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# Overview of CFTR Modulators and Gene Therapy

*Catherine Rang, Tom Kotsimbos and John Wilson*

## Abstract

Individuals with cystic fibrosis (CF) have seen a substantial change in their life expectancy since the introduction of coordinated multi-disciplinary care. This is expected to continue with the recent availability of treatment options that focus on targeting the underlying genetic defect. Two different approaches to altering the consequence of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene include “genetic medicines”, in particular gene therapy, and CFTR modulator agents. Gene therapy requires further development prior to it being a treatment option because to date the best clinical outcomes are that of a reduction in the rate of lung function decline. Modulator therapies on the other hand have provided exciting results in both clinical trials and real-world settings. Potentiator agents alter dysfunctional ion channel gating and are suitable for gating mutations. Corrector agents target abnormal protein trafficking. The combination of potentiator and corrector therapy provides options for homozygotes with the commonest mutation Phe508del and for those with Phe508del and some residual function mutations. Newer modulator therapies are in continued development with progressively impressive outcomes. It is likely that future CF care will comprise of personalized strategies with the focus centered upon an individual’s specific mutations.

**Keywords:** cystic fibrosis, CF pathophysiology, CFTR modulator therapy, gene therapy

## 1. Introduction

Cystic fibrosis (CF) is an autosomal recessive condition that results from mutations in the cystic fibrosis transmembrane conductor regulator (CFTR) gene located on the long arm of chromosome 7. The gene was identified 30 years ago and since then over 2000 CFTR mutations have been discovered with more than 300 known to be disease causing [1, 2]. The commonest mutation is Phe508del (F508del; c.1521\_1523delCTT), where a phenylalanine is substituted at position 508 on chromosome 7. Worldwide approximately 80–90% of individuals with CF have at least one copy of the Phe508del-CFTR mutation, although mutation rates varying depending upon the population cohort [3–5].

CF is a multi-system disease with the highest disease prevalence being in Europe, North America and Australia. There are approximately 80,000 people with CF worldwide. The disease is characterized by chronic airway infection, pancreatic insufficiency and malnutrition, diabetes, liver disease, absent vas deferens and premature death.

Due to the multi-system nature of the disease, treatment has classically focused on therapies and systems of care that aim to improve salt and fluid balance and nutritional status, alongside reducing airway inflammation and lung parenchymal destruction. These multi-disciplinary management approaches have been instrumental in the improvements seen in life expectancy. The median predicated survival of an individual born today with CF is 47 years, compared with 20 years at the time when CFTR was discovered in 1989 [2]. However, to have a true impact upon the management of these patients and to alter the disease trajectory, treatment options needed to also include approaches targeting the underlying genetic mutation.

This chapter will include a review of the structure of the CFTR protein, its biosynthesis and the pathophysiology of CF so as to provide a basis from which to discuss the various therapeutic strategies that have more recently been developed for modulating CFTR protein function. Also, a discussion regarding gene therapy will be included so as to enable contrasts and comparisons to be made between the different therapies being evolved to address the underlying genetic defect in CF patients.

## **2. Pathophysiology of cystic fibrosis**

### **2.1 CFTR protein structure**

CFTR codes for a complex protein, which is present in every nucleated cell of the body, however it is normally concentrated on the apical membrane of epithelial cells, primarily within the glandular epithelia. High expression of this apical anion channel is seen within the lungs, pancreas, gastrointestinal tract, vas deferens and sweat glands; reflecting the main organs affected in CF [6].

The CFTR protein is a large, unique member of the subclass C family of the ATP binding cassette (ABC) transporter proteins, which functions as an ion channel rather than an active transporter protein [7–9]. It consists of two membrane-spanning domains (MBDs) that form the ion channel. These domains are both connected to two cytoplasmic nucleotide-binding domains (NBD1 and NBD2), which function to gate the channel. This conformation of two MBDs and two NBDs that hydrolyse ATP are typical for most ABC transporters. However, CFTR has an additional cytoplasmic regulatory domain (R domain), inserted between NBD1 and MSD2 linking the two transporter domains. Phosphorylation of the R domain by protein kinase A enables channel opening to occur and channel activity is increased upon phosphorylation. Once phosphorylation has taken place, ATP binds to the NBDs resulting in the two NBDs forming tightly interacting dimers, which gates the channel. These movements are transmitted to the MBDs causing the ion pore to open. Channel closure results from ATP hydrolysis. The exact mechanisms underlying the regulation of the R domain and ATP-dependent gating are still not completely understood [10, 11].

