

Mutation-specific cystic fibrosis treatments on verge of approval

More than two decades after scientists discovered the mutated gene responsible for cystic fibrosis, the first drugs that target the defective protein involved in the disease may be on the cusp of market approval. In February, researchers announced preliminary results from a phase 3 trial showing that a pill called VX-770 led to substantial improvements in lung capacity in people with cystic fibrosis. Similar drugs in development could also reach patients within the next few years.

“This is one of the most exciting developments in [cystic fibrosis] therapies since I’ve been practicing,” says Paula Anderson, a pulmonary physician at the University of Arkansas for Medical Sciences in Little Rock. “We’ve never had any other treatment that was really specifically targeted at mutations.”

In 1989, a team that included Francis Collins, now director of the US National Institutes of Health, showed that mutations in a gene encoding a chloride channel protein called cystic fibrosis transmembrane conductance regulator, or CFTR, are always responsible for cystic fibrosis, an inherited disorder that slows mucus clearing from the airways and thereby makes individuals susceptible to deadly lung infections^{1,2,3}. After the landmark genetic discovery, researchers widely assumed that cures would be just around the corner. But no approved therapies to date target the underlying genetic defect; instead, existing therapies such as antibiotics and mucus-thinning drugs can only treat the symptoms of the disease.

VX-770 is different. This small-molecule drug from Vertex Pharmaceuticals, a Cambridge, Massachusetts-based company, interacts directly with CFTR, propping open the defective protein to allow a more normal flow of chloride ions across the cell membrane,

thereby restoring the function of airway cells. In the recently announced trial, which enrolled 161 participants who carried at least one copy of a CFTR mutation called G551D, the people taking VX-770 showed improved lung function and reported fewer respiratory problems than those on placebo. The drug also restored chloride levels in patients’ sweat to near-normal levels, indicating that the chloride pumps throughout the body were back up and running.

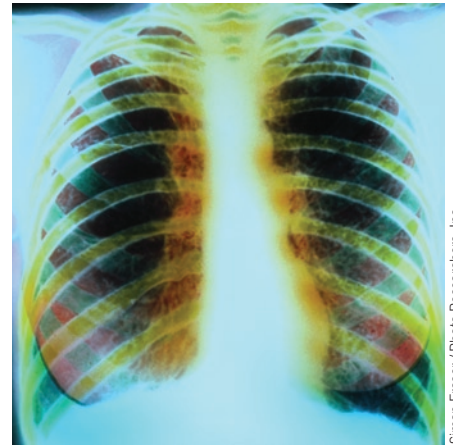
“Observing drops in the sweat test tells you you’re impacting the chloride channel,” says Bonnie Ramsey, a pediatric pulmonologist of the University of Washington School of Medicine in Seattle who led the trial. “That has not been seen in any other therapy,” Vertex plans to file for regulatory approval later this year.

Yet VX-770 is hardly a panacea for people with any of the more than 1,800 other mutations in CFTR implicated in the disease, notes Hartmut Grasemann, who studies lung ailments at the Hospital for Sick Children in Toronto. “The problem with that specific compound is that only patients who carry a specific mutation can be targeted—and that mutation is rare,” affecting only around 4% of people with the disease.

By comparison, more than 90% of cystic fibrosis sufferers carry at least one copy of a different mutation, called F508del. In addition to disturbing CFTR’s chloride pumping action, the F508del error also prevents the protein from folding properly and reaching the cell surface where it does its job. To overcome the latter problem, Vertex has been advancing a second compound, dubbed VX-809, which helps move CFTR proteins with the F508del mutation to the right location.

Combining compounds

Unfortunately, neither VX-770 nor VX-809 alone helps people with the F508del mutation, because neither drug can single-handedly overcome both cellular defects associated with the abnormality. But Vertex has data showing that the two drugs work together in the laboratory to significantly augment CFTR function in airway cells. Because the same cellular model has been predictive of results observed in clinical trials with these agents, “we’re optimistic that the two drugs together might work in the clinic,” says Steven Rowe, a cystic fibrosis researcher at the University of Alabama at Birmingham who has been involved in several of the Vertex trials. Currently, Vertex is enrolling study subjects



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Clear the way: Small molecules could help.

