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The TRIKAFTA to treat the Cystic fibrosis

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Abstract:

Cystic fibrosis currently has limited treatment options. This review focuses on the therapeutic potential of TRIKAFTA for treating this disease. We have compiled data from the National Institutes of Health (NIH) and analyzed the composition and mechanism of action of TRIKAFTA. Specifically, we examine how TRIKAFTA targets the F508del mutation, a common genetic variant in cystic fibrosis that results in the deletion of three nucleotides, leading to the loss of phenylalanine at position 508 of the CFTR protein. Our findings indicate that the components of TRIKAFTA effectively address this mutation. While this review provides a general research direction, further studies are necessary to fully understand and treat cystic fibrosis.

Keywords: Cystic fibrosis, TRIKAFTA, CFTR, F508del mutation, gene therapy

1. Background on Cystic Fibrosis

Cystic fibrosis (CF) is a genetic disorder with recessive inheritance, primarily based on mutations in the CFTR gene located on chromosome 7 at locus q31.2 encoding for cystic fibrosis transmembrane conductance regulator (CFTR) protein.

CFTR protein is localized in the epithelial cells of the organs with a main function to control the movement of salt and thus the water across the surface that is in contact with the tissues. It is common to see a production of thick and sticky mucus in people with CFTR problems, leading to blockage of airways and the pancreatic and pulmonary pancreas (Elborn, 2016). Ultimately, the sticky mucus can be the cause of bacterial lung infections, lung chronic inflammatory condition, and lung function loss.

Currently, there is no widely known cause of the cystic fibrosis at the level of molecular therapy. This genetic abnormality, sparsely identified in patients, should thus be the basis of the cure of cystic fibrosis. In fact, around 70% of persons affected with CF have inherited it from the delF508 mutation. This mutation arises from the deficiency of a phenylalanine at position 508 in the CFTR protein, implying pragmatically the destruction of the protein. In effect, only a small fraction of the CFTR protein reaches the apical surface, and the channel's chloride transport activity is abolished in the cytoplasm leading to clinical symptoms of cystic fibrosis.

2. Significance of CFTR Modulators

In general, cystic fibrosis (CF) management has been about supportive measures that aim at relieving symptoms and stopping episodes of disease worsening. These include airway clearance, proper nutrition, and use of antibiotics for fighting infections. Even though they are proven to be crucial tools in the fighting of the disease, these strategies never address the root cause of improper CFTR functioning. CFTR modulators have put the treatment of cystic fibrosis on a new and very hopeful path, as they attack the conditional factor underlying the disorder for individuals in possession of the particular mutation.

CFTR modulators can be faced with the three above mentioned scenarios that break themselves into third places-correctors, amplifiers and potentiators.

1) The correction is aimed to the naked CFTR molecule, by which it is made to fold correctly and trafficked in a correct way. Potentiators however, bring about all the channels of healthy CFTR once they reach the cell membrane, thereby enhancing their function.

2) Potentiator is an amplifier which increases overall production of CFTR protein (Ratjen *et al.*, 2019).

With D801del mutation, which is responsible for 90% of F508del mutations, TRIKAFTA seems to be the FTR of choice for the CF patients. When evaluating CFTR modulator in clinical trials, it was stated that TRIKAFTA is the most powerful of currently marketed modulators in terms of lung performance and was able to reduce incidents and ameliorate life quality (Heijerman *et al.*, 2019) due to the approval given by the US FDA in October 2019. The main purpose of this review is to take TRIKFTTA and everything that limits cystic fibrosis, from its mechanism of action to its clinical benefits and side effect profile,

and further discuss the future direction in this field. This review should serve as a knowledge synthesis platform for medical providers, clinical researchers, and patients to make informed decisions.

3. Cellular Biology of CFTR Dysfunction

Chloride transportation through cellular membranes is the main function of the CFTR protein, activating a chloride channel that allows chloride ion passage across the membrane. In well-being, normal secretions contain CFTR that contributes to the osmotic balance, relying on the function of the chloride channel. The function of the epithelial cells surfaces, tending to fluid sequestration or mucus dehydration, is disturbed when CFTR is loss-of-function due to CFTR mutations. Such mucus leads to mucociliary clearance, a situation where the lungs are not cleared of mucus, and to infections of the bronchi. Thus, the creation of a plug or the blockage of the bronchi follows. Failure of 'F508del' allele of the CF protein causes faulty processing, and perhaps designating the protein to mass degradation at the level of the endoplasmic reticulum antagonistic to its position at the cell surface. Thereby nearly at the cell surface, membrane protein has only a small amount of CFTR because the transit doesn't proceed according to the standard system (Sands *et al.,* 2015). This disorder of ionic homeostasis leads to the creation of complexions composed of hyper-viscous, as well as sticky mucus, permitting the clogging of the airways and impairment of the clearance of microbes by the system.

