TARGETED CFTR MODULATOR THERAPIES FOR CYSTIC FIBROSIS

Alyssa Bell (abell@pitt.edu)

TARGETED THERAPY APPLIED TO CYSTIC FIBROSIS

Cystic Fibrosis (CF) is an autosomal genetic disorder that affects 70,000 children and adults worldwide [1]. CF is caused by mutations that alter either the formation or function of the Cystic Fibrosis conductance regulator (CFTR) protein [2]. The CFTR protein is a specific chloride ion channel in the epithelial tissue of the lungs [3]. The third most common CFTR mutation, G551D-CFTR, is caused by the replacement of an amino acid in the 551st nucleotide base of the CFTR gene sequence. With this mutation, the channel is properly formed, but it is unable to open to transport chloride ions out of the lungs. Without chloride transport, the lungs cannot maintain the proper salt-water balance, causing the accumulation of mucus, reduced lung performance, and infection.

For 23 years, scientists and bioengineers have been working to develop targeted modulator therapies capable of overriding the altered functioning of mutant CFTR proteins [2]. As defined by the Cystic Fibrosis Foundation (CFF), a modulator is a drug designed to target and override specific defects caused by a gene mutation [4]. Simply stated, modulators correct the effects of the mutation without correcting the mutation itself. Modulator therapies fit within the broader realms of targeted therapies where a drug pinpoints a specific cell or protein to maximize precision and minimize harsh side effects [2].

Luckily, ivacaftor, a targeted CFTR modulator therapy, has been recently approved by the Food and Drug Administration (FDA), and it has shown promising results. Clinical trials demonstrated reversal of the progression of CF and restoration of the patients’ lung function, leading to a lower the likelihood of infection [5]. Ivacaftor and other targeted CFTR modulator therapies still awaiting FDA approval are safer alternatives to bilateral lung transplants, the traditional treatment of CF, where both lungs are replaced by the lungs of a deceased donor with a matching blood type [4]. Even if a patient finds a matching donor, bilateral lung transplants only have a 10-20% success rate after 10 years [4]. Therefore, scientists believe targeted therapies are the future of CF treatment, as they are the safest, most ethical treatment option.

I believe the development of targeted CFTR modulator therapies is a pressing issue in medicine and engineering because Cystic Fibrosis is a quickly progressing, deadly disease, forcing thousands of children to grow up in hospitals instead of experiencing a childhood without worry and illness. Two summers ago, I took part in a research internship that showed me first-hand the traumas that the families of CF patients face. Every day, these patients are fighting to breathe solely because of a mutation. Targeted therapies can modulate and overcome the adverse effects of these mutations to save thousands of lives in the CF community.

CYSTIC FIBROSIS DESTROYS BODIES AND FAMILIES

Although there has been a remarkable increase in life expectancy over the last two decades, the average life expectancy of a patient with CF is still only 40 years [1]. Most CF-related mortalities are linked to the progressive deterioration of lung function due to mucus buildup, inflammation, and infection [6]. Some medications have been approved to treat these secondary side effects of CF, but until recently, scientists have been unsuccessful in formulating medications to target defective proteins, the root cause of CF [1]. Many of these primitive medications are in the form of aerosols, which can be blocked by mucus buildup on the epithelial tissue [6]. This mucus subsequently provides the ideal breeding grounds for bacteria, and repeated treatment with antibiotics can lead to antibiotic resistance and even worse infections [1].

CF patients are born into a life full of hardship as they fight to breathe every day. I strongly believe these patients should be able to enjoy the simple joys in life such as attending school or playing at a playground with their friends or children. Along those lines, the families of CF patients also feel the impact of CF financially and emotionally. For all these reasons, I feel that it is imperative that researchers and engineers work to find personalized solutions to modulate the gene mutations to stop their adverse effects.

