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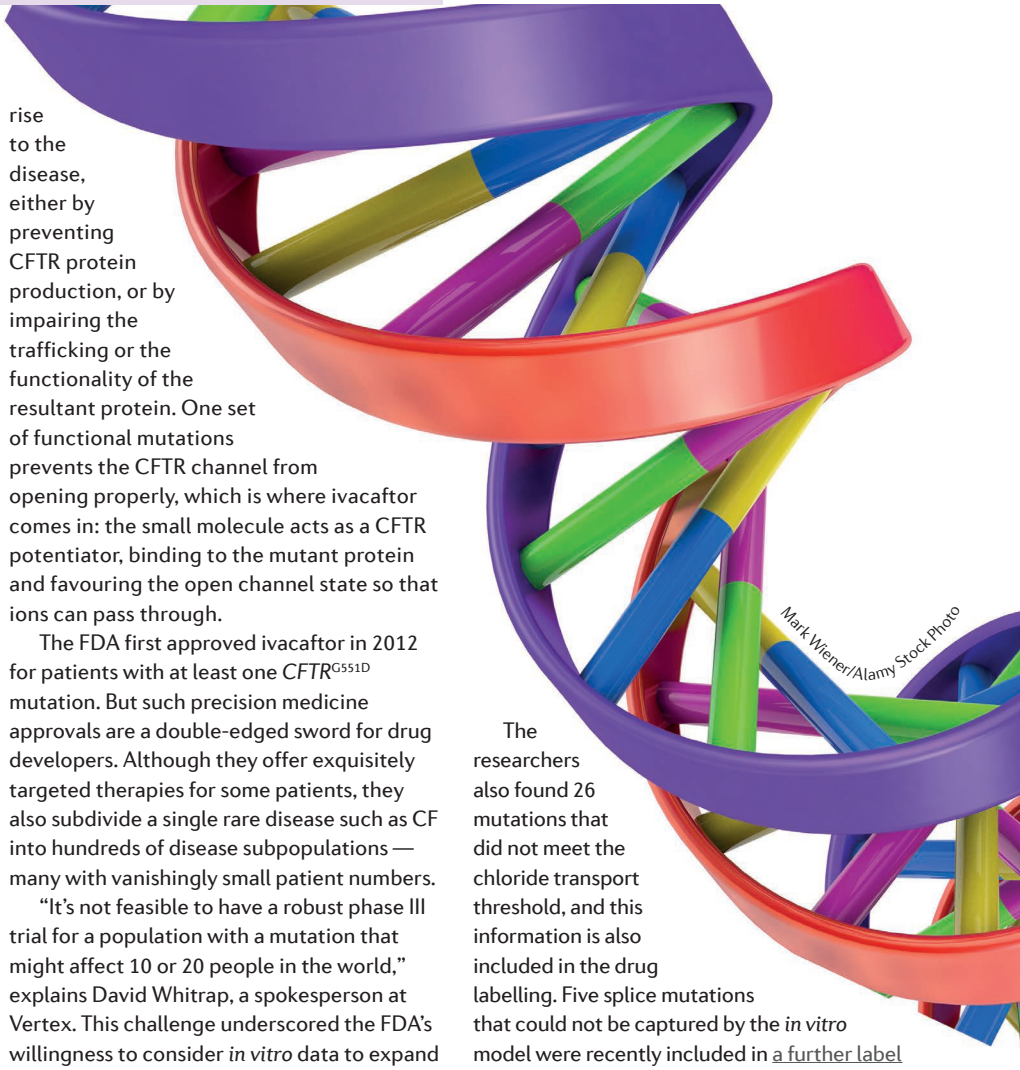
FDA OKs first *in vitro* route to expanded approval

In vitro data can be used to accelerate the approval of drugs that target specific disease-causing mutations for additional subpopulations of patients with rare diseases such as cystic fibrosis.



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Katie Kingwell

In May, the FDA granted expanded approval to Vertex Pharmaceuticals' cystic fibrosis (CF) drug ivacaftor on the basis of *in vitro* data. The change adds 23 mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene to the existing 10 mutations previously covered by the drug label, representing a further ~900 patients in the United States, or about 3% of the CF population.

When the FDA announced the approval, they noted that it could have implications beyond ivacaftor — for other drugs with well-understood safety profiles that address well-characterized diseases. "This action signals to other sponsors that for drugs that target specific mutations, *in vitro* assay data could potentially be used in place of additional small clinical trials when seeking to expand to other population subsets, provided that [specific] ... criteria are met," wrote the agency's Tony Durmowicz and Mike Pacanowski in an associated press release.

"To me, this is a real step forward," says Marshall Summar, Chair of the Board of Directors of the US National Organization for Rare Disorders. "The fear a lot of us have had in the field [of rare diseases] is that we're going to have to go through a full approval process for every single new mutation that we're addressing with a modifying drug. It would have brought the whole thing to a standstill."