The persistent state of bacterial infections, which have developed in the presence of the fundamental problem common in CF patients, as well as compromised lung, are the chief ingredients for the so-called respiratory complications of CF. The mean value of the lifespan of the cystic fibrosis parentage, which was in the order of 20-30 years in just a few decades ago, has been significantly increased/ elongated during the time, primarily on account of the progress in care and management of it (Elborn 2016). Although, cystic fibrosis still has a harmful impact on the health of both children and adults, being a prominent source of morbidity and mortality. The Symptoms of Cystic Fibrosis is a complex genetic disease to affect many organs and systems. In fact, mainly the disease is detectable within the respiratory system symptomatically:

1) Chronic, persistent cough.
2) Wheezing.
3) Increased respiratory infections.
4) Worsening Congenital Lung Diseases.

In addition to the respiratory disorders, domination of cystic fibrosis on gastrointestinal functions is noticeably significant. About 85% of the subjects with CF3 develop the cystic fibrosis relative malabsorption of which is related to low efficiency of pancreatic exocrine function comparing to same-age individuals with other diseases or conditions, like diabetes (not related to cystic fibrosis). Too, it induces pancreatic fibrosis (Elborn, 2016). The following pathologic manifestations of this include bowel obstruction, and the obstruction of the bile duct as the cause of liver disease (cholestasis, biliary atresia) in this nexus. There are also numerous complications that are cystic fibrosis-related diabetes, which is seen frequently, infectious and low vaccine of males, and skeletal system complication that happens via inadequate absorption of vitamin D and Calcium (Ratjen *et al*., 2019).

CF is currently known as a disease, which is characterized by clinical diversity among individuals, among the most significant being the broad spectrum of CFTR mutations, which potentially impact environmental exposure capable of lung pathogen entry, access to extensive health care to help to provide preventive measures related to the onset of the disease. Great milestones in the early diagnosis and management of this disease have resulted in an exponential rate of improved longevity among cystic fibrosis individuals. Still, many obstacles have encountered the way of attaining full health among these individuals.

4. How Does TRIKAFTA Work?

Components of TRIKAFTA The CFTR modulator TRIKAFTA is the newest therapeutic option developed to target the specific molecular defects related to the F508del mutant gene present in all cystic fibrosis patients. This triple therapy delivers a multifaceted strategy to enhance the function of the CFTR protein that has two classes of deficiencies for CF patients with at least F508del alleles. Molecular Components of TRIKAFTA:

1) Elexacaftor (VX-445) F508del-CFTR protein, which undergoes trafficking improvement after treatment with elexacaftor, is a new-onset CFTR corrector with superior authority. It corrects the defects of membranous CFTR-CFTR interaction by stabilizing the conformational shape among the F508del CFTR residues. Moreover, it facilitates correct protein folding and trafficking through the secretory pathway, ER, and Golgi complex, and sustains the conformation of the fully processed CFTR protein at the cell surface.

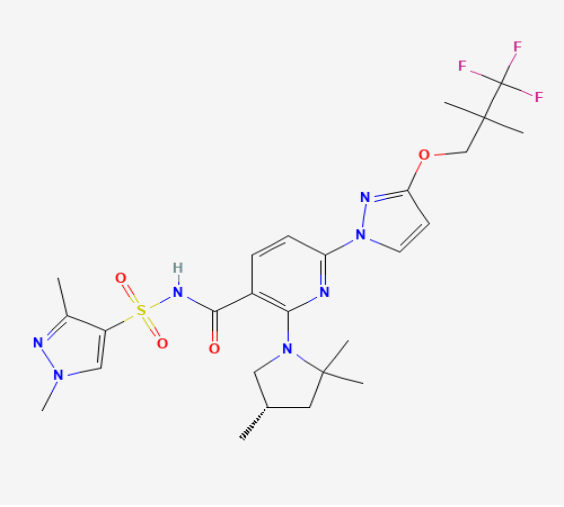

Figure 1. the chemical structure of Elexacaftor. Reproduced from https://pubchem.ncbi.nlm.nih.gov/compound/Elexacaftor#section=2D-Structure

