Research We Fund

Contents

Research We Fund ........................................................................................................................................2
  Laboratory Research Support ..................................................................................................................5
  Clinical Research Support .....................................................................................................................6
CFTR Modulation .....................................................................................................................................7
  Triple-Combination Modulators ...........................................................................................................7
  Theratyping ............................................................................................................................................8
Treating CF Complications .......................................................................................................................9
  Overview ...............................................................................................................................................9
  Infections .............................................................................................................................................10
  Mucus ................................................................................................................................................12
  Inflammation .......................................................................................................................................12
  Digestive System .................................................................................................................................13
  CFRD and Reproductive Health ...........................................................................................................13
  Lung Transplant ..................................................................................................................................14
CFTR Restoration (Nonsense/Rare Mutations) .......................................................................................15
  Readthrough Screening Programs .......................................................................................................15
  RNA Therapy ........................................................................................................................................16
Cystic Fibrosis Foundation Therapeutics Lab .......................................................................................17
Cure .........................................................................................................................................................18
  Gene Editing .......................................................................................................................................19
  Gene Delivery .......................................................................................................................................19
  Stem Cell ............................................................................................................................................19
Research We Fund
The Cystic Fibrosis Foundation remains the world’s leader in the fight against CF, and our scientific portfolio reflects our ambition to provide effective treatments and -- one day -- a cure to every individual with this disease.

We recognize that the needs of the cystic fibrosis community are complex, and no pace is fast enough when you or your loved one is waiting for a treatment. We will leave no stone unturned. Any science that we believe holds real promise will be funded. We will explore every strategy with the potential to cure CF. We will work tirelessly to ensure that all people with CF can live full, healthy lives and have hope for the future.

Over the past six years, our research budget has more than doubled. In 2019, we are projecting to spend nearly $220 million on medical awards -- and if emerging science shows promise, we will go further.

The Cystic Fibrosis Foundation’s unwavering focus on CF research has resulted in at least 10 therapies to treat the disease. We have made incredible strides, including the approvals by the U.S. Food and Drug Administration of inhaled aztreonam (Cayston®), ivacaftor (Kalydeco®), tobramycin (TOBI®), lumacaftor/ivacaftor (Orkambi®), and tezacaftor/ivacaftor (Symdeko®). We will continue to push the frontiers of science to find therapies that treat the underlying cause of this disease for 100 percent of people with CF and eventually lead us to a cure.

Accelerating the Pace of Progress

To accomplish this, the Foundation supported more than 60 multicenter trials in 2018 for a wide range of therapies and is continuing to build on this momentum by aggressively funding a comprehensive research portfolio. In 2018, the Foundation spent $141 million on awards for
laboratory research, **preclinical discovery and drug development**, and clinical and real-world research -- the largest amount ever.

This included $44 million to fund cutting-edge, innovative laboratory research. This research plays a critical role in advancing new therapies by increasing our understanding of the disease and identifying new opportunities for developing treatments. The range of laboratory research includes everything from **gene editing** to the structure and function of the **cystic fibrosis transmembrane conductance regulator (CFTR) protein** and complications associated with the loss of CFTR function. This CF Foundation-funded research is laying the groundwork for the next generation of treatments.

Additionally, because CF is a rare disease, the CF Foundation provides financial support to encourage companies to focus on CF and help advance therapies that would be unlikely to move beyond the lab and into clinical trials, spending approximately $45 million last year to fund preclinical discovery and drug development research. In 2018, the Foundation interacted with more than 150 different companies in the biotech and pharmaceuticals industries. We are committed to supporting and accelerating any potential treatment that we think may benefit people with CF and are funding more than 40 programs to help advance therapies for people with CF.