"I think that it's a great approach and the way to go for orphan diseases," enthuses Jeffery Kelly, Chairman of the Department of Molecular and Experimental Medicine at the Scripps Research Institute. At least in the short term, however, drug developers are likely to use this pathway only in exceptional circumstances.

Vertex's data

In CF, mutations in the chloride channel gene *CFTR* cause defects in chloride and water handling across epithelial membranes that line the lungs, leading to a build-up of mucus that obstructs the airways. Any one of about 300 rare mutations in the *CFTR* gene can give rise to the disease, either by preventing CFTR protein production, or by impairing the trafficking or the functionality of the resultant protein. One set of functional mutations prevents the CFTR channel from opening properly, which is where ivacaftor comes in: the small molecule acts as a CFTR potentiator, binding to the mutant protein and favouring the open channel state so that ions can pass through.

The FDA first approved ivacaftor in 2012 for patients with at least one $CFTR^{G551D}$ mutation. But such precision medicine approvals are a double-edged sword for drug developers. Although they offer exquisitely targeted therapies for some patients, they also subdivide a single rare disease such as CF into hundreds of disease subpopulations — many with vanishingly small patient numbers.

"It's not feasible to have a robust phase III trial for a population with a mutation that might affect 10 or 20 people in the world," explains David Whitrap, a spokesperson at Vertex. This challenge underscored the FDA's willingness to consider *in vitro* data to expand the label for ivacaftor.

To secure the supplemental approval for 23 additional mutations, researchers at Vertex developed *in vitro* models of the different CFTR mutations in Fisher rat thyroid cell lines. These cells were then treated with ivacaftor and assessed with Ussing chamber electrophysiology. Mutated cell lines that responded to ivacaftor with a net increase of 10% chloride transport over the baseline were considered responsive to the drug, an *in vitro* threshold that reasonably predicted the drug's clinical benefit in the large clinical trials that supported the original approvals.

The researchers also found 26 mutations that did not meet the chloride transport threshold, and this information is also included in the drug labelling. Five splice mutations that could not be captured by the *in vitro* model were recently included in a further label expansion of ivacaftor following successful phase III trials.

Although the FDA envisages that other drug sponsors will one day avail themselves of similar *in vitro* approval pathways, uptake is likely to be limited because sponsors will have to fulfil several criteria that Vertex met with ivacaftor — especially around safety.

The company had 5 years of real-world experience with the drug, and its efficacy and safety profiles were well documented. "This is different than a new drug being approved," says Whitrap. "This is clearly a [supplementary new drug application] with a well-established and well-characterized

medicine." The medical community also has an extensive body of knowledge about CF, built up over decades of research into the *CFTR* gene *in vitro* and in patients.

"Because the efficacy and safety profile of ivacaftor was well documented, our main concern was whether the validity of the assay that was used to assess the response *in vitro* was reliable," said an FDA spokesperson in an email.

Vertex initially submitted the supplementary new drug application in 2015, but the agency rejected it the following year. "Our conversations since 2015 with the FDA have just been ensuring that the FDA understands and has confidence in these assays," says Whitrap.

Conditions apply

For Kelly, this new approval pathway could be particularly useful for therapeutics for other rare loss-of-function protein misfolding diseases, including lysosomal storage diseases and channelopathies. Researchers have worked out predictive *in vitro* models for some of these orphan diseases, he says. Common multifactorial diseases such as diabetes or hypertension, by contrast, cannot be fully recapitulated *in vitro*.

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Single-gene gain-of-function disorders, such as transthyretin amyloidoses, are also difficult to model *in vitro*, because the abnormal proteins exert their toxic effect in complex ways over decades, adds Kelly. Target engagement in *ex vivo* models, such as stabilization of mutant transthyretin by the drug tafamidis in patient blood samples, may provide an alternative supplementary approval pathway in these indications, he hopes.

Adrian Krainer, a professor of molecular genetics at Cold Spring Harbor Laboratory and one of the inventors of Biogen's antisense drug nusinersen for spinal muscular atrophy, points out that the new pathway might only be applicable to a small subset of drugs that "can be used to treat different defective alleles of the same target gene." Genetically targeted therapies that need to be tweaked for each different mutation, such as antisense oligonucleotides and exon-skipping drugs, will therefore need to complete the full rigours of clinical trials. "If the oligonucleotide sequence is different, the potential off-target effects would be different, and I'm not sure there's a way around that," says Krainer.

Nevertheless, he still thinks that under the right circumstances, the potential for a 'shortcut' to expanded approval could make orphan diseases a more attractive area for drug developers. "If a company is making decisions to go after a particular disease or target, they're always keeping these sorts of things in mind. So realizing that down the line there may be expanded scope for the drug could be an incentive to go into that area," says Krainer.