fibrosis cases.

"A lot of that time was spent searching for the gene flaw. It took years to find it."

Once they identified how the gene’s mutations affected its protein function, Cebotaru and her research team engineered a virus to carry the gene to the tissue affected by cystic fibrosis. With the FDA watching closely, Cebotaru’s work has shown enormous promise in animal models and it has great potential in humans, she says. After clearing a few more regulat-
Optimizing Therapies

Enhancing health requires not only searching for a cure, as Liudmila Cebotaru is doing through her gene therapy studies, but also figuring out ways to best treat common problems currently faced by people with cystic fibrosis (CF). This issue of Partners in Discovery highlights several studies designed to do just that.

Improving the outcomes of people hospitalized with pulmonary exacerbations is critically important. Currently, the lung function of up to a third of people does not return to their pre-exacerbation baseline. Natalie West’s work is laying the groundwork for interventional studies to determine optimal exacerbation therapy. Mark Jennings is studying a novel approach to treat MRSA airway infections, which are on the rise in people with CF. Shruti Paranjape and Andrew Braun are working to understand the role that abnormal breathing during sleep may play in the health of people with CF. They are also testing a novel approach to therapy using high-flow oxygen.

The research in this issue also highlights the growth of the Adult CF Program at Johns Hopkins. Drs. West, Jennings and Braun are part of a group of seven pulmonologists who care for adults with CF. The growth in the number of physicians and the amount of research being performed in the Adult CF Program is a tribute to the improved survival that has been achieved—the adult CF population at Johns Hopkins is now far larger than the pediatric population. The future is even brighter as new drugs that treat the basic CFTR defect are being made available to the pediatric population. The future is even brighter as new drugs that treat the basic CFTR defect are being made available to the pediatric population. The future is even brighter as new drugs that treat the basic CFTR defect are being made available to the pediatric population.

INFECTION CONTROL

Attacking MRSA

While methicillin resistant Staphylococcus aureus (MRSA) infection has been increasing in the general population, its growth in patients with cystic fibrosis has been much more dramatic, says pulmonologist Mark Jennings.

In 1996, the prevalence of MRSA in patients with CF nationally was about two percent, Jennings says, but since then “it has gone up in a very steep, linear fashion so now the prevalence is around 25 percent. We don’t know why that has happened.” Equally troubling, he says, is that patients who have both MRSA and CF can develop persistent infections they can’t clear: “We always see when we look at culture results from sputum samples that those patients do worse. They have a faster rate of decline in lung function and their life expectancy is cut short.”

With growing interest in treatment protocols to treat or eradicate respiratory-tract MRSA in CF patients, Jennings and colleagues Noah Lechtzin, Michael Boyle and Christian Merlo have embarked on a trio of studies to evaluate risk factors for MRSA and look for interventions.

Through the first study, the investigators are mining the Cystic Fibrosis Foundation’s National Patient Registry database of some 30,000 patients in search of any clinical or demographic risk factors that make one patient with CF more likely to get MRSA than another, with the hope that some of those risk factors may be modifiable.

The CF team also is engaged in a clinical trial to see if an inhaled form of the antibiotic vancomycin, coupled with an oral antibiotic regimen, can eradicate MRSA from the respiratory tract of patients with CF known to be persistently infected. Though the randomized, double-blind study, supported by the Cystic Fibrosis Foundation, researchers at Johns Hopkins and Case Western Reserve/Rainbow Babies & Children’s Hospital in Cleveland are randomly assigning patients with CF to take either inhaled vancomycin or a taste-matched placebo for 28 days. Patients in both groups also will receive the oral antibiotics rifampin and trimethoprim/sulfamethoxazole, in addition to an antibiotic cream for their nasal tracts and an antibacterial body wash.

So far, 16 of a planned 40 patients with CF have been enrolled. These early participants have been age 18 and older, though Jennings says he hopes interim study data indicate the drug is safe to use in patients as young as 12, a key time period in which some patients first acquire MRSA.