In 2018, the Foundation spent around $52 million to fund academic-led clinical trials and real-world research that takes into account the realities of daily life and human behavior, and how they can affect the way treatments work and the way care is provided. Real-world research includes observational studies conducted with data from the CF Foundation **Patient Registry**, which helps us understand CF by showing trends in survival and complications among people with CF. Real-world research also includes the following types of studies:

- Post-approval
- Comparative effectiveness
- Behavioral

In addition to the funding for research, the Foundation spent more than $48 million to help provide high-quality, specialized CF care.
The research awards chart below includes $150 million that the Foundation distributed in awards (in the form of grants to academic institutions and therapeutic development contracts with industry) and financial support for its one-of-a-kind, CF-focused research lab, the Cystic Fibrosis Foundation Therapeutics Lab.
Laboratory Research Support
The Foundation funded $44 million in cutting-edge, innovative basic research (research conducted in the lab) in 2018, including $18.1 million for basic science support. These funds highlight the critical role fundamental research plays in advancing new therapies by increasing our understanding of the disease and identifying new opportunities for developing treatments.

Much of the funding for laboratory research goes to academic institutions, including $6.7 million toward the Foundation’s Research Development Program (RDP). This money helps pay for core lab facilities, pilot programs, and training at 11 pioneering academic centers. These centers have conducted innovative CF research that has resulted in some of the most significant advances in the field, including the identification of the first small-molecule CFTR modulators and the development of the original model of cystic fibrosis in a mouse.

The RDP also plays a critical role in fostering the next generation of CF scientists and clinicians. Many of today’s top CF researchers began their careers at an RDP site. New researchers are critical to ensuring that the pace of development continues, and the Foundation is therefore investing heavily in training and career development.

To harness expertise, the Foundation has also facilitated several different research consortia, including:

- Epithelial Stem Cell Consortium
- Lung Transplant Consortium
- NTM (Nontuberculous mycobacteria) Consortium
- Success With Therapies Research Consortium

Research consortia are accelerating advancements in these areas by bringing together the brightest minds in these specialized fields of study to resolve important questions and to overcome challenges. The Foundation previously funded consortia focused on solving problems related to CFTR folding, CFTR protein structure, mucociliary clearance, and the identification of inflammatory biomarkers.

To accelerate the pace of research, the Foundation also invests in the development of tools, including cell lines, antibodies, and databases; the identification of biomarkers; and the creation of animal models that replicate various aspects of the disease. All these investments play a critical role in advancing new therapies for CF.

In 2018, the Foundation launched a project to sequence the entire genome of 5,000 people with CF, using DNA (deoxyribonucleic acid) acquired from three long-term studies. Researchers completed sequencing of the genomes in February 2019. This data will enable researchers to identify genes that alter or modify the disease. This research could provide useful insight into how these modifying genes influence the progression of CF and explain why two individuals with the same CFTR genes, lifestyle, and other characteristics can have different severities of disease.

Research is also being funded to develop improved outcome measures -- a way to assess a person’s health. These measures, which include evaluating lung function, imaging, and biomarkers, are critical for research and the development of new drugs.

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Clinical Research Support

In 2018, the Foundation enabled 64 multicenter clinical trials, more than doubling the number of trials from just six years ago. The breadth of trials has also increased, focusing not only on CFTR modulators, but also on a variety of treatments for complications of the disease, such as infections, excessive mucus, inflammation, and gastrointestinal issues. The CF Foundation is currently supporting the most robust pipeline of potential new therapies for CF in the history of the Foundation with more than 25 drugs in the Drug Development Pipeline.

These trials were made possible because of the largest CF clinical trials network in the world, the CF Foundation-supported Therapeutics Development Network (TDN). This coordinated network, which receives more than $22 million annually from the Foundation, allows trials to be performed more efficiently, accelerating the development of new therapies for people with CF. The TDN includes 92 Foundation-accredited care centers with specialized research teams able to perform clinical trials and is critical to ensuring advancements aren’t delayed because of insufficient enrollment.

The Foundation also supports international clinical research initiatives in Canada, Australia, the United Kingdom, and other European countries in our ongoing effort to accelerate the delivery of new therapies to people with CF. More than 50 international research teams receive financial support to help conduct trials and ensure adequate enrollment.

