



A New Approach to Treating CF That Could Help Many Others

Bob Williamson, AO FRS
University of Melbourne
Melbourne, Australia

Did you know that there are about 1500 different mutations in the “CF gene” (the DNA sequence that codes for the protein that doesn’t work properly in people living with CF)? One of these, the famous “delta-F-508”, is very common; about three-quarters of PWCF have at least one copy of this mutation. Most of the 1500 are incredibly rare, but another dozen or so are found quite often, particularly in some ethnic groups.

Each of the mutations causes CF in its own way. The $\Delta F508$ mutation takes a building block, an amino acid called phenylalanine, out of the middle of the protein chain. Some mutations lead to less CF protein, while others change one building block for another. Two of the mutations (which are particularly common in people of Jewish ancestry, but are also found in other groups) stop the synthesis of the CF protein right in the middle of the chain. These are sometimes called “nonsense mutations”, because they substitute an instruction that doesn’t code for an amino acid (the subunit that makes up proteins) with one that codes for “nothing”, but I don’t like the word “nonsense” in this context, since it is not nonsense but good sense for a protein to have a way of saying “stop here”. It’s just that when the stop is introduced in the wrong place, it causes CF. (For the scientists reading this, the mutation changes an amino acid-specifying codon into a stop codon, causing the ribosome to terminate protein synthesis prematurely at the site of the mutation.)

It has been known for some time that drugs can be used to make the ribosome misread a stop signal and skip over it, to give a protein that is (almost) fully functional. Some of the early chemicals with this property were too toxic to consider using on patients, but an American company, encouraged by funding and patient support organised by the United States CF Foundation, has now developed a new compound (PTC124) that is less toxic but seems to give promising (if preliminary) data when given to patients.

The clinical trial took place at the Hadassah University Hospital in Israel, directed by Professor Eitan Kerem, head of the CF Centre, who (with his wife, a molecular geneticist who worked with Lap-Chee Tsui to get the CF gene) has been an important figure who has made many contributions to CF research over the years. Israel, where 60% of those with CF have at least one “stop mutation”, is probably the only place where there are enough adults living with CF to have a proper clinical test of the new drug, though even in Israel most of those tested only had one of the two CF genes with the stop mutation. (Adults are usually tested first in a clinical trial, because they can give informed consent and are often more affected.) Several U.S. Hospitals also helped to make numbers up, by providing suitable adults with CF.

Two different doses of PTC124 were tested for two weeks. The really good news is that almost half the patients on the trial showed improved ion transport when on PTC124 than before (tested via the nose, since measuring inside the lung is difficult). The other good news is that there were no serious side effects during the trial. (Because PTC124 changes the way the genetic code is read by the cell, there were worries that it might cause mistakes in reading other, normal genes, but this doesn’t seem to be a problem.)



Of course, the Israeli and American teams wonder why the improvement was only seen for some people, and will be starting a longer test (along with a French team) to check whether the change in chloride ion transport translates into better lung function. And one of the most exciting aspects of the research is that CF is not the only genetic disease that is (sometimes) caused by “stop mutations”. It is estimated that about one in eight of boys with Duchenne muscular dystrophy might also benefit. Yet again, we hope that CF will lead the way!