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Where are we with transformational therapies for patients with cystic fibrosis?

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The disease cystic fibrosis (CF) is caused by a disturbance in the synthesis or function of the CFTR anion channel. Several types of small molecules geared to overcome the underlying defect in specific patient groups are in the clinical pipeline. Two drugs have obtained regulatory approval. The potentiator ivacaftor brings major clinical benefit in patients with CFTR protein expression at the cell membrane; the combination ivacaftor plus corrector lumacaftor brings a modest benefit for patients homozygous for the most common mutation F508del. The busy drug pipeline puts pressure on the finite CF patient population. Improving CFTR function in patients has at times yielded unexpected findings. The initial success with ivacaftor has set high expectations, has pushed drug prices sky high and has resulted in inequity in drug access.

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Introduction

Cystic Fibrosis (CF) is a disease of ion channels. The primary defect is in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that encodes an anion channel protein in epithelial cell membranes. *CFTR* mutations will lead to a defect in the quantity and/or function of the CFTR channel [1••]. Depending on the underlying defect there is need for small molecules called correctors to increase CFTR expression at the cell membrane and/or small molecules called potentiators to enhance the function ('gating') of the CFTR channel (see Table 1). Therapies with read-through molecules aim to overcome premature stop codon mutations. CFTR stabilizers increase the protein residence time at the cell membrane. CFTR amplifiers stabilize the nascent CFTR mRNA and hence open the potential for more efficient protein translation to be then corrected or potentiated. At least half of the patients carry 2 different *CFTR* mutations on their CF alleles. In addition, most *CFTR* mutations lead to a combination of defects: production, function as well as residence time at the cell membrane are impacted. Hence combination therapies to overcome these several defects must be developed. This article gives a state-of-the-art overview of small molecules to improve CFTR function, with a focus on recent clinical trials and lessons learned. For a more extensive discussion of this rapidly evolving area, we refer to previous reviews [2,3•,4,5].

Current state of affairs

So far ivacaftor (^{TM}Kalydeco) and the combination lumacaftor plus ivacaftor (^{TM}Orkambi), developed by Vertex Pharmaceuticals, are licensed for clinical use [6••,7]. These drugs are in general well tolerated although side effects occur in some patients such as elevated liver enzymes (both drugs), possible lens opacities (Kalydeco), shortness of breath (on initiation of Orkambi), slight increase in blood pressure (Orkambi) [https://www.medicines.org.uk/emc/medicine/27586 and https://www.medicines.org.uk/emc/medicine/31534]. Kalydeco is approved for use in patients older than 2 years who have at least one class III mutation (associated with defective channel opening [1••]); on average, this is around 5% of the CF population worldwide, although there are large inter-country differences [8•]. Kalydeco leads to an approximate 10% predicted absolute rise in forced expiratory volume in 1 second (FEV_1) and an impressive decrease in sweat chloride concentration (~50 mmol/L) [6••,7,9,10]. Patients have fewer pulmonary exacerbations, a marked weight gain and report a better quality of life. The treatment benefit is sustained and the long-term benefits become apparent: less frequent Pseudomonas infections, slower decline in lung function, longer survival and less need for lung transplant [11,12••]. Kalydeco is also approved for patients with the class IV mutation R117H that is associated with residual CFTR function [1••]. In these patients, the benefit is modest and mainly observed in adults [13]. Orkambi has been approved for patients homozygous for the F508del mutation aged at least 12 years (by the European Medicines Agency) or 6 years (Food and Drug Administration in the USA). Almost 50% of patients worldwide are homozygous for F508del, but again with large inter-country differences [8•]. Treatment with Orkambi in F508del homozygous patients results in ~3% improvement in FEV_1 and

Table 1

Terminology used to describe small molecules designed to overcome defects in the synthesis or function of CFTR.