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CFTR Modulation

In 2018, the Cystic Fibrosis Foundation spent more than $11 million on research to develop new and more effective cystic fibrosis transmembrane conductance regulator (CFTR) modulators to restore the function of the defective CFTR protein.

For nearly 20 years, the Cystic Fibrosis Foundation has pursued a long-term strategy to develop effective cystic fibrosis transmembrane conductance regulator (CFTR) modulator treatments that target the underlying defect in cystic fibrosis and restore function for mutant CFTR proteins. Many different companies and academic investigators are testing a number of new and potentially more effective CFTR modulators.

Triple-Combination Modulators
Several companies are developing next-generation modulators that are either in clinical trials or will be entering clinical trials soon. Some of these next-generation modulators have the potential to be significantly more effective than drugs that have been approved by the U.S. Food and Drug Administration (FDA) and to benefit more people with CF than ever before.

In early 2018, the FDA approved the CFTR modulator tezacaftor/ivacaftor (Symdeko®). Tezacaftor/ivacaftor plays a critical role in next-generation triple-combination therapies. The two modulators were combined with a next-generation modulator -- either VX-659 or VX-445 -- to form triple-combinations that were tested in late-stage clinical trials in people with CF. The initial results for both triple-combination drugs were nearly identical: Individuals with two F508del mutations saw a 10 percentage point improvement in lung function over those who were given tezacaftor/ivacaftor only and people with one F508del mutation and a minimal function mutation saw an approximately 14 percentage point increase in lung function compared to participants taking a placebo.

In the third quarter of this year, one of the triple-combination modulators will be submitted to the FDA for children ages 12 and older for potential approval in 2020. The drug’s approval could eventually lead to more than 90 percent of people with CF having highly effective treatments for the underlying cause of their disease, including individuals with only one copy of the F508del mutation.

As more people with CF start taking CFTR modulators, they are more frequently asking clinicians about which treatments and therapies they can stop. In response, researchers are designing a study, known as SIMPLIFY, that will assess which medications people with CF could potentially stop taking once they start on a CFTR modulator.

The Cystic Fibrosis Foundation is also planning a study called PROMISE that will examine the short- and long-term clinical implications triple-combination therapies will have on people with CF. Researchers will investigate how the drugs affect the course of the disease, looking at lung function, mucus clearance, infections, gastrointestinal issues, and inflammation, among other aspects of CF.
Theratyping
Research is underway to categorize mutations based on how they respond to different modulators. By testing modulators on different CFTR mutations in the laboratory, scientists can identify treatments for people with mutations that are so rare as to make clinical trials impractical.

The Foundation is working with scientists, clinicians, and regulators to devise ways to use this technique, known as theratyping, to identify mutations that respond to modulators already on the market. Theratype testing is underway at three Foundation-funded labs to investigate whether 650 rare CFTR mutations -- chosen because they produce the CFTR protein -- show improvement when exposed to a modulator therapy. If any of the tests display positive results, the Foundation plans to work with the drug company that developed the modulator, as they will need to request that the FDA approve the medication for people with those mutations.

Theratyping has already proven successful. In early 2017, the FDA relied on a combination of theratyping results, clinical data, and the drug’s established safety record to expand the use of ivacaftor (Kalydeco®) to people ages 2 or older who have at least one of 23 CFTR mutations. However, it will take time for the drugs to reach all the people who could potentially benefit.

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Treating CF Complications

The Cystic Fibrosis Foundation is actively pursuing and funding a broad portfolio of new treatments for complications of the disease to bring additional lifesaving therapies to the cystic fibrosis community as quickly as possible.

