EDITORIAL

Realizing the Dream of Molecularly Targeted Therapies for Cystic Fibrosis

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The diary entry of an 8-year-old girl with cystic fibrosis indicates that Aug. 25, 1989, was an important day for her (Fig. 1). That was the day the research teams at the University of Michigan and the Hospital for Sick Children, Toronto, announced the discovery of the cystic fibrosis gene and the most common mutation, a three-base deletion that results in a missing phenylalanine in codon 508 (denoted the Phe508del *CFTR* mutation). We hoped that the gene discovery would someday lead to effective treatments for children and adults with cystic fibrosis, but we knew that would be a long road.[2,3] Now, 30 years later, that time has come. The results of a pair of phase 3 clinical trials in the *Journal*[4] and in a simultaneous publication in the *Lancet*[5] document impressive benefits from triple-drug therapy for persons with cystic fibrosis and at least one copy of the Phe508del *CFTR* mutation, who represent approximately 90% of persons affected by this life-shortening autosomal recessive disease.

The journey to gene-based therapies for cystic fibrosis began with enthusiasm over the prospect of gene therapy. But the challenges of using gene transfer to achieve long-lasting correction in the airway proved daunting. Immune rejection of corrected cells emerged quickly, and clinical trials produced disappointing results.[6] Other approaches had to be tried. Despite the high risk of pursuing small-molecule therapy for a recessive disease, drug-development efforts were initiated in hopes of restoring the function of the protein affected by cystic fibrosis, the cystic fibrosis transmembrane conductance regulator (CFTR).

It was clear this was going to be a heavy lift. Normally, CFTR serves as a gated channel for chloride ions, helping to maintain the balance of salt and water in the lungs, pancreas, gastrointestinal tract, sweat glands, and other organ systems. Drug researchers had to consider that the Phe508del *CFTR* mutation, the most common of the more than 1700 known *CFTR* mutations that can cause cystic fibrosis,[7] results in a protein with not just one — but two — serious functional

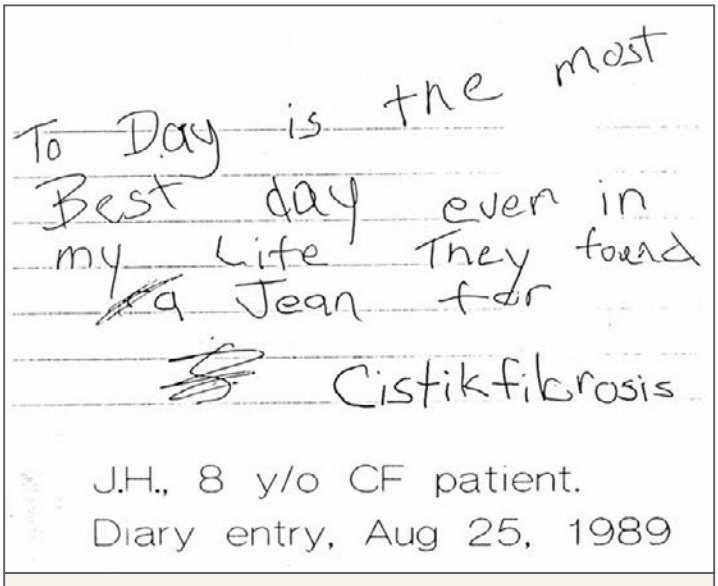

Figure 1. Diary of Child with Cystic Fibrosis.

A girl with cystic fibrosis wrote this entry in her diary on Aug. 25, 1989 — the day when researchers announced identification of the first genetic mutation that causes the life-shortening rare disease. From the Office of NIH History.[1]