2) Tezacaftor (VX-661) It is complemented and works side by side with elexacaftor as a CFTR corrector, a class that interacts with F508del-CFTR, having been shown to have conferred on adults and children the positive outcomes attached to ivacaftor use in clinical trials. It is a factor that: ·Comprises the CFTR protein the first transmembrane domain ·Evals the processing and intracellular trafficking of nascent CFTR molecules ·Is responsible for the stability of the mature CFTR to stick it on the cell surface ·The number of functional chloride channels available for transportations can be raised.

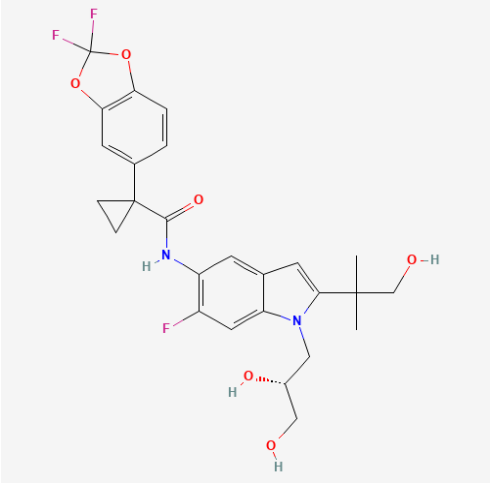

Figure 2. the chemical structure of Tezacaftor. Reproduced from https://pubchem.ncbi.nlm.nih.gov/compound/46199646#section=2D-Structure

3) Ivacaftor (VX-770) Ivacaftor is a powerful CFTR corrector and is the sole activator of ionization when through surface-localized CFTR channels it increases the function of surface-localized CFTR channels. Two functionally identical transmembrane regions, which together define the high-resolution open active state of CFTR, are involved in chimera formation.

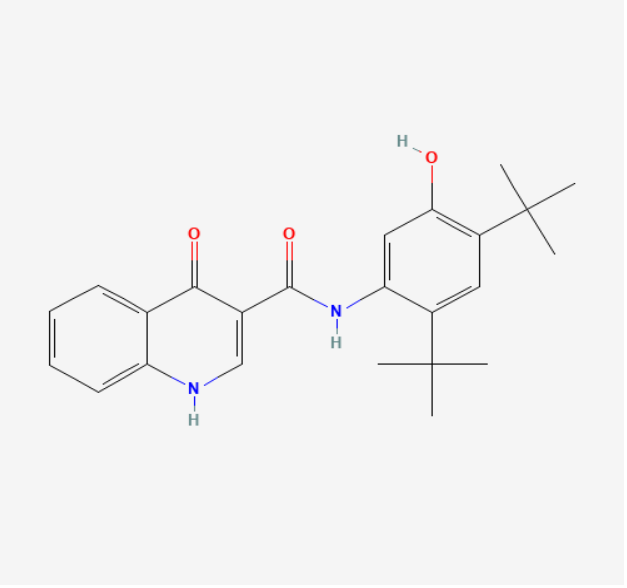

Figure 3. the chemical structure of Ivacaftor. Reproduced from https://pubchem.ncbi.nlm.nih.gov/compound/16220172#section=2D-Structure

The mechanism of action of ivacaftor includes:

1) Binding to the open-channel state of CFTR at the interface of the transmembrane helices.

2) Quickening the gating process of CFTR channels • Triggering the opening of CFTR channels.

Promoting efficient chloride and bicarbonate ion transit across epithelial cell membranes.

Synergistic Mechanism of Action Elexacaftor, tezacaftor, and ivacaftor three act then in harvesting an integral process, the result of which has a synergistic character:

1. Correction: Elexacaftor and tezacaftor are functional chaperons that walk the F508del-CFTR protein through the hindrance proper folding and transportation to the cell surface. The productive efforts from these two CFTR correctors appear to prop up the generation of not only improved but also substantial amounts of useful CFTR proteins that reach the cell surface.

