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) expanded the approval of three CFTR modulators, including Trikafta®, using in vitro data to people with certain mutations. It also expanded Kalydeco® to infants as young as four months. 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 and have already seen an 180% increase in funding for this area of research from 2018.

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 the advancement of potential therapies, we provide research funding and expertise to draw the best scientific minds and technologies into CF. Last year we held more than 230 meetings with over 120 companies – 61 of which were new to CF – and are currently funding nearly 50 different industry programs.

Despite the many challenges posed by the pandemic, in 2020 the CF Foundation funded approximately $248 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 and nearly a third more than just the previous year.
Our Investment in Research

The CF Foundation spent a total of $218.1 million on research and development as well as the CF Foundation Therapeutics Lab in 2020.
Laboratory Research Support

- The CF Foundation funded $46 million in laboratory research in 2020, including $11.3 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). The RDP provides support for 31 core lab facilities, 15 pilot projects which supported either junior investigators or researchers who are new to CF, and training at nine pioneering academic centers that focus on research critical to building our understanding of CF.

CF Foundation Therapeutics Lab

- In 2020, we directed $10.1 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 distraction, accelerating crucial research to benefit CF 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).

Clinical Research Support

- In 2020, the Foundation funded approximately $98.4 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 $42 million for clinical research support, which provides funding for critical infrastructure that helps expedite the development of drugs and is instrumental in attracting new companies into CF.
- This infrastructure includes the largest CF clinical trials network in the world, the Therapeutics Development Network (TDN), which has 90 care centers with specialized research teams able to perform clinical trials.
- The Foundation’s funding for clinical research helps to support the most robust pipeline of potential new therapies for CF in history, with approximately 40 potential new drugs in development.
- The Foundation facilitated 49 multi-center clinical trials in 2020, more than doubling the number of trials from just seven 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, 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 all people with CF. More than 50 international research teams receive financial support to help conduct trials and ensure full enrollment.

Path to a Cure

The CF Foundation launched its $500 million Path to a Cure initiative in October 2019, and we have already seen an 180% increase in funding for this area of research from 2018. This initiative centers around three core strategies to address the underlying cause of CF: repairing broken CFTR protein (for example, CFTR modulators), restoring CFTR protein when none exists, and fixing or replacing the underlying genetic mutation to address the root cause of CF with the ultimate goal of developing a cure for CF.

Each approach requires a different set of scientific tools and knowledge, leading the Foundation to bring together scientists and industry leaders from a range of disciplines to advance multiple areas of research in parallel.

CFTR Restoration

- The Cystic Fibrosis Foundation’s unwavering focus on cystic fibrosis research has resulted in tremendous progress, including more than 10 approved therapies to treat various aspects of the disease. Despite these incredible advances, at present, approximately 7% of people with CF, including those with two nonsense mutations (also known as stop mutations), still do not have a therapy to treat the underlying cause of their disease.

- 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 $20.8 million to develop mRNA therapies, nonsense-specific treatments and short nucleotide therapies (called antisense oligonucleotides) to restore CFTR for people with nonsense and rare mutations who do not produce any protein. 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.

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

- Translate Bio recently announced the 2021 results from its small, early stage clinical trial to test the safety of delivering correct copies of CFTR mRNA to the lungs.

- In January 2021, the Foundation awarded up to $2 million to Eloxx Pharmaceuticals to support the global Phase 2 clinical program of ELX-02, a potential therapy to treat people with CF who have nonsense mutations. If successful, the drug would “read through” or bypass premature stop signals in people with CF, resulting in the production of full-length functioning protein. In May, the Foundation awarded Eloxx an additional $2.6M to screen its library of compounds to identify potential readthrough agents - small molecules that override premature stop signals in nonsense mutations.

- The Foundation is also 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 company supported by the Foundation called ReCode Therapeutics is exploring the delivery of a suppressor tRNA that would allow readthrough of nonsense mutations to make a full-length CFTR protein.