“There are a lot of people in the CF community who are using vancomycin with the hope it might work, or with some anecdotal evidence that it might work, but it hasn’t been rigorously studied,” he says. “We hope results of the trials will provide guidance both for CF clinicians and for future investigative efforts directed at this increasingly important challenge in CF.”

“We hope the results of the trials will provide guidance both for CF clinicians and for future investigative efforts…”

—MARK JENNINGS, M.D., M.H.S.

A third study aims to better understand the emergence of a subtype of MRSA called small colony variant Staphylococcus aureus, which is thought to play a role in chronic lung infection among patients with CF. Working with Karen Carroll in the microbiology lab, researchers are looking for small colony S.aureus in all cultures taken from CF Center patients to note its incidence and prevalence, as well as to analyze the isolates. Researchers hope to find out if this subtype is contributing to the increasing prevalence in overall staphylococcal infections, and develop strategies to treat this specific infection.

Targeting A Bad Gene (continued from page 1)

Patient screening and challenges

Cebotaru expects the cystic fibrosis gene therapy will go to clinical trial.

Because the lungs are the first organs to be affected by cystic fibrosis, Cebotaru says the first gene therapy will be delivered to the lungs.

“We’re also working on gene therapy for the pancreas and the liver,” Cebotaru says. “The gene is the same for those organs, but the viral vector is different.”

In her genetics work with cystic fibrosis, Cebotaru is also trying to solve another mystery that has long puzzled researchers.

“For patients with cystic fibrosis to survive, they need a lot of antibiotics,” she says. “And many patients who take a lot of antibiotics develop imbalances in gut bacteria, leading to Clostridium difficile infection and dangerous diarrhea.”

One would expect such antibiotic regimens to wreak havoc on the gut flora of patients with cystic fibrosis. But for reasons yet unknown, says Cebotaru, when many cystic fibrosis patients get C. difficile infection, they do not get diarrhea.

“I’m trying to find out why,” she says. “It could teach us a lot about a problem that causes a lot of people to die around the world.”

For more information, call 410-614-0125.
Putting a STOP to Exacerbations

Pulmonary exacerbations occur frequently in individuals with cystic fibrosis (CF) and are associated with poor outcomes such as loss of lung function and decreased survival. Complicating the matter, current practices for treating the exacerbations vary widely. But a study by pulmonologist Natalie West and physicians at nine other medical centers suggest the time is ripe for an intervention trial to help standardize treatment of these flare-ups.

“We wanted to do a randomized controlled trial to best know how to treat exacerbations, but first we needed to understand current physician practices and determine the feasibility of such a study,” says West.

In a pilot observational study of The Standardized Treatment of Pulmonary Exacerbations in Patients with Cystic Fibrosis, called the STOP trial, physicians at 10 CF centers including Johns Hopkins enrolled 220 participants ages 12 years and up who were admitted to the hospital for pulmonary exacerbations. Physicians entered their treatment plans and goals, as well as their willingness to enroll patients in hypothetical interventional trials. Meanwhile, patients were asked to record their symptoms daily through the Cystic Fibrosis Respiratory Symptom Diary and Chronic Respiratory Infection Symptom Score (CFRSD-CRISS), an instrument designed to evaluate the effect of treatment on the severity of CF symptoms. The tool scores eight items such as difficulty breathing and chest tightness, and compiles a score of zero to 100, with a higher score indicating greater symptom severity. A reduction of at least 11 points is considered clinically meaningful. Spirometry readings were taken at the start of antibiotic therapy, during hospitalization, at the end of IV antibiotic therapy and at day 28. Physicians reported their primary treatment goals were recovery of lung function and symptom improvement in 53 percent and 47 percent of exacerbations respectively, and most said they would be willing to enroll patients in trials with fixed antibiotic duration of 10 or 14 days (and less so for seven days), and in which the principal investigators select the antibiotics.

Sixty-eight percent of patients had a drop in lung function of 10 percent or more from their baseline when admitted to the hospital; 52 percent had symptoms for seven to 21 days before hospital admission, and 32 percent had symptoms for over 21 days before admission. Nearly half (48 percent) already had failed outpatient antibiotics, and 43 percent had received IV antibiotics within the previous six months. Signs and symptoms present at admission included chest pain, wheezing and hypotension. Using these results, presented at the North American and European CF conferences, West and colleagues are planning a duration trial of antibiotic therapy in up to 880 patients at 40 to 50 designated CF centers.