Overview
Several generations of people with cystic fibrosis will still have complications from the disease, despite the advancement of highly effective cystic fibrosis transmembrane conductance regulator (CFTR) modulators. We estimate that 20 years from now, a significant portion of our community will still require additional therapies to treat complications, such as infections, inflammation, excessive mucus, and gastrointestinal (GI) issues. As such, improving treatments for complications of CF is critically important to the Cystic Fibrosis Foundation. In 2018, the CF Foundation spent significantly more money in this area of research than any other.

Approximately $62.5 million went to fund nearly 300 projects related to complications, including studies to improve patients’ health by refining screening and diagnosis, optimizing therapies, studying the impact of chronic therapies, and developing new treatment approaches.

There are more than 15 drugs in the pipeline to treat complications of CF, including potential anti-infectives, anti-inflammatories, mucociliary clearance therapies, and nutritional agents. One of the goals of these new treatments is to preserve lung function and maintain people’s health until they can benefit from treatments for the underlying cause of the disease as they are approved for more mutations.

Funding for CF-Related Complications

- **Inflammation**: $1.8M
- **Infections**: $7.9M
- **Mucus**: $9.0M
- **Lung Transplant**: $15.7M
- **Digestive System**: $5.0M
- **CFRD and Reproductive Health**: $1.6M
- **Other**: $21.5M

**TOTAL: $62.5M**
Infections

- The CF Foundation is investing in innovative and novel techniques to help tackle chronic, life-threatening infections.
- In 2018, the Foundation announced the new $100 million Infection Research Initiative to improve outcomes associated with infections.
- We funded more than 100 different projects in 2018 to improve our understanding of these infections and to develop new and more effective anti-infectives for people with CF.
- This includes funding for more than 10 industry antimicrobial programs, many of which are in either preclinical or early-stage clinical trials.
- It is the largest single area of funding of CF complications research.

During the 2018 North American Cystic Fibrosis Conference (NACFC), the Foundation launched the new Infection Research Initiative to improve outcomes associated with infections (bacterial, fungal, and viral) through enhanced detection, diagnosis, prevention, and treatment -- areas of focus identified with input from the CF community. The Foundation has allocated at least $100 million to the initiative, more than doubling its commitment from the previous five years and enabling the CF Foundation to fund any infection research that has the potential to benefit people with the disease. The funding will be used to further enhance our robust portfolio of basic, clinical, and industry infection-related research programs.

One project to develop better methods of detecting germs and diagnosing infections earlier is focused on nontuberculous mycobacteria (NTM). NTM infections in CF are becoming more and more common and increasingly difficult to treat. It is, therefore, one of the Foundation’s highest priority antimicrobial areas. The most common NTM infections in people with CF include *Mycobacterium abscessus* (*M. abscessus*) and *Mycobacterium avium complex* (MAC). In 2017, the Foundation created the NTM Consortium to help standardize the diagnosis and treatments of NTM lung disease. In 2019, the CF Foundation awarded up to $5.1 million to the TB Alliance to develop potential treatments for infections caused by *M. abscessus* and MAC.

In addition to NTM, there are many other concerning microorganisms prevalent in the CF community. They include fungi and the following bacteria:

- Drug-resistant *Pseudomonas aeruginosa* (*P. aeruginosa*)
- *Burkholderia cepacia* (*B. cepacia*)
- *Achromobacter*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)

Research is underway to improve our understanding of these CF microorganisms. Studying the microbial ecology of the airways as well as bacteria and fungi in the environment will help researchers develop better strategies to prevent, manage, and treat infections.

The Foundation is working with more companies on the development of new treatments for infections than any other area of our research portfolio, including CFTR modulators. This includes funding for more than 10 industry antimicrobial programs, many of which are in early-stage clinical trials.
Of particular concern to the community are drug-resistant organisms -- bacteria that no longer respond to many of the available antibiotics. Because of this, the Foundation is focused on developing new therapeutic agents with novel ways of fighting the infection.