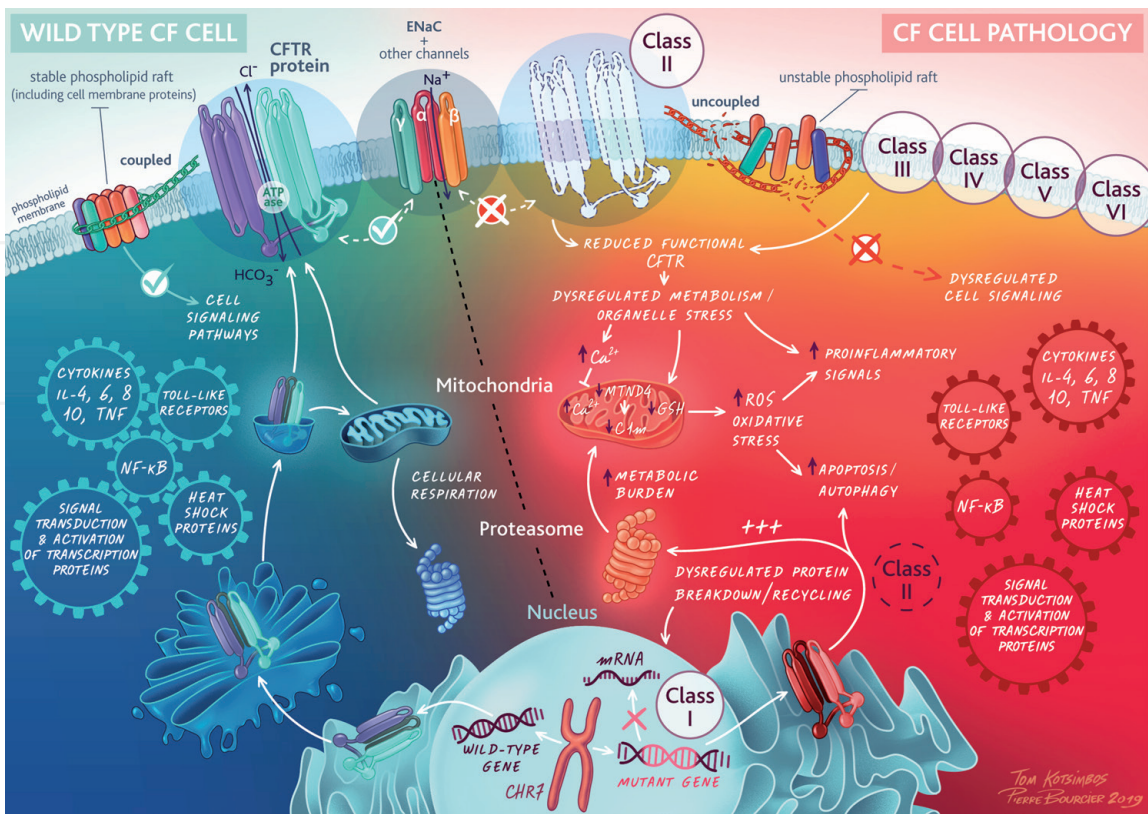
### **2.2 CFTR protein synthesis**

CFTR protein synthesis is a complex process, in part related to the size of the functional protein. As with all protein synthesis, transcription of the CFTR DNA takes place within the nucleus to create the messenger RNA (mRNA), which is transported across the nuclear membrane to the cytosolic ribosomes. There the initiation of translation occurs to create a 1480-amino acid polypeptide chain based upon the genetic code. Initially a 135- to 140-kDa core-glycosylated precursor is produced (immature CFTR). CFTR biosynthesis then proceeds through the endoplasmic

reticulum (ER) followed by the Golgi apparatus to a mature 150- to 160-kDa CFTR form which has undergone conformational folding [12]. During the secretory pathway through the ER to the Golgi and then on to the cell membrane various post-translational modifications take place (**Figure 1**).