- In 2021, the Foundation invested up to $8.4 million in SpliSense to develop an antisense oligonucleotide therapy for people with cystic fibrosis who have splicing mutations and potentially other rare mutations. Splicing mutations disrupt the production of functional CFTR mRNA, which is needed to make CFTR proteins. As a result, splicing mutations block the synthesis of normal CFTR proteins. If successful, this potential therapy would enable the creation of a full-length normal CFTR protein.

- Icagen Inc., a Ligand company, is conducting our largest high-throughput screen for readthrough agents. As part of this $11 million contract, more than two million compounds have been screened to identify candidates. Icagen has identified three potential candidate series and is advancing them through additional tests to optimize their activity to see if they can be developed further into drugs for people with nonsense mutations.

- Additional information about nonsense and rare mutations research currently underway can be found at Exploring Treatments for Nonsense and Rare Mutations.

### Repairing CFTR Protein (CFTR Modulation)

- 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, elexacaftor/tezacaftor/ivacaftor (Trikafta®), for people with CF ages 12
and older who have at least one F508del mutation, regardless of their second mutation. In December 2020, a process called theratyping, which tests mutations in the lab to see how they respond to different CFTR modulators, was used to expand Trikafta as well as other CFTR modulators to new mutations.

- 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.

- The Foundation invested more than $33.2 million in 2020 on research to understand current modulators, expand their use to additional mutations, and develop new and potentially more effective CFTR modulator drugs.

- In 2019, the Foundation entered into a licensing agreement with AbbVie to develop a CF Foundation-funded potentiator compound into a modulator therapy. In addition, AbbVie is investigating other compounds for the development of another CFTR modulator combination. Clinical studies of these modulators are in progress.

- We are also working to generate as much information about these important therapies as possible for people with CF and their care teams. The PROMISE study will examine the short- and long-term clinical implications of Trikafta 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. Another study called BEGIN, which is already underway, will look at the impact of Trikafta on children.

- 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.

- Another study called HERO2 will be using real-world data from people with CF to advance our understanding of treatment care routines while on Trikafta. This study, conducted by Indiana University, will ask people with CF to track their symptoms and treatments for 12 months using an internet-based app powered by Folia Health.

**Fixing or Replacing CFTR (Cure)**

As part of the Path to a Cure initiative, the CF Foundation is focused on developing genetic therapies that will permanently fix or replace the underlying genetic mutation. This would **achieve our mission to cure cystic fibrosis for all people with CF**, regardless of their mutations.
• Last year, we spent $26.7 million to fund 73 gene editing, gene delivery, and stem cell research projects to advance toward a cure for CF.

• 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 with the goal of repairing or replacing the 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 20 new companies, spanning a wide variety of genetic approaches that could benefit people with CF. Last year alone, the Foundation funded seven industry agreements to accelerate the development of genetic therapies for CF.

• The delivery of genetic-based therapies into the lung cells of people with CF is one of the key hurdles to developing an effective therapy. The Foundation awarded two contracts in 2020 to tackle this challenge. The Foundation invested up to $14 million in 4D Molecular Therapeutics (4DMT) to develop a customized vehicle -- an adeno-associated viral vector -- to deliver a healthy CFTR gene into the lung cells of people with CF. If successful, 4DMT plans to advance the potential therapy into early stage clinical trials for CF. The Foundation also awarded funding to enGene Inc. to develop its own customized vehicle -- a non-viral approach -- to deliver a healthy CFTR gene into lung cells.

• Also in 2020, the Foundation awarded $1.7 million in new research funding to seven academic institutions and two companies to support preclinical and lab research into key scientific challenges, such as gene delivery. These include modifying gene therapy delivery vehicles to better target specific cells in the lungs of people with CF and developing a platform capable of overcoming the innate immune defenses in the lungs to successfully deliver a potential new genetic-based therapy.

• In an pioneering approach to accelerate innovative therapies for CF, the Foundation announced a collaboration with Longwood Fund, a biotech-focused venture capital firm. Together, Longwood and the CF Foundation are dedicating resources to advance projects with transformative potential and incentivize early stage companies to prioritize CF drug discovery and development. The Foundation committed $20 million to the collaboration as part of its Path to a Cure.
Although these technologies have progressed rapidly in the last few years, it will take time for new developments to progress through clinical trials and, one day, be approved by the FDA for people with CF.

