Cystic fibrosis: Pipeline of promise

After more than a decade of work, drugs help, but a real cure is still a decade away.

BY LINDA RICHARDS

Back in 1989, a giddy optimism swept over researchers, patients, and the public when the cystic fibrosis (CF) genome and its abnormality—a single error in a quarter of a million genetic letters—became one of the first discovered. The NIH made CF a priority, and researchers at various institutions and pharmaceutical companies moved quickly on the news.

One year later, two excited research teams corrected CF cells in the lab by adding normal copies of the gene, and high expectations reigned for a drug that would replace the defective gene. However, the CF protein turned out to be too complex, unwieldy, and toxic to be made into a drug. Moreover, vectors that triggered the body's natural immune system slowed any progress in a gene therapy approach. Fourteen years later, the hoped-for genetic cure is still considered close to 10 years away.

But there is good news. The use of an adeno-associated virus for delivering a functional copy of the gene to the lungs of CF patients is showing promise, as are potential medications in a pipeline that has ramped up since the Cystic Fibrosis Foundation (CFF) founded its Therapeutics Development Program in 1998.

"Currently, the CFF has 23 drugs in various stages of clinical trials," says CFF President Bob Beall. "Prior to 1998, only two drugs specifically for CF had undergone clinical trials and been approved by the FDA."

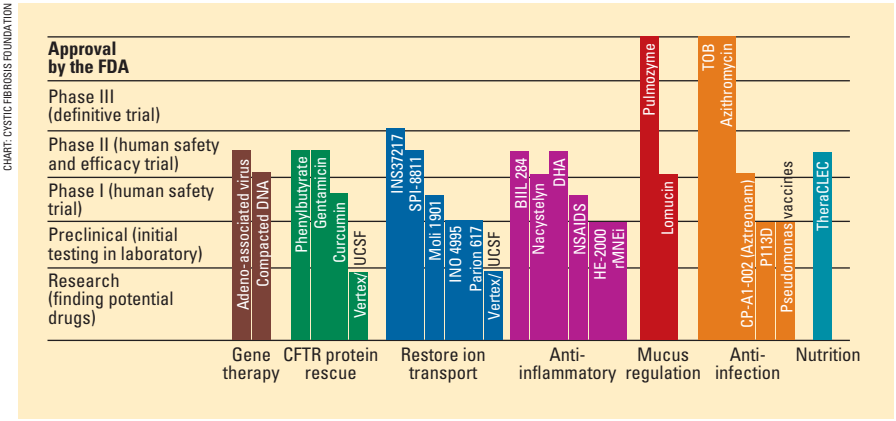
Recognition for CF, an orphan disease affecting 30,000 in the United States and 80,000 worldwide, has taken a long time. While the disease was discussed in medieval times—folklore predicted death for an infant that tasted salty when kissed—it was thought to be a form of celiac disease until it was recognized as a separate disease in 1936. Much of the confusion stemmed from its two fundamental but different components—abnormal mucus in the lungs, pancreas, and intestine; and salty sweat caused by a three- to fivefold increase in the normal amount of NaCl on airway surfaces. While researchers still disagree over a unifying hypothesis that explains both these disease features, much has been learned during the past several decades.

Helped by a better understanding of the disease, along with earlier diagnosis and aggressive treatment, the average age of death has increased since 1969 from 5 to 33 years. Still, CF is the most common life-shortening genetic disease among whites, with most dying from pulmonary failure. A surprising 1 in 20 Americans carries the autosomal recessive gene. Although carriers are usually asymptomatic, past research shows slightly higher sweat electrolyte values for CF carriers than in the normal population. Researchers have discovered more than 1000 CF mutations, with the most common form, ΔF508, comprising 70% of CF cases.

Pieces falling in place

The 1989 gene discovery ushered in a decade of expanding knowledge about the CF defect—a lack of function in a chloride channel called the cystic fibrosis transmembrane conductance regulator (CFTR), which resides on the surface of epithelial cells. Recent research shows that the CFTR not only regulates the movement of chloride, and therefore sodium, but other substances as well. The end result is a pathophysiologic cascade that leads to progressive lung disease.