One innovative approach is using gallium, a metal that acts similarly to iron, to disrupt iron-dependent biological processes that are necessary for bacteria to survive. Promising laboratory research has shown that gallium can kill antibiotic-resistant strains of P. aeruginosa and other difficult-to-treat bacteria. As a result, a Phase 2 clinical trial to see if gallium, which has already been approved by the FDA for intravenous (IV) use, is safe and effective at controlling P. aeruginosa in people with CF was completed in 2018. A second trial studying if gallium is effective in treating NTM will be starting in 2019.

Another unique approach is exploring the use of inhaled nitric oxide, a natural antibiotic that is produced by the immune system. A clinical trial is underway to determine the effectiveness of this potential therapy on people with chronic bacterial infections as well as those with NTM infections.

Because approximately 25 percent of people with CF test positive for MRSA each year, the Foundation is supporting several studies exploring the best way to fight these bacteria. This includes providing funding for a Phase 3 clinical trial that started in late 2017 to test the use of inhaled vancomycin.

The CF Foundation is also focused on improving current treatments. In 2018, the CF Foundation awarded up to $3 million to Synspira to support the development of a novel molecule that could potentially make antibiotics more effective by breaking down biofilms, the protective layer that sometimes surrounds bacteria and increases their resistance to anti-infectives.

Additionally, the Foundation is funding a clinical trial that is looking at the safety and effectiveness of three different lengths of IV antibiotic treatment for pulmonary exacerbations. The STOP 2 trial complements an initial observational study, known as the STOP (Standardized Treatment of Pulmonary Exacerbations) trial, which sought to identify best practices for treating this common complication of CF. A third STOP trial is expected to begin in 2019 that will focus on children and oral antibiotics.

Common antibiotics, including aminoglycosides (such as tobramycin), can cause hearing loss. In a Phase 2 study, researchers are testing a potential drug by Sound Pharmaceuticals called ebselen to prevent damage to the inner ear caused by antibiotics.

Bacteriophage (phage) therapy uses viruses that attack bacteria to treat bacterial infections. (Bacteriophage therapy has not been approved by the FDA for use in the United States.) The Foundation is funding basic science studies to improve our understanding of the potential use and limitations of phage therapy to treat infections. We are also working with groups of scientists to develop rigorous, controlled clinical studies that can help us answer the question of whether phage therapy may be beneficial for treating CF infections.

Bacterial infections are not the only concern in the CF community. Many fungi, including Aspergillus fumigatus, cause complications for people with CF. The Foundation is supporting...
the development of an inhaled version of itraconazole to treat an allergic reaction to *Aspergillus* called **allergic bronchopulmonary aspergillosis** (ABPA). It is hoped that an inhaled version may cause fewer side effects and reduce drug-drug interactions.

With the progress of CFTR modulators, there are many questions about how these and other future treatments could impact infections. Scientists are studying how germs respond once individuals begin modulator therapies. The **GOAL study**, and a companion study based in Ireland, investigated how we might be able to eradicate certain infections with modulator therapy. Additional studies are planned to examine the effect of future modulators on infections in people with CF. The PROMISE study will look at how triple-combination modulators affect infections in people with CF.

**Mucus**

Thick, sticky mucus is a major contributor to lung damage in people with CF. The Foundation is funding more than 35 research projects to develop new and more effective treatments to improve the clearance of mucus from the lungs of people with CF.

Some promising potential therapies include agents that thin the mucus so it can be cleared away more easily. Another approach focuses on increasing the surface liquid in the lungs by inhibiting the epithelial sodium channel (ENaC), which is overactive in CF and contributes to the thickening of mucus by drying the airways. An important aspect of these approaches is that they could potentially help all people with CF, regardless of their CFTR mutations.

**Inflammation**

**Inflammation** is a natural part of the body's immune response to infection. However, people with CF have a much longer and more intense inflammatory response, which can be just as destructive to the lungs as the infection itself. Researchers believe that cells with a defective CFTR protein send out excessive signals that cause inflammation.