The maturation process to create the final relatively compact CFTR protein structure is inefficient and slow. Less than 30% of newly synthesized wild-type (wt) immature CFTR molecules develop into mature CFTR proteins. For folding of the polypeptide chain to occur chaperones are required, in particular the 70 k-Da heat shock proteins (HSP70) and calnexin. In cells of individuals with the Phe508del-CFTR mutation, almost all immature molecules fail to reach final maturity and thus are degraded. This is due to the quality control mechanisms in place within the ER, specific signals and distinct processes exist that recruit misfolded proteins to the ER-associated degradation as a final endpoint. These proteins are then directed for degradation via the ubiquitin-proteasome pathway [12–14] (**Figure 1**).

Certain steps within the CFTR biosynthesis pathway are still unknown, however, data does support each domain folding independently. The native structure develops through a co-translational mechanism, possibly together with post-translational processes that take place to create the compactly folded domains. Domain-domain interactions are key in the creation of conformationally correct CFTR [15]. Furthermore, it appears that CFTR is more sensitive to mutations in NBD1 compared with homologous mutations in NBD2, leading to issues with the conformational maturation of the whole CFTR protein. For example, the deletion of the Phe508 does not appear to grossly alter the structure of NBD1 but subsequent issues arise during the maturation process, possibly through the disruption of the interaction between NBD1 and NBD2 and despite each domain folding independently. Maturation thus requires precise folding of each domain together with the



**Figure 1.** Cell biology of CFTR - abnormal CFTR protein results in the uncoupling of CFTR dependent processes at all levels from intracellular dynamics to cell membrane function. Reproduced with permission of the © ERS 2020: *European Respiratory Journal*; DOI: 10.1183/13993003.02443-2019: Accepted for publication and in press.



correct inter-domain assembly to create a stable structure that will not be submitted to ER-associated degradation [13, 16].

If the protein passes through all the checkpoint steps within the ER, it can exit and be transported through the Golgi apparatus in vesicles where the removal and addition of new glycan units takes place, increasing the molecular size of CFTR. It is becoming clear that some wt-CFTR might bypass these processes in the delivery pathway to the plasma membrane. Once at the membrane, levels of CFTR vary depending upon the balance of anterograde trafficking, endocytosis and recycling. Recycling of internalized CFTR to the plasma membrane is thought to assist with sustaining a functional pool of CFTR at the membrane level [15].

### **2.3 Pathophysiology**

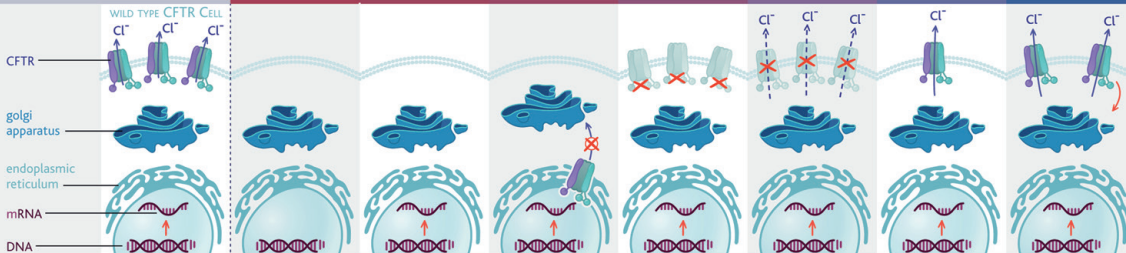
CFTR functions as a chloride and bicarbonate channel. Loss of functional CFTR proteins result in reduced chloride efflux from epithelial cells leading to depletion of the cell surface fluid and altering its pH and osmolarity. CFTR also regulates the activity of various other key processes within the cell, including the activity of other ion channels, such as the sodium epithelial channel (ENaC; the amiloride-sensitive sodium channel). Suppressed CFTR activity can lead to unopposed reabsorption of sodium and water via ENaC, causing additional dehydration of the cell surface layer [6]. Mucociliary clearance is further delayed due to abnormally adherent mucus. Dysfunctional CFTR also impacts upon mitochondrial function, the innate immunity and dysregulates inflammation [17–19]. Within the airways, this results in an environment that is susceptible to unchecked inflammation and chronic bacterial infection.