CFTR’S ROLE IN CYSTIC FIBROSIS

Cystic Fibrosis is an autosomal recessive disorder caused by mutations in the Cystic Fibrosis trans-membrane
Alyssa Bell

conductance regulator (CFTR) gene, which is inherited by each of two carrier parents [6]. The third most common CFTR mutation is G551D-CFTR, a mutation in which glycine has been replaced by aspartate in the 551st nucleotide base in the CFTR gene sequence of the Nucleotide Binding Domain (NBD) [1]. The NBD is the end of the CFTR protein responsible for the binding and transport of charged ions, such as chloride. The G551D-CFTR mutation has been shown to alter the electrostatic interactions of the NBD by introducing a negative charge [7]. This negative charge causes a closed channel configuration, inhibiting the movement of chloride through the membrane of lung cells. Without the proper transport of chloride ions, mucus accumulates inside the warm lungs, creating the perfect breeding ground for bacteria. Fortunately, G551D-CFTR has been identified by researchers as the mutation most likely susceptible to targeted gene therapy [3].

In fact, I took part in preliminary research on this mutation two summers ago during an internship with the University of Pittsburgh Cancer Institute Academy. Through the Bioengineering and Genetics Department, I worked under Dr. Patrick Thibodeau to test the conformational and functional alterations of the G149D mutation expressed in E. Coli. This mutation is the genetic equivalent of G551D-CFTR in humans. Dr. Thibodeau and I hypothesized that the introduction of charge caused by this mutation may alter the protein’s ability to bind chloride ions. Our results verified that this mutation alters the electrostatic interactions in the NBDs, blocking the ion channel and therefore inhibiting its transport activity.

Based on my summer research, I believe engineering a medicine able to counteract the G551D-CFTR’s altered electrostatic properties would be revolutionary in the progression of targeted therapies for CF mutations. Scientists are currently working towards a method of stabilizing the closed channel of the mutant G551D-CFTR to maximize its openings, thereby allowing for proper chloride transport [3]. Ideally, researchers would like the synthesize a drug to achieve the equal average opening times in the G551D-CFTR protein channel as in wild type [7]. Luckily, one therapy recently developed has shown promising results with the G551D-CFTR mutation, giving it the potential to save thousands of lives in the CF society [2].

IVACAFTOR: THE FIRST TARGETED CFTR THERAPY

One successful targeted drug therapy for CFTR modulation is ivacaftor. Ivacaftor, also referred to as Kalydeco, is a CFTR potentiator developed by Vertex Pharmaceuticals [5]. A potentiator is one type of modulator in which a substance is designed to increase the function of mutant CFTR proteins by extending the time that the ion channel is open [5].

Overall, clinical trials of ivacaftor have demonstrated increased chloride-transport in the G551D-CFTR protein, leading to a better quality of life overall for the patients involved (based on the CF Questionnaire) [5]. These findings validate the idea of targeting specific CFTR mutations [5]. In the 24-week double-blind trial, patients were either given 150mg of ivacaftor or a placebo every twelve hours while continuing their preexisting regimens. [1]. Over this period, those receiving ivacaftor had a lower risk of pulmonary exacerbation (the worsening of symptoms requiring stronger medications) and improved lung function by about 10% [5]. CFTR is responsible for the reabsorption of chloride in sweat ducts, and ivacaftor is also the first drug able to reduce sweat chloride levels past the threshold of CF diagnoses [5]. Therefore, it is believed that ivacaftor is the first targeted drug to improve the CFTR chloride ion transport specifically for G551D-CFTR, to stabilize progressive lung disease [8].

Ivacaftor was approved by the FDA for treatments of CFTR mutations affecting the function of the protein (like G551D-CFTR) [1]. FDA Commissioner Margaret Hamburg believes “Kalydeco is an excellent example of the promise of personalized medicine – targeted drugs that treat patients with a specific genetic makeup” [9]. Within the first two years of its approval, ivacaftor has successfully treated nearly 2,000 patients with G551D-CFTR worldwide [10].

The continuation into the development of targeted therapies will attempt to cure CF at its source without the harmful side effects associated with broad treatment regimens, such as aerosols and antibiotics. Ivacaftor and the similar targeted therapies currently being developed will enable CF patients to move freely through their lives without struggling to breathe. Targeted therapies not only work more effectively than broad treatments, but they also lead to less resistance and tolerance over time [2].

