EDITORIALS

Therapy for Cystic Fibrosis — The End of the Beginning?

Pamela B. Davis, M.D., Ph.D.

Over the past four decades, implementation of therapies directed entirely at symptoms have improved the quality of life in patients with cystic fibrosis and have increased the median survival age from 11 years to 37 years. Now, in this issue of the *Journal*, Ramsey et al.[1] provide the first proof that a treatment, ivacaftor, that is directed at the basic defect in *G551D-CFTR* produces sustained improvement in signs and symptoms of cystic fibrosis in patients 12 years of age or older who have at least one *G551D* allele.

This report is the destination of a long journey that began with the discovery of the gene for cystic fibrosis in 1989[2] and that has taken us through the definition of the basic defect, the identification of drug candidates by high-throughput screening, the testing in cell and animal models, and initial human trials[3] to the present gratifying results. Sustained reductions in respiratory symptoms and sweat chloride concentrations, improvements in pulmonary function, and weight gain were observed, without substantial adverse effects. Despite concern that correcting the basic defect in cystic fibrosis may not be effective once permanent structural damage has occurred in the airways, improvements in patients with poor pulmonary function were similar to those in patients with only mild functional impairment, though function did not normalize in most patients. It is not yet clear whether ivacaftor will halt the deterioration in pulmonary function. Progression of lung disease in patients with cystic fibrosis is now so gradual that follow-up of many patients for many years is required to determine whether decline has been arrested. A second key question is whether ivacaftor activates other *CFTR* alleles that reach the cell surface; if it does, many more patients can benefit than just the 4 to 5% with the *G551D* mutation.

The biggest prize for allele-specific therapy will be the most common mutant form of *CFTR*, ΔF508-CFTR, which occurs in more than 90% of patients with cystic fibrosis in the United States. In vitro, ivacaftor stimulates activity in ΔF508-CFTR, but to a much lesser extent than it does in G551D.[4] Whether such a level of stimulation is sufficient for clinical benefit is unclear. ΔF508-CFTR is degraded in the endoplasmic reticulum because the protein is recognized as misfolded by the quality-control machinery of the cell.[5] The tiny amount that reaches the cell surface opens less often and is retrieved from the membrane much faster than the wild-type protein. These complexities suggest that no single drug will be entirely suitable as a therapeutic agent.[6] Nevertheless, the success of ivacaftor gives new impetus to allele-specific therapies. Drugs that improve the processing of ΔF508-CFTR and drugs that suppress single-stop codon mutations are also being tested in clinical trials.

This success of ivacaftor is a triumph resulting from the discovery of the cystic fibrosis gene in 1989,[2] followed by insightful and collaborative basic-science studies conducted by academic and industry investigators that led to clinical trials in an established clinical-research network to produce and validate a novel therapeutic agent for a dread disease. Investments in research infrastructure and projects by the National Institutes of Health and the Cystic Fibrosis Foundation, sustained over decades, culminated in a potentially curative drug for some patients with cystic fibrosis and powerful hope for others. Derivative discoveries, such as the identification of inhibitors of the CFTR channel for cholera,[7] appreciation of pulmonary defense mechanisms,[8] and uncovering of disease-modifying genes for cystic fibrosis that may be relevant to other lung dis-

eases,[9] may also be exploited for therapeutic purposes. Even with this near-optimal configuration of scientists, it took more than 20 years from the time of the discovery of the cystic fibrosis gene to produce this result. This timeline suggests that much of the promise of the Human Genome Project has yet to be fulfilled and that realizing the therapeutic benefits will take persistence and determination. Society cannot allow support for research and development to be compromised in the current rush to cut the federal budget.

As significant as this report is, critical questions remain. Is ivacaftor safe for infants and children, and is it safe when taken for many years? Although involvement of some organ systems in cystic fibrosis occurs in utero, such as congenital absence of the vas deferens and probably a good deal of pancreatic destruction, the most serious complications — lung disease and liver disease — begin after birth. If ivacaftor is administered before lung disease develops, will lung disease be prevented? In most states in the United States, neonatal screening now includes screening for cystic fibrosis. The dream is that nearly all patients with the *G551D-CFTR* mutation can be identified before lung disease begins and will live nearly normal lives with ivacaftor therapy. In 1942, Winston Churchill marked a great World War II Allied victory with these words: "Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning." This study is also a great victory in the war against genetic diseases and marks the end of the beginning for the treatment of the cystic fibrosis defect.

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

From Case Western Reserve University School of Medicine, Cleveland.

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Eliminating Cells Gone Astray

Michel Sadelain, M.D., Ph.D.

The therapeutic use of cells from healthy donors or patients is increasing. Decades ago, transfusion medicine and bone marrow transplantation provided the first successful cell therapeutics and established the foundations for cell delivery. Clinical investigation soon uncovered the double-edged facets of some cell products, which, for example, could correct anemia but also cause alloimmunization or eradicate minimal residual leukemia while inducing potentially lethal graft-versus-host disease (GVHD).[1]

Cell therapies have acquired a new dimension during the past 15 years with the emergence of engineered cells that are directed to differentiate toward a particular function, are genetically modified, or are reprogrammed before their infusion. Such cells are not merely isolated from the donor but are expanded or selected in some way to optimize their properties. Successes with the use of cultured cells are accumulating, as exemplified by the genetic correction of severe combined immune deficiency[2] and the design of tumor-targeted T cells with increased potency.[3] Here too, clinical investigation rapidly revealed the potential risks of engineered cells, ranging from insertional oncogenesis in hematopoietic stem cells[4] to cytokine release[5] and tumor lysis syndrome[6] triggered by adoptively transferred T cells.

In the early 1990s, cell therapists came up with a genetic solution to these safety concerns. Such a solution was based on the concept of on-