Although multiple processes both intra- and extra-cellularly are altered by dysfunctional CFTR proteins, chloride transport at the cell surface is generally considered to be the major driver of the pathophysiological disease. Functional chloride channel changes are thus likely to represent an easily accessible surrogate marker of all processes affected in CF, with sweat chloride testing being relatively easy to perform. In vitro studies have shown that only 6–10% of residual CFTR function is required to restore chloride transporting properties seen in 100% correct cells, with cell-cell coupling providing a means of amplification of the functional properties [20]. Individuals with CF who have approximately 10% CFTR expression per cell do not generally develop lung disease or the full range of classical CF disease. To date, it is unclear whether low level expression (10%) of CFTR in all cells is comparable to 10% of CFTR cells with full correction [21]. In addition, even individuals with a single CFTR mutation may have organ dysfunction in the context of a second “hit” such as smoking [22].

The general identification of mutations in the structure of CFTR has been centralized for clinician reference. CFTR2.org identifies over 2000 variants of the protein, of which over 400 are disease-associated. The majority of variants are rare and not confirmed to be disease-associated, however the large number of variants indicates the lack of stability of the CFTR gene in population dynamics [1].

### **3. Classification of CFTR mutations**

Classification systems of common CFTR mutations have been developed to assist with understanding of the consequential molecular defect. The established classification system includes six different classes (**Figure 2**). Different mutations can result in no functional protein production, impaired protein trafficking, altered channel gating, decreased channel conductance, reduced protein synthesis and decreased protein stability [6]. Each class confers a different disease severity, which

Traditional classification	CLASS I		CLASS II	CLASS III	CLASS IV	CLASS V	CLASS VI
Marson, Bertuzzo and Ribeiro's classification	CLASS IA	CLASS IB	CLASS II	CLASS III	CLASS IV	CLASS V	CLASS VI
De Boeck and Amaral's classification	CLASS VII	CLASS I	CLASS II	CLASS III	CLASS IV	CLASS V	CLASS VI
	No mRNA	No functional protein	No protein trafficking	Impaired channel gating	Decreased channel conductance	Reduced protein synthesis	Decreased protein stability
Specific mutation examples	Dele2,3(21kb), 1717-1G → A	Gly542X, Trp1282X	Phe508del, Asn1303Lys, Ala561Glu	Gly551Asp, Ser549Arg, Gly1349Asp	Arg117His, Arg334Trp, Ala455Glu	Ala455Glu, 3272-26A → G, 3849+10 kg C → T	c.120del23, rPhe508del
Treatment strategies	Unrescuable	Rescue synthesis	Rescue protein trafficking	Restore channel activity	Restore channel activity	Correct splicing	Promote protein stability
Medications	None	None	Lumacaftor-Ivacaftor, Tezacaftor-Ivacaftor	Ivacaftor	Ivacaftor (some mutations)	Tezacaftor-Ivacaftor (some mutations)	Tezacaftor-Ivacaftor (some mutations)
Clinical features	More-severe disease				Less-severe disease		

**Figure 2.**  
CFTR classification table. The classification systems divide mutations into discrete groups determined by the predominant CFTR defect. However, these systems may not be mutually exclusive for all mutations. For example, the p.Phe508del-CFTR is predominately class II but does also have some class III and class VI properties. Reproduced with permission of the © ERS 2020; European Respiratory Journal; DOI: 10.1183/13993003.02443-2019; Accepted for publication and in press.

is related to the degree of CFTR dysfunction and has prognostic implications for patients. However, each mutation may have features of more than just one class. For example, Phe508del is predominately a class II mutation but also has both class III and class VI properties. More recently, other classification systems have been proposed, which subdivide class I mutations (no functional CFTR protein) into two groups so as to take into account whether the mutation leads to no mRNA or no functional protein [23].