2. Potentiation: once CNBF patients have their CFTR genes corrected, the corrected CFTR proteins are forced to the cell membrane where their function is restored using ivacaftor. The latter acts via enhancing the channel gating.

3.Stabilization: Members of the elexacaftor-tezacaftor-ivacaftor triplet boosts the combination by helping the CFTR protein to remain longer at the core of the cell surface and

thus prolong access to functional chloride ions' transport. This system of operation ensures a higher transfer of chloride ions through the cellular membranes as the basal defect in cystic fibrosis is corrected.

The binding between the being in contact with TRIKAFTA components and the CFTR protein in numerous phases of the protein's cycle is the core mechanism by which TRIKAFTA works:

Figure 4. this graph is shown as What the TRIKAFTA treat process. Reproduced from https://www.trikafta.com/

1. Co- and Post-translational Modification: The developing protein CFTR is joined by elexacaftor (and tezacaftor) during its synthesis and inception as soon as it enters the endoplasmic reticulum which facilitates domain folding. The assembled domain complex undergoes premature degradation by endoplasmic reticulum-associated degradation (ERAD) factors.

2. Protein Transport Boost: The enhancers manage to guide stable value CFTR transport through the Golgi network and to the cell surface because of the former [enhancers '»"correctors"] interacting with the protein-protein interactions and with the molecular chaperone modulation.

3. Functional Surface Retention: At the cell membrane, the enhancers have been implicated in this as they play a role in density/functionality of mature CFTR which reduces turnover of this protein and in turn increases its residence time in the cell surface.

4. Channel Activation: Ivacaftor hooks to the channel-open state forming near the surface-localized CFTR. This causes changes in its physical shape and facilitates opening of it, which in turn allows for ion flow.

The combined approach is the basically balanced regime, which eliminates the cause of the disease at three levels: a mutation-prevention, a cure for ER retention and reduced channel function. This elexacaftor-tezacaftor combination is responsible for correcting the errors, and when oxymoronic ivacaftor, a CFTR potentiator acting on the CFTR channel open and allowing chloride ion passage, it allows much more function protein to be delivered to the cell surface, which will result in effective cAMP-dependent regulation of sodium transport and mucus removal.

5. Pharmacokinetic and Pharmacodynamic Pharmacokinetics

Pharmacokinetic characteristics of TRIKAFTA, namely its absorption, distribution, metabolism, and excretion, has been conducted.

Elexacaftor and tezacaftor that are oral administrations are portrayed by shorter maximum plasma concentrations within 3 hours. Both drugs reach a steady-state rate, approximately 12 hours, and ultimately slough off within days after the onset of the administration of medication (Heijerman *et al.*). Both drugs elexacaftor and tezacaftor undergo extensive hepatic metabolism, which facilitates the induction of cytochrome P450.

This development in its metabolism is what causes it to use a few enzymes CYP3A4, its isoenzymes, in its activity. It is for this reason that there is high potential of drug-drug interactions with drugs that have a mechanism of release like that of TRIKAFTA. Moreover, the ethics should be observed of considering what the drugs the patient is on, especially when prescribing TRIKAFTA. This is the case even for other medications. It remains true also that the second oral absorption of Ivacaftor occurred with linear pharmacokinetics, which led to peak levels 4-6 hours after administration (twice daily). CYP3A is the principal pathway for a major part of ivacaftor metabolism, so that another CYP3A inhibitor with another structure might change the pharmacokinetics of ivacaftor. The coadministration of such agents might require the dose modification or can be monitored carefully.

According to the pharmacodynamics characteristics of TRIKAFTA, handling in the patient's lung function, lower rate of escalation of pulmonary symptom episodes, and a tendency of good life quality can be applied. It gets its breath aided in reinforcing the mechanism of defects repair which is achieved by the potentiators and correctors combination and raising the overall CFTR defect back to normal levels far beyond the increase achieved by the two classes individually.

It's showing that combo approach creates better disease modifier combinations available than that provided by the single class, which gives improved hope for people with F508del mutation (with the significance of restoration of CFTR function; for instance: ivacaftor-potentiator; lumacaftor-corrector) Interaction with the CFTR Protein In regard to biological importance of TRIKAFTA, we cannot ignore the poise of its parts to CFTR. The similar performance of elexacaftor and tezacaftor suggests that they are both have a comprehensive approach to target the same

CFTR portals that are functional under normal conditions and require different activation intervening its life cycle at the same time.

