EDITORIALS

Targeting the Basic Defect in Cystic Fibrosis

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Therapies for cystic fibrosis have been limited to alleviating clinical manifestations, and although the duration and quality of patients' lives have improved, cystic fibrosis continues to inflict major burdens and shorten lives.[1] In this issue of the *Journal*, Accurso and colleagues[2] have taken a different tack, directly targeting the defective cystic fibrosis transmembrane conductance regulator (CFTR) with a new drug that appears to be safe and to work in vivo. This research represents a milestone along the pathway of discovery leading to better preventions, treatments, and cures. It also illustrates the usefulness of genetic testing in identifying a select subgroup of patients for treatment with an agent that targets a specific mutant protein.

Reaching this milestone invites three questions. How did we get here? Where are we now? Where do we go from here?

How did we get here? This journey began with the discovery that mutations in the gene encoding CFTR cause cystic fibrosis.[3] Soon thereafter, experiments showed that CFTR is an anion channel located in the apical membrane of epithelial cells, including those in the airways. Investigators proceeded to identify more than 1000 disease-causing mutations. The most common mutation, Δ*F508*, deletes phenylalanine at amino acid position 508 and accounts for about 70% of cystic fibrosis alleles; approximately 90% of persons with cystic fibrosis carry at least one Δ*F508* mutation. Another mutation, G551D-*CFTR*, swaps an aspartate residue for a glycine residue at position 551 and accounts for 4 to 5% of alleles. Subsequent studies revealed that these and other mutations disrupt function by means of distinct mechanisms.[4] For example, the Δ*F508* mutation causes CFTR to misfold, thereby disrupting its biosynthesis and delivery to the cell surface. In contrast, G551D-CFTR channels reach the cell membrane but rarely open. Additional experiments suggested the possibility of reversing some abnormalities. These discoveries ignited efforts to identify small molecules that would correct distinct defects in CFTR.

With financial support and scientific advice from the Cystic Fibrosis Foundation and contributions from the scientific community, scientists at Vertex Pharmaceuticals initiated high-throughput screening and chemical engineering to develop an orally bioavailable drug targeting CFTR in all organs. The goal was an agent that would facilitate the opening of G551D-CFTR channels. VX-770 emerged from that effort as a "potentiator" of CFTR activity[5]; it increases the fraction of time phosphorylated G551D-CFTR channels are open, thereby increasing chloride and bicarbonate flow across epithelial apical membranes. These studies set the stage for testing VX-770 in patients bearing a G551D-*CFTR* mutation.

Where are we now? Accurso and colleagues assessed the effect of VX-770, after 14 and 28 days of treatment, on two outcomes — CFTR function and disease manifestations. They examined CFTR activity in both nasal epithelia and sweat glands. Measurement of the electrical potential difference across nasal epithelia (the nasal potential difference, an electrophysiological assay of CFTR channels) revealed partial restoration of chloride conductance. Similarly, measurement of the sweat chloride concentration (the elevation of which is indicative of cystic fibrosis) showed partial restoration of chloride transport in the sweat glands. With respect to disease manifestations, the investigators found that VX-770 increased the forced expiratory volume in 1 second (FEV_1). Given that

all the patients were at least 18 years of age and had established lung disease, it seems surprising that VX-770 would improve function so rapidly, but it did. These are encouraging results.

Where do we go from here? More studies involving more patients and longer test periods are needed to test the safety and efficacy of VX-770 in patients with a G551D-*CFTR* mutation. Might VX-770 be effective in patients with other *CFTR* mutations? In vitro experiments have shown that VX-770 increased the activity of CFTR-ΔF508 channels, provided they reached the cell surface.[5] Thus, although the precise mechanism by which VX-770 increases channel activity remains uncertain, this drug might have usefulness in patients with other mutations.

As compared with G551D, ΔF508 is the 800-pound gorilla because of its prevalence — thus, the problem of CFTR misfolding should also be addressed. High-throughput screening has identified candidate "corrector" molecules that improve in vitro processing of CFTR-ΔF508, and these are being tested. Although developing a combination of two agents to treat cystic fibrosis is fraught with pitfalls, one can envision combining a potentiator and a corrector, each with partial effects, to boost CFTR function over the bar required for a preventive or therapeutic effect.

How high is that bar? We do not know. First, we cannot quantitatively assay CFTR function in vivo. The nasal potential difference and sweat chloride concentration provide little quantitative information about CFTR chloride permeability and involve other complex transport processes. Moreover, their relationship to CFTR activity is nonlinear; for example, the nasal potential difference and sweat chloride concentrations are normal, or nearly so, in people who are heterozygous for *CFTR* mutations and thus have half the normal amount of CFTR. Second, our measures of disease are crude. For example, although the FEV_1 is of value in older patients with established lung disease, it has little usefulness in assaying very early disease before the onset of extensive infection, inflammation, and airway obstruction. Third, the relationship between CFTR function and disease could differ in the lung, pancreas, and liver; in patients with disease-modifying genetic variations distinct from *CFTR*; and also in the prevention versus the treatment of established disease. Thus, our limited ability to quantitatively assay either CFTR function in vivo or the severity of early disease leaves knowledge about the relationship between the two on shaky ground.

Screening of newborns for *CFTR* mutations, which is now universal in the United States, provides a tremendous opportunity to intervene early and thus heightens the urgency in understanding relationships between CFTR function and disease. Given that infants have a defect in pulmonary host defense that allows bacterial infection to initiate a cascade of inflammation and remodeling, an ideal scenario would be to begin therapeutically targeting CFTR soon after birth. However, if we are to commit babies to a lifetime of treatment, we must have quantitative metrics to guide factors such as dosing, continuous or intermittent administration, and intervals between treatments. Even the treatment of patients with established disease would benefit from more sensitive and quantitative biomarkers. Acquiring knowledge of the pathophysiology of cystic fibrosis and developing new assays with the use of that knowledge should be priorities. One hope is that studies of the use of agents such as VX-770 will advance these goals. The reaching of this milestone along the pathway of discovery leaves me optimistic for people who have cystic fibrosis.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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