4. Genetic medicines

Traditional CF care has focused upon the management of the systems affected in individuals with CF. However, the identification of the CFTR gene enabled researchers to focus on treatments strategies, which could address the underlying genetic defect. The major cause of morbidity and mortality in CF is secondary to lung disease. Hence, if abnormal CFTR in the lungs could be replaced with wt-CFTR during the neonatal period, prior to parenchymal lung damage or bacterial colonization, morbidity and mortality could be significantly altered within the CF population [24]. Various approaches have been investigated within the field of “genetic medicines” and unfortunately to date none are a viable treatment option outside of clinical trials.

“Genetic medicines” comprise of four different treatment approaches:

- i. **Gene therapy:** the delivery of wt-CFTR to the cell nucleus resulting in the production of normal CFTR protein;
- ii. **mRNA therapy:** the delivery of correct CFTR mRNA to the cytoplasm resulting in the production of normal CFTR protein;
- iii. **Gene editing:** repair of the mutant CFTR DNA with normal CFTR protein resulting. This requires wt-CFTR DNA to be delivered to the nucleus together with mRNA encoding a nuclease that causes a break in the DNA leading to recombination occurring;
- iv. **mRNA editing:** CFTR mRNA delivery to the cytoplasm leading to repair of the CFTR mRNA [21].

The potential benefit of these therapies is that theoretically they should be suitable for the treatment of all individuals with CF, regardless of genotype. Currently gene therapy has made the greatest advancement towards being a clinical treatment and so the main focus of this section will be around gene therapy.

As the respiratory system is so central to CF disease and because initial thoughts were that gene therapy targeting the lungs would be easy to deliver, locally directed gene therapy to the respiratory epithelium was the method of choice. Furthermore, gene therapy can complement any CFTR causing mutation. However, for such treatment to be successful various issues had to be addressed, including the choice of delivery vector, method of delivery to the airways, translocation of the genetic information and ultimately ensuring that there was appropriate expression of the normalized CFTR gene [25]. These various issues will each be discussed to provide insight in the difficulties experienced in trying to develop “genetic medicines.”

The lungs are comprised of terminally differentiated epithelial cells, which are slowly replaced by stem/progenitor cells. Any form of gene therapy must be able to be either repeatedly delivered to the terminally-differentiated cell surface or be able to alter the stem/progenitor cells within the lungs. However, the lung has evolved physical and immune mechanisms to protect against pathogens and particulate materials, which impacts upon choice of vector delivery [26, 27].

Delivery vectors are largely either viral or non-viral in nature with viral ones felt to be more efficient. This is because they have evolved to overcome the barrier mechanisms present within the lungs. Adenoviruses (Ad) and adeno-associated viruses (AAV) have a natural tropism for the lungs, are DNA-based and thus were the initial choices to study. Adenoviruses are small in size and thus to insert the CFTR DNA correctly within the adenoviral genome, viral DNA must be removed, impacting upon the viral cytopathic effect. These vectors were found to have poor efficacy due to the pre-existing and induced immune responses, and thus cannot be repeatedly administered as required for these treatments because of the short life span of bronchial epithelial cells.

Other viral vectors that have been investigated are recombinant lentivirus (rLV). These agents are RNA-based and can integrate into the genome. This can be advantageous as it ensures that the vector is passed down the cell lines during division but it also does have the risk of inducing insertional mutagenesis [21, 26, 28]. However, ultimately other vectors were needed to be formulated, ones which had a minimal risk of immunogenicity and thus could be repeatedly administered.

Non-viral gene transfer agents complexed to plasmid DNA were therefore developed [21, 29]. These have been more successful than their viral vector counterparts



and have been investigated in Phase IIb studies. Patients who were 12 years and older were treated with the non-viral CFTR gene-liposomal complex pGM169/GLG7A as a nebulized therapy over a one-year period. The repeated nebulization each month resulted in a reduction in the progression of CF lung disease by a modest amount when compared with placebo. The percentage change in the forced expiratory volume in 1 second (FEV<sub>1</sub>) over 12 months was −0.4% versus −4.0% in the placebo arm. Hence, although no improvement in lung function was seen, this study was promising as rate of lung function decline does impact morbidity and mortality in CF. However, disappointingly also there were no improvements in quality of life measures [30].

