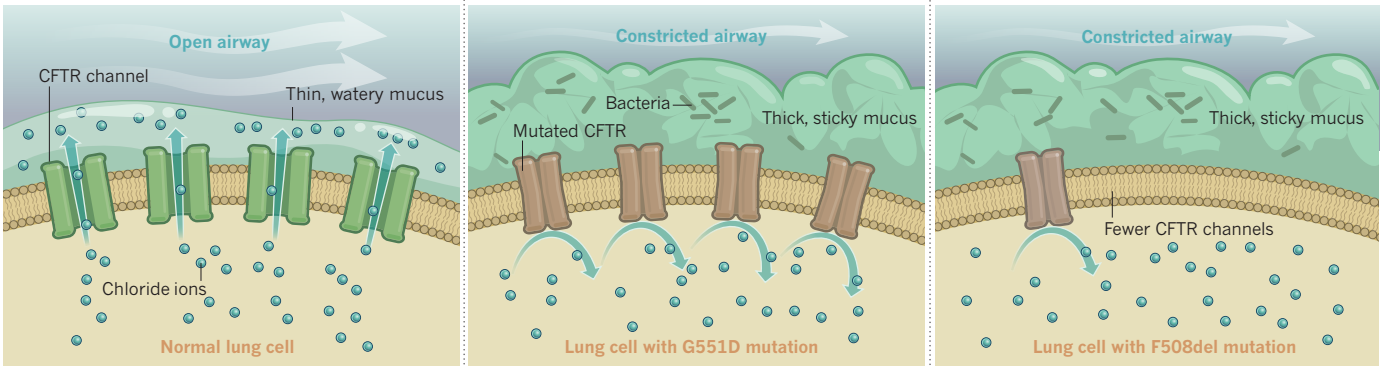
REOPENING A CHANNEL

The gene mutated in cystic fibrosis normally produces a channel that allows chloride ions to pass through the cell membrane, keeping the protective layer of mucus fluid.

A new drug corrects the effects of the rare G551D mutation, which stops the channel opening correctly, causing thick mucus that promotes bacterial infection.

Most people with cystic fibrosis have the F508del mutation, which stops the CFTR protein from folding properly and limits the number of channels.



HEALTH

Drug bests cystic-fibrosis mutation

First treatment to tackle protein behind the disease wins approval — but only a small fraction of patients will benefit.

BY HEIDI LEDFORD

In a blinded clinical trial, neither the patient nor the clinician should know who is receiving placebo and who the active drug. But during a trial of Kalydeco (ivacaftor), a cystic-fibrosis treatment approved by the US Food and Drug Administration on 31 January, Drucy Borowitz says it was sometimes easy to tell the difference. "We had two brothers in the trial," says Borowitz, a paediatric pulmonologist at the State University of New York in Buffalo. After two weeks, she says, the pair stepped out of the lift together and it was clear who was taking the drug. "The younger brother looked sturdier," she says. "It reminded me of the change in appearance that we see in patients with cystic fibrosis after they have lung transplants."

Kalydeco, made by Vertex Pharmaceuticals of Cambridge, Massachusetts, is the first drug to target a cause of cystic fibrosis rather than the condition's symptoms. In doing so, it fulfils a promise made more than 20 years ago when a mutated gene, called cystic fibrosis transmembrane conductance regulator (*CFTR*), was first discovered and researchers spoke optimistically about developing drugs to correct it.

"This is a seminal turning point in the treatment of cystic fibrosis," says Matthew Reed, chief executive of the Cystic Fibrosis Trust in London. "But there is much further to go until we've cracked the cystic-fibrosis problem." As many as 1,500 different mutations have been found to affect *CFTR*, and Kalydeco targets just one — G551D, found in 4% of patients.

The CFTR protein forms a channel that allows chloride ions to cross the cell membrane — a key step in the production of mucus, digestive enzymes and sweat (see 'Reopening a channel'). In patients with the G551D mutation, the channel fails to open properly, so ions are unable to pass through. About 90% of people with cystic fibrosis have a different mutation, called F508del, which results in proteins that do not fold into their proper shape and so get targeted for degradation, reducing the number of channels. Either way, the resulting imbalance of ions causes mucus to become thick and sticky, blocking airways and opening the door to infection.

In the beginning, the idea that a chemical could correct the cystic-fibrosis protein was a tough sell. Most drugs work by blocking a protein's function, often by binding to an important site on the protein to gum up its activity. "It's easy to break things," says Eric Olson, head of cystic-fibrosis research at Vertex. "It's a lot harder to think about how to fix a protein."

Drugs are on the horizon for countering other cystic-fibrosis mutations. VX-809, another Vertex compound, seems to protect proteins affected by the F508del mutation from degradation. Trials of this drug in combination with Kalydeco are under way to see whether VX-809 will get the protein to the cell membrane so that Kalydeco could then get it working. Last year, Vertex announced that early tests of this combination reduced the amount of chloride in sweat — a marker used to judge how well CFTR is functioning. But whereas Kalydeco nearly halved sweat chloride in people with G551D, the combination therapy cut it by just 13% in those with F508del. That, says Borowitz, may be because the dose used was not high enough. A larger dose is now being tested in a clinical trial, with results expected later this year.

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For more on the story of the cystic-fibrosis gene, see:
go.nature.com/iilwz8

Meanwhile, PTC Therapeutics, based in South Plainfield, New Jersey, is developing a therapy to target a set of mutations that insert a 'stop' signal in the middle of *CFTR*, preventing the cell from producing a full-length protein. That therapy, called ataluren, is in late-stage clinical trials, with results due later this year. And several institutions in the United Kingdom, working with Genzyme, a biotech company also based in Cambridge, are trying to use gene therapy to help the cell to express normal CFTR. They expect to get backing from the British government for their next clinical trial, says Reed.

The Cystic Fibrosis Foundation in Bethesda, Maryland, has helped to drive the development of new drugs. It supports another project at Genzyme and is co-sponsoring a project with Pfizer in New York, which recently bought FoldRx, a firm based in Cambridge that develops therapies for misfolded proteins. The foundation hopes that more sophisticated chemical screens — for instance, testing drugs in cells cultured from patients with cystic fibrosis rather than in rat cells, as was done originally — may yield new hits.

Despite the latest success, researchers and patient advocates say that combinations of all these approaches may be needed to tackle the disease fully. When *CFTR* was first cloned, "we were naive as to the complexity of curing a genetic disease", says Jack Riordan, a biochemist at the University of North Carolina at Chapel Hill who worked on the team that discovered *CFTR*. "We thought we could find a silver bullet, but we don't use that terminology any more." ■