Treating and Preventing Complications

The Foundation knows that treating and preventing complications of CF — such as infections, inflammation, excessive mucus, and digestive issues — is critical for those living with cystic fibrosis.

In 2020, approximately $73.9 million went to fund 380 projects related to addressing these complications.

There are also more than 20 drugs in the pipeline to treat complications of CF, including potential anti-infectives, anti-inflammatory, mucociliary clearance therapies, and nutritional agents.

In 2019, researchers completed a project to sequence the entire genome of 5,000 people with CF using DNA acquired from three long-term studies. This data will enable researchers to identify genes that alter or modify the disease. Future research using this data could shed light on how these modifying genes influence the progression of CF, including complications from the disease, and explain why two individuals with the same CFTR genes, lifestyle, and other characteristics can have different disease trajectories. It may also provide insight into who may or may not be able to benefit from various therapies.

FUNDING FOR CF-RELATED COMPLICATIONS – 2020

TOTAL: $73.9M

Infections

Despite advances in treatments for the underlying cause of CF, infection remains a top concern of both people with cystic fibrosis and clinicians.
• 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 more than $80 million to new infection programs, and we will continue to fund any science that we believe holds real promise to address infections.

• In 2020, the Foundation funded 17 industry programs to improve our understanding of infections and to develop new and more effective anti-infectives for people with CF.

• The Cystic Fibrosis Foundation awarded up to $5 million to Armata Pharmaceuticals for the first-ever controlled clinical study of oral phage therapy in CF, reaffirming the Foundation’s commitment to advance innovative solutions to the growing challenge of antibiotic resistance.

• The Foundation invested in two potential treatments that would target all infections in people with CF, regardless of their bacteria. The Foundation awarded up to $5.6 million to Microbion to develop a novel antibiotic, pravibismane, that could help break down biofilms and kill drug-resistant bacteria. It also funded $2.4 million to Calithera Biosciences for a potential treatment that minimizes the growth of germs in the lungs of people with CF.

• In addition, the Foundation focused on specific bacteria that pose a problem for people with CF. The Foundation targeted multi-drug resistant strains of *Pseudomonas aeruginosa* with two awards: $3 million to Kinnear Pharmaceuticals for preclinical testing of a broad-spectrum antibiotic and $3.3 million to Polyphor AG for an inhaled version of the antibiotic murepavadin. *Pseudomonas* is the most prevalent bacteria in adults with CF.

• Difficult-to-treat nontuberculous mycobacteria also were targeted. The Foundation awarded up to $4.23 million in total to Matinas BioPharma to develop an oral version of the antibiotic amikacin and, in 2021, awarded $2.17 million to Beyond Air® to develop a portable nitric oxide treatment.

• In 2019, the Foundation also awarded nearly $700,000 to Calibr to screen for a compound that could be used to treat *Burkholderia cepacia* complex infections. Although rare, these infections are severe and few treatments are available.

• To advance our understanding of the factors that impact COVID-19 outcomes in people with CF, the Foundation awarded $2.76 million for 11 laboratory studies that will investigate whether there are underlying biological differences in the way people with CF may be infected by or respond to the novel coronavirus.

• Earlier this year the Foundation hosted a two-day fungal workshop, bringing together researchers from across the globe to begin designing what will be the largest ever clinical study for *Aspergillus* in CF.

• For a detailed overview of our research into infections, please visit the Infection Research Initiative.

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**Advanced Lung Disease**

• Lung transplant continues to be an important option for people with advanced lung disease, and the Foundation is determined to improve the lung transplant journey.

• Last year the CF Foundation invested $8.4 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.
• In 2019, the Foundation created an advanced lung disease registry to capture data from CF patients. Data from approximately 3,000 individuals with advanced lung disease are included in this database.