The CF Foundation is providing funding for 35 projects to identify the causes of this excessive signaling and devise methods to block these signals. This includes support for four promising anti-inflammatories in clinical trials and another one in preclinical development that could benefit everyone if approved.

Researchers involved in one of these clinical trials sponsored by Corbus announced promising results from an **early-stage study**. To advance the development of this novel anti-inflammatory drug, in early 2018 the Foundation **awarded up to $25 million** to help fund a Phase 2b trial, which is underway.

A recent Phase 2 trial by Celtaxsys, testing a different anti-inflammatory agent, demonstrated a reduction in pulmonary exacerbations for patients with forced expiratory volume in one second (FEV₁) greater than 75 percent. Plans are currently underway for a follow-up late-phase trial in 2019.
Digestive System
Although the lungs are usually the most seriously affected part of the body in CF, most people with this disease also experience complications in the digestive system. Getting adequate nutrition can be a problem for people with CF because a lack of fluid and bicarbonate in the pancreatic ducts can cause them to become blocked, preventing digestive enzymes from reaching the small intestine to digest food. Resolving these digestive problems is important because data show that lung function and nutrition are closely linked. Other problems include abdominal pain, poor absorption of nutrients like vitamins, constipation, and liver disease.

The Foundation funded nearly 20 projects in 2018 related to gastrointestinal (GI) complications and has helped organize a group of GI specialists who focus specifically on the treatment and research of GI issues in CF called the Developing Innovative Gastroenterology Specialty Training program, or DIGEST. This group of GI doctors is developing best practices and a better understanding of abdominal symptoms to lead to better treatments. DIGEST is also working on a study called GALAXY to gauge which GI symptoms affect people with CF the most so that researchers can prioritize them for further study.

In an innovative partnership with the National Institutes of Health, the Foundation is also investigating the best methods of screening for liver disease. Results from the recently completed PUSH study suggest that specialized ultrasound measurements can be utilized to identify individuals at risk of having progressive CF liver disease. This finding helps to set the stage for future trials aiming to intervene and prevent CF liver disease.

In addition, the Foundation is supporting clinical trials for glutathione, an antioxidant that is important to the normal functioning of the intestines and lungs. Glutathione levels have been shown to be lower in people with CF. Preliminary data suggest that oral glutathione may improve growth and decrease GI inflammation in children with CF.

At the end of 2018, the Foundation convened a group of CF clinicians and scientists who specialize in GI complications to discuss how to overcome challenges, such as abdominal pain and nutrition. Based on these discussions, the Foundation is building a research strategy to improve clinical outcomes and management of GI complications for people with CF.

CFRD and Reproductive Health
For many, CF affects more than just their lungs and GI system. The endocrine system, which uses hormones to regulate many aspects of the body, is also affected by the disease. To better understand the impact of CF on the endocrine system, the Foundation provided $1.6 million in 2018 for research into CF-related diabetes (CFRD), reproductive health, and bone health.

CFRD is typically found in adults but also affects adolescents. This unique form of diabetes can accelerate lung complications if not properly controlled. The Foundation is funding research to better understand the underlying cause and genetics of CFRD, improve screening, how best to manage CFRD, and the potential benefit of CFTR modulators on preventing the development of CFRD.
Lung Transplant
With more than 250 people with CF undergoing lung transplantation every year, the Foundation is working to improve the lung transplant experience and to extend the lives of transplant recipients. To accomplish this, we launched the Lung Transplant Initiative in 2016, and so far, we have committed $23.5 million to this effort.

As part of this initiative, the Foundation created and funded the Cystic Fibrosis Lung Transplant Consortium which is dedicated to the following goals:

- Defining and implementing best practices
- Enhancing quality improvement
- Conducting clinical trials to improve the delivery of lung transplant clinical care
- Improving our understanding of chronic rejection
- Developing new therapies for transplant recipients

At the forefront of the initiative is the development of clinical practice guidelines to improve and standardize the care received by people with CF for whom transplant is an option. This year, the initiative produced guidelines to improve the way CF-Foundation-accredited care centers refer patients to lung transplant centers. Initiative committee members also are working on two sets of guidelines for the CF and lung transplant communities -- advanced lung disease guidelines, and post-transplant guidelines.