As described in the above study the agents utilized were delivered via inhalation methods. This has been found to be the easiest method for repeated treatment applications. However, difficulties have arisen ensuring adequate lung deposition of drug, related to particle size and the type of nebulisers used. Additionally, any aerosolised drug delivered must retain its biological function post-delivery [31, 32].

Other strategies for ensuring corrected CFTR protein production is through mRNA therapy and mRNA repair as described above. The benefit of these approaches is that they do not require translocation of the therapy across the nuclear membrane. Nanoparticle-chemically modified mRNA has resulted in lung function improvements in animal models without any immune reactions despite repeated applications. Also, there is evidence that these therapies can restore chloride channel activity [33, 34]. Ongoing work and investigation are required prior to these options being viable in the clinical setting.

## 5. CFTR modulator agents

CFTR modulator agents are small molecules which ‘modulate’ the function of the abnormal CFTR protein. Unlike gene therapy, they do not alter the CFTR gene. However, these agents do manipulate the underlying genetic consequence of CF mutations. Currently two different classes of modulator agents have been developed;

- i. potentiators which ‘potentiate’ the cAMP-mediated gating of the CFTR channel; and
- ii. correctors which ‘correct’ defects in protein trafficking.

### 5.1 CFTR modulator drug design

High-throughput drug discovery programs enabled the development of such agents. These discovery programs were established to identify active compounds (“hits”) from large chemical libraries suitable for industrial-scale screening. High-throughput screening (HTS) assays need to be robust, have high throughput using small sample volumes together with adequate sensitivity, reproducibility and accuracy to ensure differentiation between a very large amount of compounds [35]. Ion channels are key targets for drug design and thus HTS have been an important part of such drug discovery processes, including for CF [36, 37].

The two classes of small molecules for CFTR protein modulation were identified via HTS techniques from libraries that consisted of chemically diverse drug-like and lead-like compounds acquired from both commercial vendors and internal medicine chemistry programs. If compounds had an activity >2.5 standard deviations (SD) from the mean, then they received further testing. For example, from



~164,000 synthetic compounds initial screened, approximately 100 were suitable for further study in one study [38]. The molecules identified were optimized and evaluated in terms of pharmacokinetics and toxicology [39, 40].

## **5.2 Potentiator therapy**

The first small molecule clinically available for individuals with CF following HTS was Ivacaftor (Kalydeco®). It is an oral CFTR potentiator agent, which can be given to CF individuals who have gating, residual function, splice or conduction mutations [41–44]. It was originally developed for the Gly551Asp-CFTR mutation (G551D; a class III mutation), which results in defective cAMP CFTR channel gating. The gating of the channel reflects the opening and closed states of the CFTR protein. If gating is defective, then a low probability of CFTR channel opening occurs and in turn reduced overall CFTR function. Ivacaftor treatment results in increased chloride transportation across the cell membrane by improving channel gating and thus the time that activated CFTR channels remain open.

The initial phase 3 studies in individuals aged 12 years and older (STRIVE) and those aged between 6 and 12 years of age (ENVISION) evaluated ivacaftor or placebo in patients with at least one Gly551Asp-CFTR mutation. STRIVE identified a significant improvement in percentage predicted (pp) FEV<sub>1</sub> in the treatment arm of 10% at 24 weeks (primary endpoint) that was maintained at 48 weeks. This was together with a 3 kg weight gain, an 8-point increase in the Cystic Fibrosis Questionnaire Revised (CFQ-R) score (an increase in the score out of 100 reflects an improvement in quality of life with a 4-point change being clinically relevant) alongside a reduction in sweat chloride to below the definite diagnostic threshold for CF to a mean of 47.8 mmol/l [41]. Similar results were demonstrated in children in ENVISION [45]. Participants from both of these studies were then enrolled into the open-labeled extension study (PERSIST) where all individuals received ivacaftor therapy. These individuals maintained the improvements in lung function, weight and exacerbation rates at 144 weeks [46].

