CYSTIC FIBROSIS FOUNDATION®

Research We Fund

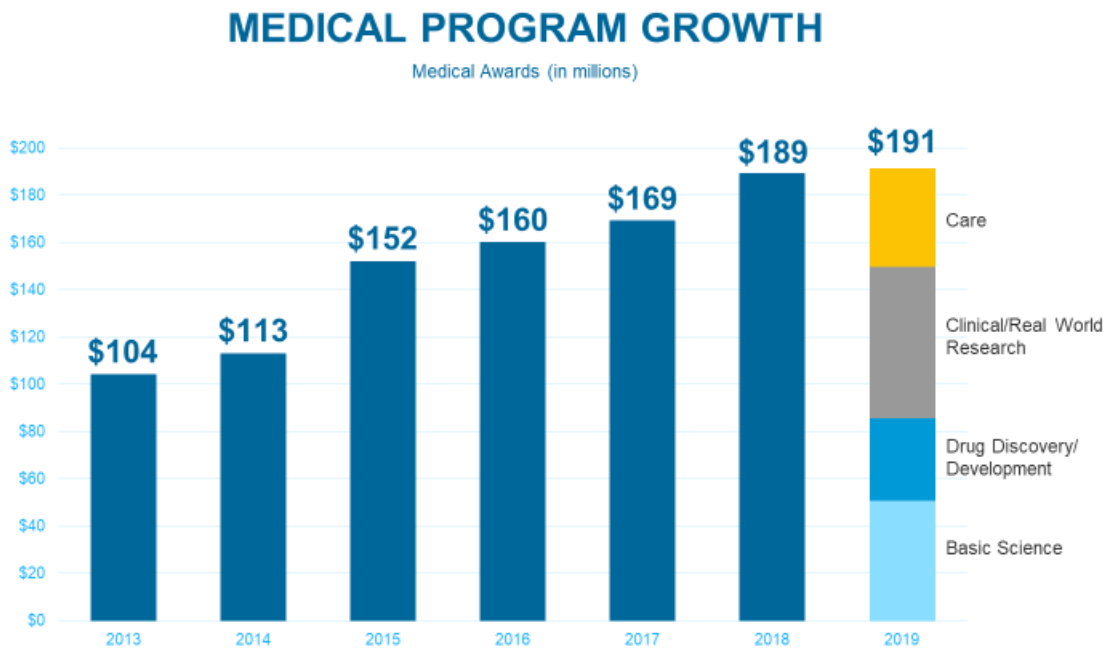
Cystic Fibrosis Research

The Cystic Fibrosis Foundation is the world's leader in the fight against CF, and our scientific portfolio reflects our drive to provide effective treatments and -- one day -- a cure to every individual with this disease.

We continue to make tremendous progress towards these goals. Last year the U.S. Food and Drug Administration (FDA) approved the CFTR modulator Trikafta® (elexacaftor/tezacaftor/ivacaftor), which will eventually benefit more than 90 percent of people with CF. However, we will not rest until everyone has a therapy that addresses the underlying cause of their disease. With this commitment in mind, the Foundation launched our ***Path to a Cure***, an ambitious research initiative to accelerate treatments for everyone with CF and ultimately deliver a cure. We intend to allocate a **half billion dollars** to the effort through 2025.