To improve post-transplant survival rates, the Foundation is supporting research on the complications that often develop after transplant. We have funded nine basic science lung transplant studies and seven research studies focused on improving our understanding of chronic lung allograft dysfunction (CLAD) and identifying paths toward developing therapies that might either prevent or treat CLAD.

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CFTR Restoration (Nonsense/Rare Mutations)

The Cystic Fibrosis Foundation is funding groundbreaking new approaches to develop treatments for individuals who have nonsense or other rare mutations that do not respond to cystic fibrosis transmembrane conductance regulator (CFTR) modulators.

We have drastically increased the size of our investment in this area and last year spent more on research to develop treatments for people with nonsense and rare than on research into cystic fibrosis transmembrane conductance regulator (CFTR) modulators.

Additionally, by the end of 2018, we had committed more than $90 million to the Nonsense and Rare Mutations Research and Therapeutics Initiative, which encompassed nearly 100 ongoing projects in academic and industry settings around the world. It is estimated that approximately 7 percent of people with CF will be unable to benefit from CFTR modulators and will require these types of innovative therapies to fix the underlying cause of their disease.

Readthrough Screening Programs

In 2018, the Cystic Fibrosis Foundation spent more than $16 million on nearly 20 projects focused on CFTR restoration, including readthrough screening programs.

In people with CF who have nonsense mutations (also known as “x” or “stop” mutations), CFTR protein production stops prematurely. This leads to a shorter, incomplete protein that usually doesn’t function. One unique strategy to develop new treatments for these mutations involves small-molecule compounds known as readthrough agents. These compounds would “read through,” or override, premature stop signals in the CFTR gene to make a full-length CFTR protein.

In 2018, researchers achieved nonsense readthrough in primary cells, giving a fresh sense of possibility to the extensive screening efforts we have underway across the country. The Foundation is working with three organizations to screen millions of compounds that could be developed as readthrough agents. With funding from the Foundation, the nonprofit organization Southern Research, in collaboration with the University of Alabama at Birmingham, is using a novel and sophisticated screening process to identify readthrough compounds in its chemical library. In addition, more than half of the research being performed at the Cystic Fibrosis Foundation Therapeutics Lab is focused on therapies that could help provide new treatments for individuals with nonsense mutations.

In May 2018, the CF Foundation awarded up to $11 million to the biotech company Icagen to fund the largest high-throughput screen for readthrough agents the Foundation has conducted to date. As part of this contract, more than two million compounds will be screened to identify candidates that may be developed into drugs for people with nonsense mutations.

To further expedite the development of new treatments for individuals with nonsense mutations, the RARE cell-collection study was launched in early 2018. The study will collect cells from
individuals with two stop mutations to enable the development of promising new therapies (readthrough agents as well as other compounds).

Transfer ribonucleic acid (tRNA) is a key component in the cell’s ability to translate deoxyribonucleic acid (DNA) into a protein. A new company supported by the Foundation called ReCode is exploring the delivery of a suppressor tRNA that will also allow readthrough of nonsense mutations to make a full-length CFTR protein.

RNA Therapy
Another innovative treatment that is part of the Foundation’s strategy is ribonucleic acid (RNA) therapy. This treatment restores the messenger (mRNA) that is used in the cell as a template to create the CFTR protein. One of the benefits of this treatment is that it could potentially benefit everyone with CF regardless of their mutations.

For RNA therapy, we are pursuing two different approaches in parallel. The first approach would replace the defective mRNA by delivering normal mRNA to cells. The second approach is to repair the defective mRNA responsible for producing the CFTR protein. Both strategies would enable full-length, functional CFTR protein to be created.