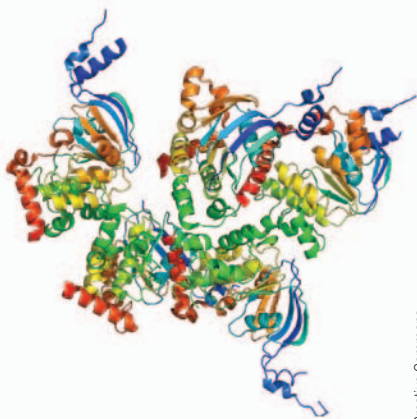
with two copies of the F508del mutation in a phase 2 trial combining the two drugs.

Meanwhile, Marko Pregel, senior research manager at FoldRx Pharmaceuticals, a Cambridge, Massachusetts-based company that was acquired last year by Pfizer, says that his team has discovered a family of compounds that can correct both the trafficking and the gating defects associated with F508del mutation with just one molecule. “Our goal is to do as well or better than the Vertex compounds with a single drug,” Pregel says. He notes, however, that the work is still at the preclinical stage. “We’re not finished. We have a lot of ongoing work to do to improve this family of compounds to the point that it can be a clinical candidate.”

New Jersey-based PTC Therapeutics is also conducting its own phase 3 study of another cystic fibrosis drug called ataluren. Unlike Vertex’s products, ataluren targets other mutations in the CFTR gene that cause truncated proteins, which are seen in around 10% of people with cystic fibrosis. The drug works in part by binding the ribosome to allow the protein synthesis machinery to read through the premature stop signals in the RNA code. According to PTC president and chief executive Stuart Peltz, a preliminary analysis of 20 study subjects found that the drug led to a 4–6% increase in a measure of patients’ lung capacity and a 33% decrease in coughing.

“This is the forefront of personalized medicine,” Peltz says. “You’re treating patients based not only on their diagnosis of cystic fibrosis but also the type of mutation that leads to disease.”

The Cystic Fibrosis Foundation (CFF) has so far invested \$75 million in Vertex’s research and another \$6 million in PTC. But, to avoid



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Pumped for change: The CFTR protein.

putting all of the foundation's eggs in one basket, the organization's president and chief executive, Robert Beall, says the Bethesda, Maryland-based nonprofit plans to spend an extra \$100 million over the next five years in its drug discovery and development program on top of the estimated \$300 million already committed. "We have to make sure that we've created a very, very robust pipeline of backups—and we're doing that," Beall says.

Melissa Ashlock, an independent consultant in New Hampshire and former vice president of drug discovery for Cystic Fibrosis Foundation Therapeutics, the drug development affiliate of the CFF, notes that if the trial testing Vertex's two lead compounds fails, then researchers will be back to square one in trying to tackle the common F508del mutation. So "there's a need to have backup if the combination isn't safe or the combination isn't effective," she says.

To that end, in February, David Thomas and his colleagues at McGill University in Montreal, with funding from the CFF and its Canadian counterpart, discovered a compound called RDR1 that partially rescued CFTR function in

both cell assays and a mouse model with the F508del mutation⁴. "This may be important in the stabilization of the protein on the cell surface," says Thomas, who, in January, inked a collaborative agreement with London-based GlaxoSmithKline to further develop cystic fibrosis therapeutics.

Similarly, last year a team led by William Balch from the Scripps Research Institute in La Jolla, California showed that inhibitors of histone deacetylase enzymes partially restored CFTR's capacity to pump chloride out of lung cells affected by the same common mutation⁵. "It seems that a lot of potentiators are out there in the world waiting to be discovered," says Tzyh-Chang Hwang, a molecular biologist at the University of Missouri in Columbia who is looking for new CFTR-targeted agents in chemical libraries of traditional Chinese medicines.