Participants will be enrolled on the first day of their exacerbation; any patient admitted to the hospital or started on home intravenous antibiotics will be asked to return to the clinic seven days into therapy for assessments of lung function. Those whose FEV1 is improved by at least 8 percent, and a reduction in CRISS score by at least 11 points, will be entered into an expedited arm of the study in which they will be randomized to receive either 14 or 21 days of antibiotics. Other subjects will be entered into a prolonged arm in which they will be randomized to receive either 14 or 21 days of antibiotics. Enrollment should start in the summer of 2016, West says.

“I think that for the expedited group that 10 days of antibiotics will be just as good as 14,” West says. “Predicting results for those in the prolonged group is not as easy, she adds, as patients often change antibiotics if lung function doesn’t improve right away, “but we’re hoping to find that 14 days of therapy is just as good as 21 so we can avoid the side effects of antibiotics, decrease time in the hospital and improve quality of life.”

Putting Weight Loss to Sleep

With persistent lung infections and difficulty breathing, it’s no wonder that cystic fibrosis (CF) patients often report poor sleep, increased daytime sleepiness and fatigue.

“Sleep is really an important aspect of good general health,” says pediatric pulmonologist Shruti Paranjape. “I think it has not been fully appreciated or recognized as a clinical entity that has to be assessed in CF.”

Studies by Paranjape and colleague Andrew Braun of the CF Center’s adult clinic, presented this fall at the North American Cystic Fibrosis Conference in Phoenix, indicate that both children and adults with CF breathe faster during sleep and expend more energy doing so than expected—a process that may contribute to their difficulties maintaining weight. The study team’s early finding that children with CF breathe faster compared to children without CF were recently published (Pediatrics November 2015;136(5):920-926).

“There’s a suggestion in our data that the increased work of breathing leads patients to burn excess calories during the night,” Braun explains. “Because CF has a huge nutritional component to it, we’re looking to see if there are ways to reduce this excess calorie expenditure and over time hopefully impact patients’ nutritional state.”

Through two ongoing clinical trials, Paranjape and Braun are investigating whether a new intervention can resolve some nighttime difficulties.

“We are very excited about the implications of evaluation of sleep and maybe uncovering something that can help children improve their lung function, as well as their nutrition and growth.”

—SHRUTI PARANJAPE, M.D.

Using a technique called high flow nasal insufflation (HFNI), which delivers warm, humidified air through a nasal cannula, the researchers hypothesize that increased ease of breathing can reduce the energy needed, preventing patients’ weight loss over time. The device is FDA-approved for conditions like chronic obstructive pulmonary disease.

In one study, patients spend two nights in the
hospital sleep lab, one without intervention and one with HFNI, to measure any differences in respiratory rate, breathing patterns and gas exchange. In a second study, patients with CF will be given the HFNI device to wear at home every night for six months, to see if it can help improve or maintain pulmonary function, quality of life and weight over time.

Like patients who report eased breathing while showering “we think that just breathing in warm, humid air can help to add moisture to secretions and facilitate clearance that way,” Paranjape says. “The HFNI device also provides a little bit of pressure similar to what sleep apnea patients experience when using a continuous positive airway pressure mask, which may help reduce the load of breathing.” In addition, says Braun, it could make breathing more efficient.

Many patients with CF spend up to three hours a day giving themselves different respiratory treatments, says Braun. By contrast, “this therapy is quite passive…just turn it on and go to sleep. We’re hoping it is quite easy to put into a daytime routine.”

“We are very excited about the implications of evaluation of sleep and maybe uncovering something that can help children improve their lung function, as well as their nutrition and growth,” adds Paranjape.

The investigators are recruiting about 30 patients for both trials, which are supported by the Cystic Fibrosis Foundation, Fisher & Paykel Healthcare, and the American Sleep Medicine Foundation.

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