Elexacaftor increases a misfolded variant of exogenous CFTR by promoting correct cellular trafficking of the CFTR, which results in the CFTR being transported to the cell surface. And so, it transcends the fundamental inalterability of CFTR misfolding and mis localization in endoplasmic reticulum as was shown by (Sands *et al.*,2015). Once being folded and trafficked to its proper site of the cell membrane, Ivacaftor can effectuate not just the potentiated, but optimum functioning of the chloride ion transport channels.

The ongoing treatment systems contain the dual mechanism of action (CFTR and ENaC) that restores the ion-water environment to a physiological level, which is an efficient way of facilitating mucociliary transport in CF airways; this effect comes from the relevant hydration states (Heijerman *et al.*, 2019). Clinical trials have shown that TRIKAFTA not only provided therapy to the CF patient population, but also demonstrated remarkable improvements in the cystic fibrosis lung function, the quality of life, and the patient overall health status. This demonstrates that the genetic defect correction which result to great enhancement of CFTR activity, and particularly F508del mutations.

6. Clinical efficacy of TRIKAFTA

6.1 Improvement in lung function

The outcomes of clinical research on the efficacy of TRIKAFTA in lung function enhancement have been published in many clinical trials. A multicenter clinical trial, the PROGRESS study, assessed TRIKAFTA as triple therapy in patients aged 12 and older with at least one F508del mutation; the average increase in lung function from the baseline is around 13.8% and this level is considered clinically important. (Heijerman *et al.*, 2019).

6.2 Reduction in Pulmonary Exacerbations

The management of pulmonary exacerbations is one of the significant concerns in cystic fibrosis. This condition may lead to increased morbidity, frequent hospital admission, and, finally, pulmonary function deterioration. The clinical effectiveness of TRIKAFTA in pulmonary exacerbation reduction is demonstrated in several studies. In the PROGRESS study, which monitored the participants' pulmonary function, those who were receiving TRIKAFTA experienced a 63% reduction in pulmonary exacerbation rate in comparison to participants receiving the placebo (Heijerman *et al.*, 2019). Such a reduction in pulmonary exacerbations would mean an improved quality of life for the affected individuals and a decrease in healthcare utilization burden.

Long-term studies have also indicated that the sustained use of TRIKAFTA leads to a continuous decrease in exacerbation rates over time, reinforcing its potential as a cornerstone of cystic fibrosis management (Ratjen *et al.*, 2019). Through the repair of the underlying CFTR gene, TRIKAFTA manages or halts the impact of various factors that cause acute crises on the patient, thereby giving the patients a sense of lesser impact of the disease's course.

6.3 Impact on Nutritional Status

The nutritional status is the main component of caring the individuals with cystic fibrosis, too. Due to the presence of exocrine pancreatic insufficiency, they usually suffer from malabsorption of essential nutrients. The influence of TRIKAFTA on nutritional status has been researched in clinical trials, in which body mass index (BMI) and other nutritional markers subsequently improved in patients who received the drug.

Patients assigned to TRIKAFTA treatment in the PROGRESS trial recorded an average increase in BMI of 0.9 kg/m², while their nutritional measurements also significantly improved (Heijerman *et al.*, 2019). This difference part can be assured by promising factors like enhanced functionality of a pancreas and a better nutrition because of increased health status. At the same time, keeping an optimal nutritional status is crucial to every person with cystic fibrosis as it contributes not only to a better lung function, but also the correct growth, and a common health state.

6.4 Quality of life assessment

The effect of TRIKAFTA on the psychological and social aspects of QoL has generated much clinical interest, and several research were done utilizing well-validated patient-derived tools to assess these. To measure the quality of life in cystic fibrosis patients, the Cystic Fibrosis Questionnaire-Revised (CFQ-R) is a frequently used measurement tool.

During clinical studies, patients receiving the treatment have shown a significant increase in their CFQ-R scores upon treatment, signaling physical, emotional, and social improvement (Heijerman *et al.*, 2019).

6.5 Long-term Efficacy and Outcomes

The long-term efficacy of TRIKAFTA in the management of cystic fibrosis has become one of the hot issues in research, considering the chronic nature of the disease. As part of this, research is being conducted to find out whether long-term TRIKAFTA treatment can help with air moving in lungs, decrease of exacerbation incidence, and improvement of patients' overall health status.