ENGINEERING GOING FORWARD

The understanding of the G551D-CFTR mutation and then the successful engineering of ivacaftor are the first steps down a long road of engineering targeted therapies to improve CFTR protein function to treat CF at its source. Researchers are currently working towards more specific, highly efficient CFTR modulator therapies to correct the adverse effects of various CFTR mutations [4]. However, there are over 200 known CFTR mutations causing CF, which makes the creation of any form of targeted treatment both painstaking and intricate [2]. With that, prescribing targeted CFTR modulation therapies requires genetic testing to pinpoint the CF-causing mutations, which is a controversial topic in medicine [7]. However, I believe this genetic testing is worthwhile, because doctors will be able to accurately diagnose the specific mutation causing the patient’s CF and then prescribe the correct therapy accordingly. Still, targeted therapies are a safer, more effective option to aerosol treatments (that can be blocked by mucus) or bilateral lung transplants (that carry a low survival rate).
There are now over 24 drugs in the “Cystic Fibrosis Foundation Therapeutics Pipeline” waiting to gain FDA approval, each of which may take one to three years to pass through all of the stages of clinical trials [8]. However, the CFF is in the process of staffing a specialized laboratory devoted to precise drug development for all CFTR mutations, making CF patients and their families are ecstatic over the recent push for CF drug discovery [11].

Coincidentally, the extreme success of ivacaftor funded this endeavor [11]. The CFF is the perfect example of the possibilities within the medical and engineering fields when academia, industry, government, patients, and the community work as one unit to develop a cure [10]. Even the FDA Commissioner admires the work of the CFF, praising “the unique mutually beneficial partnership that led to the approval of Kalydeco [because it] serves as a great model for what companies and patient groups can achieve if they collaborate on drug development” [9]. I would like to join this effort to provide therapies for all forms of CF, because I believe drug discoveries are still vital for rare forms of diseases. In my eyes, any therapy that will save lives is a complete success no matter the profit.

Ivacaftor, the first targeted CFTR modulator therapy, was approved 23 years after the initial discovery of the CFTR gene [2]. The CFF is continuing its efforts, believing that “as genetically-targeted treatments move through the CF drug pipeline and on to patients, this disease is at the forefront of a new era in personalized medicine and is a model for what can be achieved when stakeholders collaborate on the development of treatments for a rare disease” [10]. The concept of targeted therapies and precision medicine opens many opportunities in the world of engineering in medicine, as scientists and engineers work to create more precise medicines with fewer harsh side effects.

Although I lean towards precision medicine and targeted therapies, I am aware of the alternative options currently being researched, such as gene editing and stem cells. I believe our current focus should remain in targeted therapies, but I am hopeful that researchers may one day discover ways to permanently restore dysfunctional CFTR proteins with gene editing, RNA therapy, or stem cells rather than simply chemically repairing the effects of the CFTR mutation [8]. As William Skach, vice president of research affairs at CFF, has stated, “If we can use gene-editing tools to fix the mutations in CF patients, then we can basically cure CF once and for all. That’s where we want to go” [11]. Although the definitive cure of CF may be gene editing, I believe it is best to focus on the modulation therapies currently in development to reverse the side effects of CF and extend patients’ lives.

SOURCES


ACKNOWLEDGMENTS
First, I would like to thank my parents and my sister, Sam, for always supporting me. They have always made sure I’ve succeeded in everything I’ve done. I would also like to thank Mr. Fredrick Ebert, my high school chemistry teacher for teaching me to believe in myself. I would not be at Pitt typing this paper for my engineering class if it weren’t for him.

Thirdly, I’d like to thank Dr. Patrick Thibodeau for welcoming me into his lab as a high school student and showing me that research is a collaborative field, as well as helping me throughout the college decision process. Lastly, I’d like to thank Laura Waxman and Barbara Edelman, for reviewing my paper in the Writing Center.