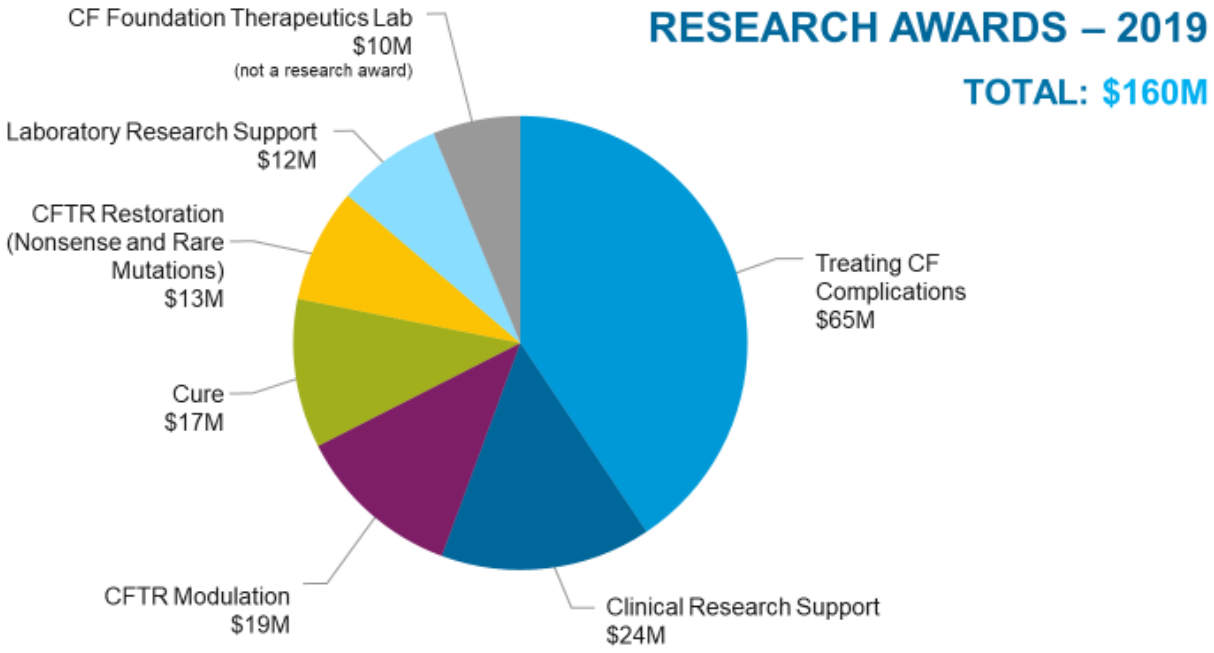
It is also critical to continue to develop new and improved treatments for complications from the disease. We are building on the current momentum, funding an innovative research portfolio and collaborating with top scientists from around the world to deliver the next generation of transformative breakthroughs in CF. To ensure that we continue to enable therapies to advance that otherwise would be unlikely to move beyond the lab and into clinical trials, we provide research funding and expertise to draw the best scientific minds and technologies into CF.

Our research funding has more than doubled over the last six years. Additionally, last year we funded approximately **$191 million** in laboratory research, preclinical drug development, clinical and real-world research, and high-quality, specialized care and training — more than at any other time in the history of the Foundation.



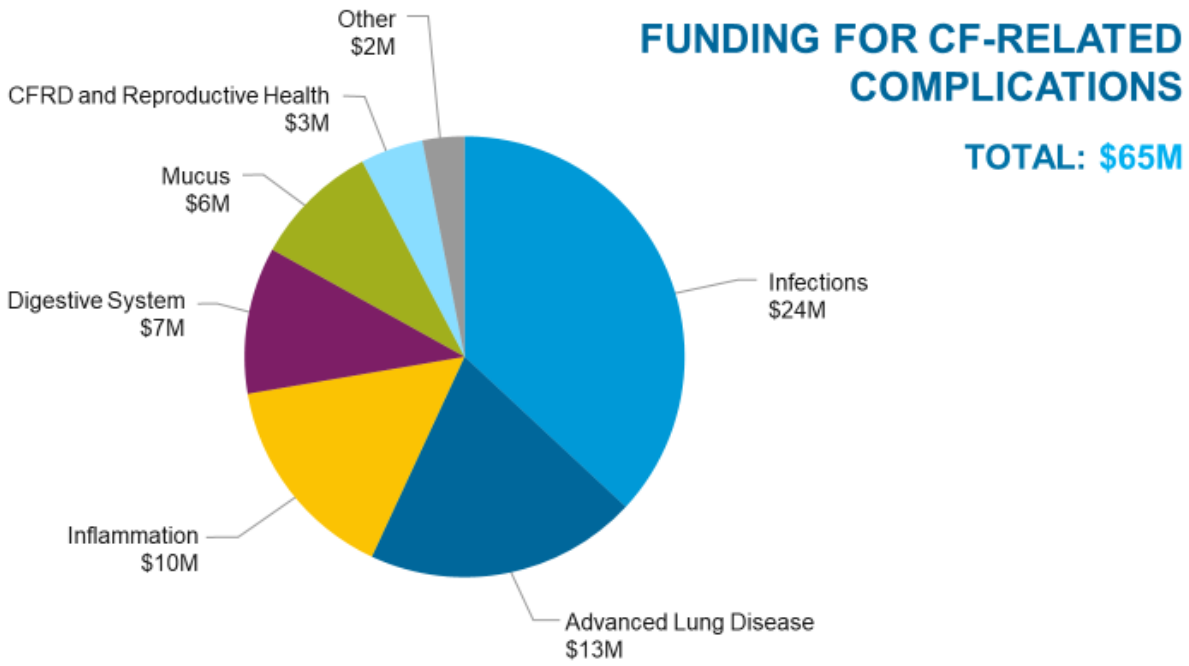
Our Investment in Research

The CF Foundation invested **$160 million** on research and development awards and the CF Foundation Therapeutics Lab in 2019.