The available preliminary data give an indication that the

early effects noticed with CFTR modulating treatment tend to be perpetuated or even become more impactful with longer use of the treatment. The experience of gainful change in lung function, nutritional status, and quality of life underlines the necessity of consistent use of CFTR modulating therapy in the long-term regimen. Ongoing use of effective CFTR modulation therapies will continue to inform clinical practice and treatment guidelines as more real-world data become available.

7. Safety and Tolerability

7.1 The occurrence of the common ones

TRIKAFTA safety is also established through clinical trials and real-world studies. Respiratory symptoms: In the first several weeks of treatment, some people may experience an intensified occurrence of these symptoms, like these found in bronchitis. Respiratory symptoms that appear might be explainable by improved sputum clearance and a drying of sputum during this period. Further analysis is required. Gastrointestinal symptoms: The reports like diarrhea, abdominal pain, and difficulty of nausea are noticed. These symptoms can be short-lived and mild (Heijerman *et al.,* 2019). A common adverse effect such as a headache could be associated with patient's overall health or medication change. A moderate and mostly transitory elevation of the liver enzymes has been observed as a side effect in some patients on TRIKAFTA (Ratjen *et al*., 2019).

Subtitle: The rate of the prescription combination of TRIKAFTA used along with plenty of medications can impose some patients' liver enzymes' rate. Overall, safety issues with TRIKAFTA are tolerable (most of the time, and they are under control), with tolerable intensity, which will generally outweigh risks, especially with substantial improvements to lung function and quality of life.

7.2 Long-term safety

As TRIKAFTA has been recently introduced to the mainstream medical practice, regular continuation of monitoring and research is essential to get the residual addition of potential risks to the existing knowledge about its safety. Evidence from post-marketing studies and real-world data will throw light on potential long-term consequences of TRIKAFTA use.

Over the timespan, clinical trials produce data regarding TRIKAFTA's (in general) well-toleration for the patients who use it.

Monitoring of drug interaction

Because of the CYP450 enzyme system playing a key role in drug metabolism, certain dosage corrections should be planned providing caution when using other drugs that also are CYP3A substrates.

Concomitant treatments that the patient is following, and which are metabolized by CYP3A may require their doses to be adjusted or proper monitoring to avoid an adverse reaction.

Future Directions in Cystic Fibrosis Research

7.3 Ongoing Clinical Trials

The discovery of TRIKAFTA has resulted in the initiation of new research programs in patients with cystic fibrosis, with numerous ongoing clinical trials examining its effectiveness in a variety of conditions including those with different CFTR mutations, severity of illness, and children. Active clinical trials have been investigating the long-term safety and efficacy of TRIKAFTA along with its outcomes on vital issues such as lung function, nutritional status, and quality of life over successive durations of time. Also, other potential therapeutic agents for the modification of CFTR's function in combination therapies will be explored.

7.4 Personalized Medicine Approaches Investigation

The cell and gene therapy in rare diseases like cystic fibrosis probably will expand over time, directing medications booming with tailored patients' individuality, defined by their CFTR mutation, course of disease, and genetic profile.

Medical professionals empower cystic fibrosis patients through the personalized medicine approaches, which allow to optimize treatment systems that take fully into account individual patients' diversity. This (method) certainly would contribute to increase effectivity, alleviate adverse side effects, and improve general patient well-being.

8. Conclusion

The introduction of TRIKAFTA has brought a new dimension to the management of cystic fibrosis, and it's mostly effective for those with the F508del mutation. As a molecular therapy correcting the basic defect of CFTR, TRIKAFTA has shown the impressive result in improvement of the lung functions, prevention of frequent exacerbations, and quality of life. Regarding the adverse effects, TRIKAFTA is secured by safe and endurable diminished frequency of life-threatening events.

Considering the nature of cystic fibrosis as incurable, continuous research is fundamental, with the hope of finding new ways to treat the disease, such as personalized treatment strategies, novel CFTR modulators, and the like. A patient-centered care model favors access to new therapies and, thus, facilitates more efficient treatment of individ-

uals with cystic fibrosis. Consequently, it fosters better health care experience and a situation where people with the disease don't have to struggle with a treatment with a non-local cure.

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