• The CF Foundation awarded funding to the Cleveland Clinic to set up a biorepository and coordinating center for lung transplant samples from both non-CF and CF patients. The samples are being linked to data that is being kept in the 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.

Inflammation

• In 2020, the CF Foundation funded 30 projects to identify the causes of excessive inflammation and devise methods to reduce it.

• There are currently three ongoing clinical trials to test potential anti-inflammatory medications.

• Laurent Pharmaceuticals is conducting a Phase 2 trial for a compound that is a form of the retinoid fenretinide, which is related to Vitamin A. Fenretinide may help reduce inflammation.

• Santhera Pharmaceuticals recently announced positive results from its Phase 1b trial of lonodelestat, a compound designed to block the function of neutrophil elastase. Neutrophil elastase is a type of protein associated with inflammation in the lungs.

• The Foundation awarded $2.4 million to Calithera Biosciences in 2020 to advance CB-280, which aims to limit the activity of an enzyme called arginase that, when elevated, reduces nitric oxide in the lungs. The lack of nitric oxide creates favorable conditions in the airways for bacteria and other microorganisms to colonize. By inhibiting arginase, nitric oxide levels may increase, reducing all types of infection and inflammation and improving lung function in people with CF.

• For additional information about research currently underway, visit inflammation.

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 spent $7.1 million to fund 33 separate programs in 2020 to address gastrointestinal (GI) complications.

• 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.

• The Foundation-funded GALAXY trial, the largest-ever study of GI symptoms in CF, was designed to gauge which symptoms affect people with CF the most. Researchers are using these results to inform and prioritize future studies, including research to address adult malnutrition, constipation, small intestinal bacterial overgrowth, and the use of proton pump inhibitors in CF.
• The Cystic Fibrosis Liver Disease Network, a collaboration between the CF Foundation and the National Institute of Diabetes and Digestive and Kidney Diseases, is conducting the PUSH study, a study aimed at finding non-invasive measures to help understand who may be at risk of developing cirrhosis; the ELASTIC study, a study of a newer, noninvasive method to identify scarring in the liver; and a study using MRI as a tool to identify individuals with CF who have advanced liver disease.

• Another innovative study will evaluate the use of a “bionic pancreas” (iLET™) to treat cystic fibrosis-related diabetes (CFRD). If successful, this approach could simplify management of diabetes and improve glucose control.

• For additional information about the GI research currently underway, visit GI Issues and CFRD.

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**CFRD and Reproductive Health**

• The endocrine system, which uses hormones to regulate many aspects of the body, is also affected by cystic fibrosis. To better understand the impact of CF on the endocrine system, the Foundation provided $3.1 million in 2020 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.

• One of the first studies led by this group, the MAYFLOWERS study, will study pregnancy in women with CF, including those taking Trikafta, to understand a range of maternal and infant health outcomes and the overall impact of pregnancy in CF.

• Other studies will look at the safety and effectiveness of contraceptives in CF, parenting experiences in people with CF, and whether an app can be used to assess CF symptoms throughout the menstrual cycle of a person with CF.

• For additional information about the CFRD research currently underway, visit GI Issues and CFRD.

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**Mucus/Airway Hydration**

• The Foundation is funding 43 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.

• AlgiPharma has conducted Phase 2 clinical trials of OligoG, a dry powder drug that has been shown to decrease the thickness of mucus in the lungs.

• Other approaches would either activate or block channels in lung cells to hydrate the mucus to make it easier to clear from the lungs.

• Roche Pharmaceuticals intends to develop a set of compounds that could increase the activity of a non-CFTR chloride channel in lung cells. If successful, the drug could help mucus become more hydrated in people with CF. Roche acquired the compounds from Enterprise Therapeutics,
which was awarded $7 million in 2019 to develop one of the compounds, ETD002, which recently entered Phase 1 clinical trials.

- In addition, the FDA recently approved inhaled mannitol (Bronchitol®), a dry powder form of mannitol and a naturally occurring osmotic agent, which works by drawing water into the airways.

- For additional information about the research currently underway, visit Mucus.