Beyond small molecules, Eric Alton, a professor at Imperial College London who coordinates the UK CF Gene Therapy Consortium, has been developing gene therapy for cystic fibrosis for close to two decades.

"The main challenge was and is delivery, delivery and delivery," he says. At present, the consortium is in the midst of a 120-person clinical trial examining whether an inhalable spray of circular fragments of DNA that encode working CFTR protein embedded in a fatty transport molecule can deliver the gene to the lungs of people with cystic fibrosis. If it works, Alton notes, "gene therapy will be applicable to any CF patient," including those with the common F508del mutation.

Likewise, the rest of the cystic fibrosis research community is not resting on its laurels following Vertex's early success. As Philip Thomas, a cystic fibrosis researcher at the University of Texas Southwestern Medical Center in Dallas, points out, "we're continuing to look for something better."

Elie Dolgin

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Orphan cystic fibrosis drugs find sister diseases

With fewer than 80,000 people in the world diagnosed with cystic fibrosis, the disease hardly presents itself as a lucrative market for drug development. But it's not just people with cystic fibrosis who harbor mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. "There are other diseases that CFTR mutations are associated with," notes Melissa Ashlock, former vice president of drug discovery for Cystic Fibrosis Foundation Therapeutics. As such, CFTR modulators designed for one ailment—be it cystic fibrosis or otherwise—could have broader market potential beyond the single orphan disease.

Although most people with mutations in CFTR develop cystic fibrosis, some individuals experience less severe disorders, including chronic pancreatitis, male infertility, sinusitis and airway abnormalities. These people are also likely to benefit from CFTR-targeted agents such as Vertex Pharmaceutical's VX-770 and VX-809. But, given that many of these more mild diseases are more sporadic than cystic fibrosis, "whether they would be good candidates for being treated with a chronic therapy that's going to be quite expensive is unclear," says Sam Moskowitz, director of the cystic fibrosis basic science program at MassGeneral Hospital for Children in Boston.

Likewise, PTC Therapeutics's lead cystic fibrosis compound ataluren also might find a broader audience beyond cystic fibrosis by helping ribosomes read through premature stop codons associated with other genetic disorders. Currently, ataluren is being tested in people with forms of hemophilia and a metabolic disorder called methylmalonic acidemia, but the drug could also prove beneficial to people with certain forms of muscular dystrophy, lysosomal storage disorders and some types of cancer. "That definitely has potential generalizability," Moskowitz says.

Taking a different tack, some drug companies are also trying to block rather than enhance the function of CFTR to treat a range of diseases associated with the loss of bodily fluids. For example, two years ago the Swiss pharma giant Novartis teamed up with the Institute for OneWorld Health, a San Francisco-based nonprofit, to discover and develop new CFTR inhibitors to combat chronic secretory diarrhea. Similarly, San Francisco-based Napo Pharmaceuticals is advancing CFTR blockers that have proven effective in treating rodent models of cholera-induced diarrhea and polycystic kidney disease.

But it could be VX-770—a drug possibly on the brink of regulatory approval—that first proves to have wide-reaching utility. In work presented at last year's Annual North American Cystic Fibrosis Conference in Baltimore, Steven Rowe of the University of Alabama at Birmingham showed that the drug improved CFTR activity and mucus clearance in human lung cells exposed to cigarette smoke extract. The potential of this drug application was reinforced last month when molecular biologist Neeraj Vij of Johns Hopkins University School of Medicine in Baltimore reported that CFTR is involved in regulating cell death and degradation responses in mice with smoke-induced lung damage (*Am. J. Physiol. Lung Cell. Mol. Physiol.* doi:10.1152/ajplung.00408.2010, 2011).

Given that chronic obstructive pulmonary disease is the fourth leading cause of death in the US and Europe and no pharmacological treatments are available that address the mucus buildup associated with this disease, "agents that potentiate CFTR activity could be a useful addition to the treatment armamentarium if the approach can be successfully translated to humans," Rowe says.

Elie Dolgin