However, much debate continues about CF pathophysiology. Paul Quinton, professor and pediatric pulmonary chair at the University of California, San Diego, says that while all agree that CF pathology stems from the CFTR channel defect, the real question is how the defect relates to the various organ injuries.



Therapeutics currently in development for cystic fibrosis, supported in part by Cystic Fibrosis Foundation Therapeutics, the drug discovery and development affiliate of the Cystic Fibrosis Foundation.

"We understand how the defect relates to the sweat gland, and we have a reasonable idea how it relates to the pancreas," he says. "The most controversial link is between the molecular defect and the pathology of the lung—clinically, that is the most important, but the most difficult to explain."

"Unfortunately, we don't even have a great understanding of how the normal lung works to defend itself and how it keeps itself sterile with the constant threats of pathogens, dust toxins, and general leftover garbage," he continues. "Normally, it's as clean as a culture hood. The question is, what fails in CF?"

According to James Chmiel, assistant professor of pediatrics at Case Western Reserve University School of Medicine,

"Early in life, CF patients become infected with a limited spectrum of bacteria," which leads to chronic infections, an overzealous inflammatory response, and significant airway damage. "Until a cure is discovered, further investigations into therapies that relieve obstruction, control infection, and attenuate inflammation offer the best hope of limiting damage to host tissues and prolonging survival."

Two drugs approved by the FDA in the 1990s have contributed to an improved quality of life for CF patients. Pulmozyme (dornase alpha or DNase), the first drug developed specifically for CF, is a genetically engineered enzyme that liquefies the DNA in mucus. Launched by Genentech in 1993, Pulmozyme has reduced the frequency of exacerbations and improved pulmonary function in patients. Chiron's TOBI, an inhaled form of the antibiotic tobramycin, followed in 1997, and it has resulted in improved lung function and reduced hospitalizations, which are common among CF patients.

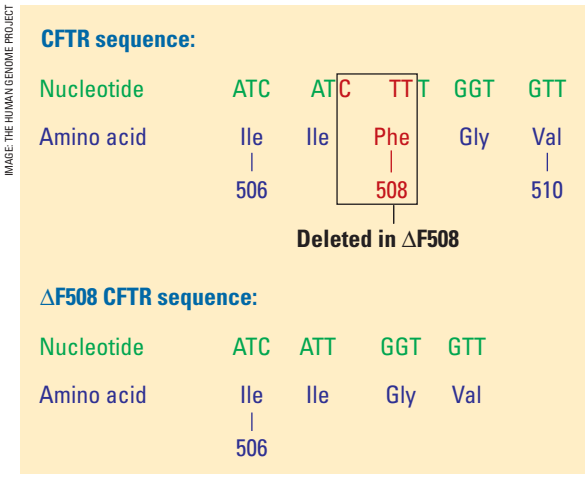


IMAGE: THE HUMAN GENOME PROJECT

Approximately 70% of the mutations in cystic fibrosis patients correspond to a specific deletion from three base pairs in CFTR's nucleotide sequence, resulting in the loss of an amino acid, phenylalanine, at position 508 (Δ508).

A rich pipeline

Faced with an orphan disease lacking attention from pharmaceutical companies, the CFF has dedicated $100 million to its Therapeutics Development Program. The program provides biopharmaceutical companies with matching funds ranging from $25,000 to $25 million.

Tapping its network of CF care centers for clinical trial recruitment, the CFF model funds traditional drug discovery along with two other CF pipeline targets: high-throughput screening (HTS) and already approved drugs that may be useful in CF. Screening up to 20,000 compounds per day, the HTS program has identified 10 candidate compounds that have some impact on CFTR. Azithromycin, an already approved antibiotic, is an example of what Beall calls the search for "low-hanging fruit." A trial using the macrolide antibiotic in 185 patients reduced hospitalizations by 50%. And the anti-inflammatory drug Celebrex is considered another possibility.

Because of the pressure of shortened patient life spans, CF drugs in development are routinely assigned orphan drug status and fast track designation by the FDA. Aided by this and an aggressive agenda, Beall says the typical 14-year drug development timetable is being whittled down to 8 to 10 years for CF drugs. His hope for the next CF drug approval is 3 years. Some promising CF pipeline drugs include compounds that activate the chloride channel, correct or restore the ion transport system, or act as anti-infectives, nutritional products, or mucus regulators.