Treating and Preventing Complications

- Treatments for complications of CF — such as infections, inflammation, excessive mucus, and digestive issues — are so important that in 2019, the CF Foundation spent significantly more money in this area of research than in any other.
- In 2019, approximately $65 million went to fund over 300 projects related to complications.
- There are also more than 20 drugs in the pipeline to treat complications of CF, including potential anti-infectives, anti-inflammatories, mucociliary clearance therapies, and nutritional agents.
- Last year researchers completed a project to sequence the entire genome of 5,000 people with CF using DNA (deoxyribonucleic acid) acquired from three long-term studies. 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 disease trajectories.



Infections

- In the fall of 2018, the CF Foundation announced the **$100 million Infection Research Initiative** as part of a sweeping effort to address the chronic and intractable infections that are a hallmark of cystic fibrosis. Since the launch, the Foundation has committed approximately $25 million to new infection programs with industry.
- In 2019, the Foundation funded 150 different projects to improve our understanding of infections and to develop new and more effective anti-infectives for people with CF.
- For a detailed overview of our research into infections, please visit: cff.org/IRI.

Advanced Lung Disease

- With more than 250 people with CF undergoing lung transplantation every year, the Foundation is determined to improve the lung transplant journey.
- Last year the CF Foundation invested $13 million in research into advanced lung disease, including research to standardize and improve the delivery of lung transplant clinical care; increase understanding of post-transplant complications, including chronic rejection; and develop new therapies for lung transplantation through clinical studies.
- As part of the Lung Transplant Initiative, the Foundation established a consortium that currently includes 15 lung transplant sites and funded a biorepository and coordinating center for lung transplant samples from both non-CF and CF patients to be used for research purposes. The samples will be linked to data in a new post-transplant patient registry.
- The Foundation also is supporting a two-year extension of a multicenter study focusing on the causes of chronic lung allograft dysfunction (CLAD), or the failure of a lung transplant.
- In 2019, the Foundation created an advanced lung disease registry to capture data from CF patients. There are about 3,000 individuals with advanced lung disease, who will be included in this database.

Inflammation

- In 2019, the CF Foundation funded 27 new projects to identify the causes of excessive inflammation and devise methods to reduce it.
- These projects include five ongoing clinical trials to test potential anti-inflammatory medications.
- One of those clinical trials is a Phase 2 clinical trial being conducted by Corbus Pharmaceuticals as part of a $25 million drug development contract.

Digestive System

- Although the lungs are typically the most commonly affected part of the body in CF, most people with the disease also experience complications linked to the digestive system. The Foundation funded nearly 30 separate programs in 2019 to address gastrointestinal (GI) complications.
- The Foundation spearheaded the formation of a group of GI specialists to focus on the treatment and research of GI issues in CF. This group conducted the GALAXY study to gauge which GI symptoms affect people with CF the most, so that researchers can prioritize them for further study.
- In 2020, the CF Foundation entered into an agreement with Synspira Therapeutics Inc. to develop a non-porcine enzyme replacement therapy with improved activity to offer an alternative to people with CF with pancreatic insufficiency – a condition in which thick, sticky pancreatic secretions damage the pancreas and block the release of enzymes needed to break down food for digestion.

CFRD and Reproductive Health

- 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 $3 million in 2019 for research into CF-related diabetes (CFRD), reproductive health, and bone health.
- To address the unique and emerging needs of women with CF, the Foundation has established the Therapeutics Development Network Women's Health Research Working Group to identify knowledge gaps, determine research priorities, and develop the infrastructure needed to conduct the research.

Mucus

- The Foundation is funding 34 projects to understand CF mucus abnormalities and develop new and more effective treatments to improve the clearance of mucus from the lungs of people with CF.
- Some promising potential approaches include agents that thin the mucus, so it can be cleared away more easily.

Clinical Research

- In 2019, the Foundation funded approximately $64 million in academic-led clinical trials as well as real-world research that takes into account the realities of daily life and human behavior. This includes $24 million for clinical research support, which provides funding for critical infrastructure that helps expedite the development of drugs and is instrumental in drawing in new companies into CF.

