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 mutation[4]. "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 mutation[5]. "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."

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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.

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