The drug furthest along is INS37217, a new class of P2Y2 receptor agonists that activate an alternate chloride channel. "Chloride secretion drives water movement, which rehydrates at the same time it activates airway secretion and increases ciliary beat frequency," says Ben Yerxa, senior vice president for discovery at Inspire Pharmaceuticals. "The net result is that patients clear out the goop in their lungs, when normally they go to heroic measures to get it out."

Results of the company's Phase IIa trial are expected at midyear, with an optimistic plan for a product launch in three years. "With CF being such a tough genetic disease, we're hoping for therapeutic intervention early on; then we can decrease the decline in lung function and prevent the early devastation of the lungs," Yerxa explains.

With gastrointestinal problems affecting 9 of 10 CF patients, pancreatic enzyme replacement therapy that became available in the 1950s represented a major advance in CF treatment. The medication is made from homogenated hog pancreas extracts, and patients currently take an average of 20 capsules per day with their meals to aid digestion. Some older adults take 60 to 70 capsules, an incredible pill burden that will be eased by a one-capsule-per-meal medication, if all goes according to plan.

"TheraCLEC is a non-animal source product that allows better compliance and well-controlled manufacturing," says Bob Gallotto, vice president of commercial development at Altus Biologics. With Phase II trials scheduled this summer, the company expects to launch TheraCLEC in 2008.

Meanwhile, another nutrition-focused candidate is docosahexaenoic acid (DHA), an omega-3 fatty acid. The University of Massachusetts is conducting a study on the pathogenesis of CF in 120 newly diagnosed patients, using an infant formula with DHA.

Other interesting drugs in development include curcumin, which also appears to correct abnormal movement of CFTR. Research on this drug is sponsored by Seer Pharmaceuticals and Yale University. "It's early, but the immediate data is very interesting," Beall says.

SEER Pharmaceuticals is conducting a Phase I clinical trial on curcumin, the component of the spice turmeric, following a positive study that showed both clinical benefits and a correction of the CFTR defect in mice carrying the most common CF mutation.

Two other drugs entering Phase II trials are Sucampo Pharmaceuticals' SPI-8811, an oral agent believed to bypass transport of chloride ions, and Genaera's Lomucin, an oral small molecule designed to block excess mucus production.

The CFF had been considering funding a trial in Germany on inhaled glutathione, based on a theory spurred by CF parent and political scientist Valerie Hudson that postulates the natural antioxidant also acts as a mucolytic and immune response modulator. However, the CFF is awaiting Galephar Pharmaceutical Research's Phase I results on Nacystelyn, a potential mucolytic and anti-inflammatory drug.

"Glutathione is a controversial subject, although there's more and more evidence it's playing a potentially important role and is directly linked to altered CFTR function in the lung," says Brian Day, associate professor at the National Jewish Medical and Research Center (see "A mother's fight against CF," *Modern Drug Discovery*, April 2002, p 19; *http://pubs.acs.org/subscribe/journals/mdd/v05/i04/html/04health.html*).

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An ultimate cure

"The ultimate therapy is gene therapy," Beall says. Furthest along in the pipeline is an adeno-associated virus called tgAAVCF. A double-blind randomized placebo trial involving 36 patients demonstrated an excellent safety profile.

"A secondary end point was measuring pulmonary function, which trended positive and on 30 days reached statistical significance," says Barrie Carter from Targeted Genetics, which is conducting the trials. "A second finding was a 5–10% improvement in pulmonary function that was maintained out over 90 days. Both of these—the safety and impact on pulmonary function—were very encouraging and get people enthusiastic," he adds.

Enrollment for a larger Phase IIb trial is expected by year-end. Whereas getting the therapy directly into the airways is easy, the difficult part is measuring gene expression, which requires an invasive bronchoscopy procedure that itself affects pulmonary function. Carter hesitates when asked to project a timetable for FDA approval of tgAAVCF. "Much less than 10 years," he finally concedes, pointing out that "we'll have a better prediction after this next trial."

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