Therapy type	Aim	Mutation class targeted	Administration route	Stage of development
Correctors	Improve mutant CFTR trafficking and folding	Class II	Oral	Lumacaftor in use; Next generation correctors in clinical trial
Potentiators	Increase mutant CFTR channel opening	Class III (Class IV, Class V)	Oral	Ivacaftor in use; Alternative potentiators in clinical trial
Amplifiers	Increase mRNA stability	All	Oral	In clinical trial
Stabilizers	Increase protein residence time at cell membrane	All	Oral	Preclinical (after failure of cavosonstat)
Read-through compounds	Overread premature stop codons during translation	Class I	Oral	Preclinical (after failure of ataluren)
Antisense oligonucleotides		-F508del -Splicing mutations	-Inhalation -Most likely inhalation	-In clinical trial -Preclinical

Many CFTR mutations have characteristics of more than one mutation class. Mutation class defects include: class I failure of synthesis (mainly large deletions or premature stop codons mutations); class II defective folding or trafficking (F508del, many missense mutations); class III defective channel opening (specific missense mutations with retained trafficking to cell membrane; mutant CFTR protein rescued by corrector therapy); class IV defective conductance (R117H, some missense mutations); class V decreased normal protein synthesis (mostly splicing mutations); class VI decreased protein stability at the cell membrane (specific mutations and mutant protein rescued by correctors).

a 35% decrease in pulmonary exacerbations [7]. There is some indication that the drug decreases lung function decline [14]. In children aged 6–11 years, lung clearance index, a sensitive measure of ventilation homogeneity, improved by 1 unit and sweat chloride concentration decreased on average by 25 mmol/L but was highly variable [15].

Tezacaftor (Vertex Pharmaceuticals) is an F508del corrector with improved pharmacokinetic properties. Although not yet published, clinical trial data have been press-released showing that the combination of tezacaftor (100 mg once daily) plus ivacaftor (150 mg twice daily) given for 24 weeks to more than 500 patients homozygous for F508del older than 12 years resulted in a 4% predicted improvement in FEV_1, a 35% decrease in pulmonary exacerbations, a significant improvement in body mass index as well as in the patient reported outcome 'CFQ-R' [http://investors.vrtx.com/releasedetail.cfm?ReleaseID=1019156]. Although the improvements seen with 1 corrector (lumacaftor or tezacaftor) plus a single potentiator (ivacaftor) are significant, the combination of 2 correctors with different mechanisms of action appears to be needed to induce a robust improvement in F508del protein folding and trafficking and obtain a much improved expression of F508del CFTR at the cell membrane [16]. In Ussing chamber studies on human bronchial epithelial cells [HBE] triple combination with either VX-152 or VX-440 (Vertex Pharmaceuticals) improved chloride transport to respectively 75% and 68% of normal in F508del/F508del HBE and to about half that in F508del/minimal function HBE's [17]. These results in F508del/F508del HBE are even superior to the *ex vivo* efficacy of ivacaftor in G551D/F508del HBE (48% of normal) [17]. And indeed, the results of the phase 2 trial (4 weeks intake of VX-440 plus ivacaftor and tezacaftor) show a 10–12% improvement in FEV1 in F508del/minimal function patients compared to placebo. Homozygous F508del patients were first treated with ivacaftor/tezacaftor and on addition of VX-440 a further 10% improvement in FEV_1 was seen. Patients reported a marked improvement in wellbeing, and sweat chloride dropped significantly. The combination treatment was overall well tolerated and safe (http://investors.vrtx.com/releasedetail.cfm?ReleaseID=1033559). Vertex Pharmaceuticals has alternative second generation correctors in the phase 1 clinical pipeline, including VX-659.

Galapagos/Abbvie have similar triple combinations (first and second generation correctors, C1 and C2, plus potentiators) under development but their program is less advanced: C1 GLPG2222 and potentiator GLPG1837 are in phase 2 clinical trials and C2 GLPG2737 is in phase 1 [http://www.glpg.com/clinical-pipelines]. Several backup compounds are in the preclinical phase. Additional companies that are developing CFTR modulators include Flatley Discovery Lab, Proteostasis, Novartis, Genzyme, Pfizer and Reata.

QR010 is being developed by ProQr Therapeutics. Through an as yet incompletely understood mechanism, the small chemically modified RNA oligonucleotide inserts the 3 deleted bases in the F508del-CFTR mRNA. Although to be used via inhalation, the biodistribution and long half-life in mice suggest the potential of a systemic treatment benefit [http://www.asgct.org/the-vector/volume-1-issue-17-july-2015/meeting-center/gene-modulation-and-editing-for-lung-disease]. In an open label study of nasal administration of QR010, the CFTR function measured via nasal potential difference test improved in patients homozygous for F508del [18]. Safety and efficacy of single and multiple ascending doses of QR010 via inhalation are currently being tested.