A clinical trial for the first-ever mRNA therapy directed at CF began enrolling participants in mid-2018. This early-stage study by Translate Bio is testing whether normal mRNA can be transmitted into the cell safely to make CFTR protein. A second company, Arcturus, is pursuing a similar approach in the laboratory with the goal of identifying a safe, effective delivery system for mRNA.

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Cystic Fibrosis Foundation Therapeutics Lab
The CF Foundation’s one-of-a-kind CF research facility bridges the gap between discoveries made at academic institutions and the development of new medications by the pharmaceutical industry. Based in Lexington, Mass., the unique structure of the Cystic Fibrosis Foundation Therapeutics Lab enables the scientists they employ to be laser-focused on their research without the distraction of meeting financial or academic targets, accelerating crucial research that otherwise might not move forward.

Currently, more than half of the work at the Cystic Fibrosis Foundation Therapeutics Lab is concentrated on nonsense mutations. The Lab is screening for potential new therapies, including readthrough agents for nonsense mutations and new CFTR modulators, to treat the underlying cause of CF in these individuals.

Additionally, the lab has created a cell culture bank to house cells from people with CF who have rare mutations, including those collected through the RARE study. This cell culture bank will aid in the development of nonsense-targeted therapies and may result in the extension of available therapies to people with rare mutations.

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Cure

Our long-term goal is to create a cure that would benefit every person with cystic fibrosis regardless of their mutations.

The most promising options for a cure for cystic fibrosis are either adding normal cystic fibrosis transmembrane conductance regulator (CFTR) genes to cells using gene therapy or repairing the defective CFTR genes using gene editing.

For gene editing or gene therapy to work, the gene editing tools or the correct CFTR gene must get inside the cells of a person with CF. For this reason, one of primary focuses is on gene delivery, devising ways to successfully deliver a healthy gene or gene editing tools into airway cells. This is a particular challenge in CF because of the body’s natural defenses against foreign bodies, such as viruses and bacteria, in the lungs.

In 2018, the Foundation devoted more than $6 million to fund more than 30 groundbreaking gene editing, gene delivery, and stem cell research projects. Using the latest scientific discoveries in these areas of research, we are trying to tailor gene editing techniques for CF with the goal of one day curing the disease.

Although these technologies have progressed rapidly in the last few years, it will be many years before they reach patients.
Gene Editing
Gene editing and gene therapy are emerging technologies that could be used one day to correct the mutations in the CFTR genes that cause CF. Gene editing tools would repair the mutations in a patient’s DNA, while gene therapy would introduce a healthy CFTR gene into the cells of people with CF.

Gene Delivery
Gene delivery refers to the process of transporting specifically engineered DNA molecules into cells, and it is an essential component of gene editing and gene therapy. The Foundation is providing funding to 4D Molecular Therapeutics and Talee Bio to expand preclinical work to develop and test their gene delivery vehicles, which would transport a healthy CFTR gene into the lung cells of people with CF. The Foundation is also investigating nonviral approaches (i.e., lipid nanoparticles) to package DNA or ribonucleic acid (RNA) for delivery to the lung and other tissues.

To advance gene editing for CF, in the summer of 2018 the Foundation organized a conference focused on gene editing and gene delivery. The same year, we also held a workshop with some of the world’s leading experts on gene editing and co-hosted a workshop with the National Institutes of Health on the barriers of gene delivery. In February 2019, the Foundation hosted a workshop with international experts to address overcoming the obstacles for delivering molecular therapies (such as gene editing and gene therapy) for CF.

Stem Cell
In April 2018, the Foundation launched the Epithelial Stem Cell Consortium. The inaugural meeting brought together stem cell experts from across the country to focus on advancing our understanding of airway stem cells and how they may be targeted by gene therapy or other therapeutic approaches.

Additionally, the CF Foundation Therapeutics Lab has hired both gene editing and stem cell biologists to work together to explore and advance new treatments and to get us one step closer to our ultimate goal of a cure.

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