## **5.3 Monotherapy for Phe508del mutations**

Such exceptional clinical outcomes were a major advancement in the treatment options for individuals with CF. However, initially modulator therapy was only suitable for approximately 5% of CF individuals as it was only available for gated mutations. Agents that could alter abnormal protein trafficking together with CFTR channel gating and cell membrane surface stability that results from the Phe508del-CFTR mutation (class II mutation) would have a far greater impact upon the CF community. As multiple stages in the CFTR conformational maturation process are affected with the Phe508del-CFTR mutation, different treatment approaches were needed.

HTS therefore progressed to evaluating agents that would be suitable for other mutation classes, focusing on agents could have an impact on dysfunctional protein trafficking [38]. Lumacaftor is an oral corrector agent, which in vitro studies have demonstrated can corrects protein misfolding [47]. However, monotherapy with either ivacaftor or lumacaftor did not lead to clinically relevant improvements in individuals homozygous for the p.Phe508del-CFTR mutation [48, 49].

## **5.4 Combination therapy: potentiator and corrector agents**

As monotherapy only lead to minimal clinically relevant outcomes for Phe508del-homozygotes, the argument strengthened for the use of lumacaftor in

combination with ivacaftor. Hence, these two therapies were trialed in combination (Orkambi®). Phase 3 multicentre studies (TRAFFIC and TRANSPORT) of this combination versus placebo elicited a modest gain in absolute pp. FEV<sub>1</sub> of 3% at 24 weeks (primary endpoint) together with significant increases in body mass index (BMI) [50]. The lung function increase being comparatively small to that seen with ivacaftor for gated mutation. However, importantly the 96-week open label extension study (PROGRESS), where all individuals within the initial trials received lumacaftor in combination with ivacaftor, did demonstrate a 42% reduction in the annual rate of lung function decline when compared with matched US registry controls [51]. As rate of lung function decline is known to correlate with morbidity and mortality, this is still a significant outcome [52, 53].

Although lumacaftor in combination with ivacaftor is associated with stabilization of lung disease together with weight improvement, patients can experience various side-effects. Respiratory related adverse events were the commonest complications in the trials and up to 7% of patients discontinued treatment in PROGRESS. In real-world experiences, there have been even higher discontinuation rates of up to 30% [54, 55]. Also, lumacaftor is a potent inducer of the CYP3A4 enzymes and can have interactions with various concurrent medications. Development of other corrector agents with an improved side-effect profile and the potential for enhanced correction of the protein trafficking were therefore required.

This led to the development of tezacaftor, another small molecule corrector agent. Tezacaftor in combination with ivacaftor (Symdeko®/Symveki®), for individuals homozygous for the Phe508del-CFTR mutation, when compared with placebo resulted in a 4% absolute improvement in ppFEV<sub>1</sub>, together with a five-point improvement in CFQ-R scores but without any significant change in BMI (EVOLVE). Although the increments in lung function were still not as substantial as that seen in ivacaftor use for gating mutations, the adverse events were much lower than with lumacaftor/ivacaftor treatment. The discontinuation rate in the active treatment arm was only 2.9% and none of these were due to respiratory events [56, 57]. It thus appears that the corrector lumacaftor has a poorer side-effect profile than tezacaftor, rather than it being a complete class effect. Tezacaftor/ivacaftor can also be given to patients who have certain residual function and splice mutations (*E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, D579G, 711+3A→G, E831X, S945L, S977F, F1052V, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5G→A, 3272-26A→G, 3849+10kbC→T*) [58]. Patients with Phe508del and a residual function mutation were studied in the phase III trial EXPAND, which was a crossover study where patients either received tezacaftor-ivacaftor, ivacaftor monotherapy or placebo. The patients were studied for two 8-week intervention periods separated by an 8-week washout period. Change in ppFEV<sub>1</sub> (the primary endpoint) was greatest in the treatment arms with a 6.8% increase with tezacaftor-ivacaftor and 4.7% increase with ivacaftor. Both therapies were associated with significant improvements in CFQ-R.