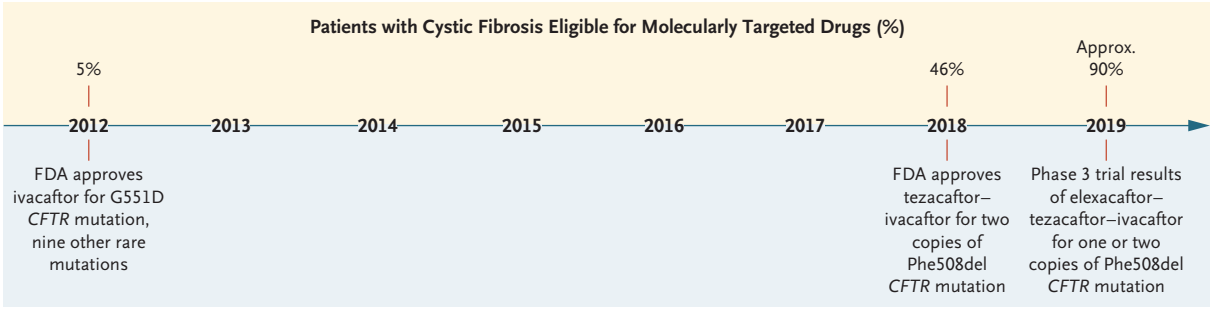

Figure 2. Progress in Molecularly Targeted Therapies for Cystic Fibrosis.

In 2012, the first drug to address the molecular cause of cystic fibrosis, ivacaftor, was approved by the Food and Drug Administration (FDA); this monotherapy benefits the approximately 5% of patients with cystic fibrosis with the G551D *CFTR* mutation and nine other rare mutations. In 2018, the FDA approved a dual-combination therapy, tezacaftor–ivacaftor, that benefits the approximately 50% of patients with cystic fibrosis with two copies of the Phe508del *CFTR* mutation or a single copy of 26 other mutations. Now, results from two phase 3, multicenter clinical trials[3,4] show the safety and efficacy of a triple-combination therapy, elexacaftor–tezacaftor–ivacaftor, for the approximately 90% of patients with cystic fibrosis with either one or two copies of the Phe508del *CFTR* mutation. Adapted from the Cystic Fibrosis Foundation.[8]

deficits. Not only do patients with this mutation have a CFTR protein that is misfolded and trapped in the endoplasmic reticulum of the cell, but any CFTR that does manage to reach the proper location in the cell membrane is deficient in activation. So the search for therapeutics had to include both small molecules that could correct the misfolding of the CFTR protein ("correctors") and those that could activate its function when it reaches the cell membrane ("potentiators").

Academic investigators, many funded by the National Institutes of Health, derived a deep understanding of CFTR function in the first 10 years after gene discovery. Building on that fundamental platform of knowledge, the Cystic Fibrosis Foundation and a small company called Aurora Biosciences (later, Vertex Pharmaceuticals) joined forces in the late 1990s to embark on a high-throughput search for small-molecule correctors and potentiators. These collaborative efforts, now spanning more than two decades, can be seen as an important model for other rare genetic diseases.[8] In 2012, the Food and Drug Administration (FDA) approved the first drug, the potentiator ivacaftor, to address an underlying cause of cystic fibrosis: the relatively uncommon G551D *CFTR* mutation, which codes for a protein that does not have the misfolding problem — it just needs activation at the cell membrane.[9] Although only approximately 5% of patients with cystic fibrosis stood to benefit from ivacaftor, their heartening clinical response served to stimulate vigorous pursuit of drugs for more common cystic fibrosis–causing mutations, especially the Phe508del *CFTR* mutation. Encouragingly, the past 7 years have seen a steady, stepwise expansion of small-molecule treatment options for more patients with cystic fibrosis (Fig. 2).

The pair of phase 3, multicenter clinical trials reported now document the efficacy and safety of elexacaftor–tezacaftor–ivacaftor triple-combination therapy (two correctors, one potentiator) for patients with one or two copies of the Phe508del *CFTR* mutation. Given the recent approval of this therapy by the FDA, these findings indicate that it may soon be possible to offer safe and effective molecularly targeted therapies to 90% of persons with cystic fibrosis.

This should be a cause for major celebration. Yet we must not abandon the patients with cystic fibrosis who have null mutations[7] and will not have a response to these drugs. Even beyond that, the "best day ever" for all of us traveling down this long road together will be the day when the more than 70,000 persons with cystic fibrosis worldwide[10] do not need to take drug therapy at all and there finally is a permanent cure for cystic fibrosis that works for everyone. Although the challenges are substantial, one can imagine

such an ultimate approach involving in vivo somatic-cell gene editing of airway epithelial cells.

Shortly after our identification of *CFTR*, I wrote a song entitled "Dare to Dream." The lyrics expressed hope that the gene discovery would lead to effective treatments for cystic fibrosis — that someday we would see "all our brothers and sisters breathing free."[11] It is profoundly gratifying to see that this dream is coming true.

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

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