- This infrastructure includes the largest CF clinical trials network in the world, the Therapeutics Development Network (TDN), which has 91 care centers with specialized research teams able to perform clinical trials.
- Funding for our clinical research helps to support the most robust pipeline of potential new therapies for CF in the history of the Foundation with more than 40 new drugs in development.
- The Foundation enabled 62 multi-center clinical trials in 2019, 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 digestive issues.
- 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 full enrollment.

Laboratory Research

- The CF Foundation funded $51 million in laboratory research in 2019, including $12 million for basic research support.
- This CF Foundation-funded research is laying the groundwork for the next generation of CF 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 the Foundation's Research Development Program (RDP), which also supports core lab facilities, pilot programs, and training at 11 pioneering academic centers that focus on research critical to building our understanding of CF.

CF Foundation Therapeutics Lab

- In 2019, we directed $10 million to the CF Foundation Therapeutics Lab, the one-of-a kind CF research facility that bridges the gap between academic discovery and the pharmaceutical industry.
- Based in Lexington, Mass., the unique structure of the lab enables scientists 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.
- More than half of the work at the CF Foundation Therapeutics Lab is concentrated on nonsense and rare mutations, including an initiative to create a cell culture bank with cells from people with CF who have rare mutations. For the RARE cell-collection study, researchers are collecting cells from individuals with two stop mutations as well as other ultra-rare mutations to enable testing of promising new therapies (readthrough agents as well as other compounds).

Path to a Cure

The CF Foundation launched its **$500 million** *Path to a Cure* initiative in October 2019. This initiative centers around three core strategies to address the underlying cause of CF: repairing broken CFTR protein, restoring CFTR protein when none exists, and fixing or replacing the underlying genetic mutation to address the root cause of CF.

Each approach requires a different set of scientific tools and knowledge, leading the Foundation to bring together researchers and industry leaders from a range of disciplines to advance multiple areas of research in parallel, driving progress toward our goal to make **CF stand for Cure Found**.

CFTR Restoration – Nonsense and Rare Mutations Research

- The Cystic Fibrosis Foundation's unwavering focus on cystic fibrosis research has resulted in tremendous progress, including over 10 approved therapies to treat various aspects of the disease. Despite these incredible advances, at present, there is no therapy that targets the underlying cause of the disease for those with two nonsense and rare mutations.

- As part of the *Path to a Cure* initiative, we are pursuing new approaches to restoring CFTR activity in individuals who have nonsense or other rare mutations that will not respond to CFTR modulators. Some of these approaches would help everyone with CF, regardless of their mutation.

- Last year we spent $13 million to develop treatments for people with nonsense and rare mutations. Funding is expected to dramatically increase over the next several years through *Path to a Cure*.

- One potential treatment that could benefit all mutations, including those with nonsense and rare mutations — messenger ribonucleic acid (mRNA) therapy — is already in clinical trials. Delivery of CFTR-encoded mRNA would allow lung cells to create normally functioning CFTR protein, regardless of an individual's specific CFTR gene mutation. Translate Bio began enrolling a Phase 1 clinical trial in 2018 to test the safety of delivering correct copies of CFTR RNA to the lungs. Results from the trial are expected to be announced in 2021.

- In 2019, the CF Foundation increased its award to Arcturus Therapeutics up to $15 million to advance their potential mRNA therapy toward the clinic.

- SpliSense, another company supported by the Foundation, is developing an antisense oligonucleotide therapy. These "short nucleotide" therapies aim to bypass a splicing mutation (or regulate DNA expression) to produce a functional CFTR protein.

- The Foundation is investigating an approach to RNA therapy that would focus on transfer ribonucleic acid (tRNA), a key component in the cell's ability to translate DNA into protein. A new company supported by the Foundation called ReCode Therapeutics, which recently was acquired by TranscriptX, will continue exploring the delivery of a suppressor tRNA that would allow readthrough of nonsense mutations to make a full-length CFTR protein.

- Icagen Inc., a Ligand company, is conducting our largest high-throughput screen for readthrough agents, small molecules that override premature stop signals in nonsense mutations. As part of this $11 million contract, more than two million compounds have been screened to identify candidates. Icagen is advancing these candidates through additional tests and initial chemistry efforts to identify compounds that can be developed further into drugs for people with nonsense mutations.