## 5.5 Future modulator therapy

The combination corrector therapies described, enable individuals with the commonest CF mutation the potential of receiving modulator therapy. However, lumacaftor/ivacaftor and tezacaftor/ivacaftor do not fully restore CFTR protein function. Furthermore, there is still no small molecule therapy for 30% of the individuals with CF who are heterozygotes for Phe508del and have a minimal function (MF) mutation. MF mutations give rise to either the production of defective proteins or no protein production. They include insertion, deletion, nonsense and canonical splice mutations. As up to 90% of CF individuals have one

Phe508del mutation, if small molecule therapy could significantly increase the amount of functional protein for this mutation, a greater range of CF individuals could be treated as then the therapy would be suitable for those individuals with the Phe508del-MF mutations.

Next generation CFTR correctors are under evaluation in combination with tezacaftor/ivacaftor. Phase 2 and 3 trials of these triple therapy agents; VX-659 and VX-445 have provided further exciting results. These corrector agents have a different structure and mechanism of action and provide additive function to the other two agents. For individuals homozygous for Phe508del an increase in absolute ppFEV<sub>1</sub> was 9.7% for VX-659 treatment and 11% for VX-445 therapy. Greater increases in lung function were seen for patients with Phe508del-MF mutations; the absolute change in ppFEV<sub>1</sub> was 13.3 and 13.8% for VX-659 and VX-445 respectively. These increases were also alongside significant improvements in quality of life and have been maintained in subsequent phase 3 interim report analyses [59–62]. These are incredible outcomes for individuals with more severe mutations and thus who typically have more severe disease phenotypes.

## **6. Implications of modulator therapy**

Important advances in the clinical outcomes for individuals with CF have been possible since the introduction of modulator therapy. Unfortunately these treatments are currently associated with a substantial cost and as a result are not available for all eligible patients. In the United States the Food and Drug Administration (FDA) has approved all four of the currently available modulator therapies. Some European countries and Australia, have access to ivacaftor, lumacaftor/ivacaftor and tezacaftor/ivacaftor [63]. However, worldwide there is significant inequality of access to these agents.

As an increasing number of modulator agents become available, the CF community will need to determine how they can enable patients to receive these expensive therapies. If funding bodies are going to approve them, it is likely that they will require significant clinical outcomes from their use, especially when funding is through a public system.

## **7. Future directions**

The introduction of modulator therapy, particularly when its use becomes widespread, is likely to have an impact upon the range of CF phenotypes. The amount of phenotypic variations should decrease as fewer patients have significant CFTR channel dysfunctional, and it is likely that the disease manifestations will be less severe. It is well known that respiratory related CF disease is associated with less than 10% CFTR channel function and so there is the potential for modulator therapy to have an impact upon this [21]. However, measurements of the degree of change in CFTR channel functionally with the use of modulator therapy is not being undertaken in the clinical setting. The markers being assessed are all surrogate markers of CFTR channel function and include lung function, sweat chloride, weight and quality of life questionnaires. Hence, it will be interesting to see the long-term impact of significant CFTR modulation on the CF cohort when individuals have been on such treatment for many years from birth. Currently a significant improvement is felt to be an increase in ppFEV<sub>1</sub> greater than 10%. Time will tell as to whether such changes have a significant impact upon this long-term multi-system disease.

## 8. Conclusion

The advancements in CF care over the last decade have been remarkable. The use of HTS drug discovery programs have been instrumental in enabling the development of the CFTR modulator agents, first the potentiators and subsequently the corrector agents. The fact that such therapies target the underlying consequence of the CFTR mutation has led to exciting clinical outcomes for individuals with certain CFTR mutations because altering the function of the CFTR protein at the molecular level is essential for true disease change to occur. “Genetic medicines” require a significant improvement in their clinical outcomes before they can become a viable option to modulator therapy. They do however have the advantage that they are not specific for individual mutation classes and could be used as treatment for all patients.

The introduction of newer targeted therapies is transforming CF care, although it remains to be seen how these treatments will impact the CF community in the longer term. Nevertheless, a shift is starting to occur whereby treatments are determined based upon an individual’s genetic mutations. It is likely that this will lead to a more personalized model of care and it is hoped a step closer to a cure for this life-limiting disease.

## Conflict of interest

CR – no conflict of interest. TK – Clinical Trial Support and Consultancy fees for Vertex Pharmaceuticals, Inc. JW – Clinical Trial Support and Consultancy fees for Vertex Pharmaceuticals, Inc.

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