CFTR Modulation – Repairing CFTR Protein

- For nearly 20 years, the Cystic Fibrosis Foundation has pursued the development of cystic fibrosis transmembrane conductance regulator (CFTR) modulator treatments that target the underlying defect in cystic fibrosis and repair mutated CFTR proteins.

- In October 2019, the U.S. Food and Drug Administration (FDA) approved the first triple-combination modulator, Trikafta, for people with CF ages 12 and older who have at least one F508del mutation, regardless of their second mutation. This next-generation modulator is significantly more effective than current FDA-approved CFTR modulators for people with two copies of the F508del mutation. Research is underway to expand the drug's use to younger age groups.

- The Cystic Fibrosis Foundation is also conducting a study called PROMISE that will examine the short- and long-term clinical implications that Trikafta will have on people with CF. Researchers will investigate how the drug affects the course of the disease, looking at lung function, mucus clearance, infections, gastrointestinal issues, and inflammation, among other aspects of CF.

- To determine whether people on Trikafta can begin to reduce their other medications, the Foundation is funding the SIMPLIFY study. Researchers will measure the effects of discontinuing inhaled hypertonic saline or dornase alfa (Pulmozyme®) on study participants who take Trikafta®.

- Although modulators have transformed the treatment of CF, more and better CFTR modulator options are needed for people who do not respond to, or cannot tolerate, these therapies.

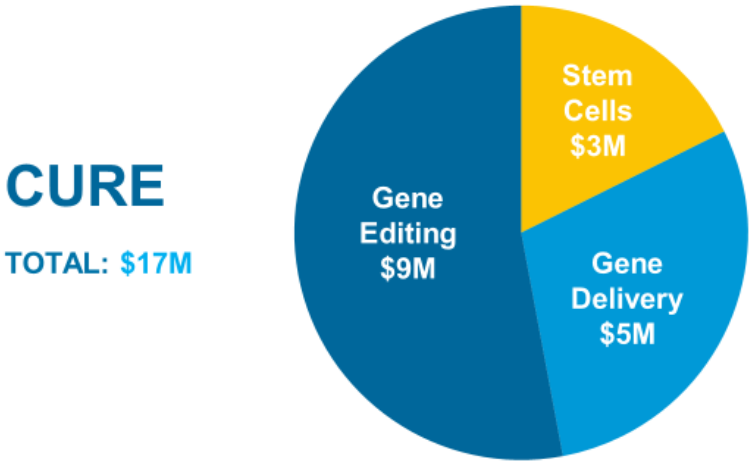
- To that end, the Foundation invested more than $19 million in 2019 on research to understand current modulators, expand their use to additional mutations, and develop new and potentially more effective CFTR modulator drugs.

- Last year the Foundation entered into a licensing agreement with AbbVie to develop a compound into a modulator therapy. In addition, AbbVie is investigating combinations of other compounds for the development of another CFTR modulator.

- In addition to funding new modulator development, the Foundation is using a technique called "theratyping" to categorize mutations based on how they respond to different CFTR modulators. Theratyping could enable pharmaceutical companies to use lab tests to expand treatments to patients whose very rare mutations make clinical trials impractical.

Cure – Fixing or Replacing CFTR

As part of the *Path to a Cure* initiative, the CF Foundation is focused on developing a genetic-based therapy that will fix or replace the underlying genetic mutation. This would achieve our long-term goal to create a cure that would benefit all people with cystic fibrosis regardless of their mutations.



- Last year, we spent more than $17 million to fund 65 gene editing, gene delivery, and stem cell research projects to advance towards a cure for CF – twice the amount of the previous year.

- We are investing in research programs to develop new approaches to targeting the disease at the genetic level, including gene therapy, gene editing, gene delivery, and the identification of stem and other cell populations that will repair and replace defective CF cells in the lung and other tissues.

- Since announcing the *Path to a Cure* initiative, the Foundation has met with and evaluated more than 17 new companies, spanning a wide variety of genetic approaches that could benefit people with CF. Six groups have been invited to apply for Foundation funding to accelerate their drug development in CF.

- In 2020, the Foundation announced that it is investing up to $14 million in 4D Molecular Therapeutics (4DMT) to develop a customized vehicle to deliver a healthy CFTR gene into the lung cells of people with CF. The delivery of genetic-based therapies is one of the key hurdles to developing an effective therapy. If successful, 4DMT plans to advance the potential therapy into early stage clinical trials for CF.

- Although these technologies have progressed rapidly in the last few years, it will be many years before they reach people with CF.