Infection Research Initiative

Executive Summary

The mission of the Infection Research Initiative is to improve detection, diagnosis, treatment, and outcomes of infections for people with CF. It builds on the broad infection research portfolio already funded by the CF Foundation. The initiative focuses on all aspects of CF-related infection, including improving the detection of microorganisms (e.g., bacteria, viruses, and fungi), the diagnosis of infection (i.e., when to consider treatment), and our understanding of CF-associated microorganisms. The initiative also supports the development of safe and effective treatments for infections, research to improve current treatments, the evaluation of long-term antimicrobial use, and studies to assess the impact of treatments that address the underlying cause of CF on the future of CF infection.

Infection Research Initiative

To improve detection, diagnosis, treatment, and outcomes of infections for people with CF

Areas of Research Focus:

- Improving Detection and Diagnosis
- Understanding CF Microorganisms
- Developing New Treatments
- Optimizing Current Treatments
- Evaluating Long-Term Antimicrobial Use
- The Future of CF Infection

Altogether, these six key areas of research constitute a robust, comprehensive program developed after extensive input from people with CF and their family members, researchers, and clinicians.

Background

People with cystic fibrosis are prone to infections because of the thick, sticky mucus that clogs their airways. These infections impact people with CF's lives with the symptoms they cause, the treatments and hospitalizations they may require, and their negative impact on lung function. The most common infections in people with CF are Pseudomonas aeruginosa (*P. aeruginosa*), Staphylococcus aureus (S. aureus), and methicillin-resistant *Staphylococcus aureus* (MRSA), Hemophilus influenzae, nontuberculous mycobacteria, *Achromobacter xylosoxidans*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* (*B. cepacia*) complex. The prevalence of infection changes with age, with *S. aureus* more common in children, and *P. aeruginosa* more common in adults. The table below displays the prevalence of the most common respiratory microorganisms detected in people with CF in 2017 along with the median age that patients first culture the bacteria.

Culture Data for Individuals Seen in 2017				
Bacteria		**Percent with Infection**	**Median Age in Years at First Infection**	**Distinctive Features in CF**
	P. aeruginosa	44.6	5.2	• A leading cause of airway infection • Associated with a decline in lung function • 17.9% of strains are multidrug-resistant
	B. cepacia complex	2.4	19.4	• Small proportion of people with CF infected • Can lead to rapid deterioration • Multidrug-resistant
	MRSA	25.2	11.1	• Prevalent among people with and without CF • Multidrug-resistant • Health care and community-associated strains
	S. maltophilia	12.6	9.4	• Found in water, soil, plants, animals, and hospital environments • Often multidrug-resistant
	Achromobacter xylosoxidans	5.8	13.8	• Inhabits natural environment, including soil and water • Often multidrug-resistant
	Non-tuberculous mycobacteria	12.6	20.7	• Found in water and soil • Sporadic reports of person-to-person spread • Treatment is rigorous and often poorly tolerated

Bacteria and mycobacteria are not the only microorganisms detected in people with CF. In 2017, 3,915 individuals reported positive aspergillus cultures, and 1,445 reporting allergic bronchopulmonary aspergillosis (ABPA). Further research is required to fully understand the impact of fungi and whether detection of fungi without ABPA causes harm.

Although a great amount of progress has been made in infection prevention and treatment, more work needs to be done to prevent infections and improve outcomes of infection for people with CF.

The Cystic Fibrosis Foundation announced the Infection Research Initiative in November 2018 to expand efforts to fight CF infections, committing at least $100 million over five years (2019-2023). The goal of this initiative is to expand the existing research into CF infections with the mission of improving detection, diagnosis, treatment, and outcomes of infections for people with CF. Although most CF infections are in the lung, sinus infections and infections following lung transplants also cause serious problems and have been included in the initiative.

The Infection Research Initiative is led by:

- Ann Field, PhD
  Senior Director of Drug Discovery and Development, Cystic Fibrosis Foundation

- Dara Riva, MS
  Director of Clinical Research Awards, Cystic Fibrosis Foundation

How the Foundation Funds Research

Currently, researchers in academia and industry can request funding for infection research through numerous CF Foundation funding channels. The Foundation receives applications for these awards on a variety of topics. Reviewers include experts in CF research and some mechanisms also incorporate direct input of CF community members (people with CF and their families into the review process. Applications are reviewed and funded based on the scientific merit of the proposal and the relevance to the CF Foundation's mission.

Although the CF Foundation receives funding applications across a broad range of subjects, sometimes a more specific request for applications (RFA) is needed to ensure research priorities are addressed. An important component of the Infection Research Initiative is a targeted request to infection researchers for applications to address key scientific questions that have been identified as priorities. This type of specific request will encourage researchers to develop proposals to address critical gaps in current knowledge.

The Infection Research Initiative-specific RFA for 2019 will be published in the second half of 2019. All other funding mechanisms will remain available to academic and industry researchers for broader infection-related research and therapeutic development. Applications received through other mechanisms will be assessed for alignment with the Areas of Research Focus and may also be considered part of the initiative.

Steering Committee

Another key component of the Initiative was the establishment of the Infection Research Steering Committee. The steering committee is made up of CF community members and individuals with experience in CF clinical care, several types of research (clinical, translational, and basic), and drug development.

The steering committee reviewed and evaluated the current CF Foundation research portfolio to identify gaps in our knowledge and recommended opportunities for further research. These recommendations influenced the Foundation's key research priorities in each of the six Areas of

Research Focus. The steering committee will continue to advise the Foundation, meeting annually to review the portfolio and update recommendations for research priorities.

Infection Research Steering Committee:

Clinicians/Researchers	CF Community members	CF Foundation staff
Co-Chair: Jennifer Bomberger, PhD	Co-Chair: Mary Leigh Phillips	Mike Boyle, MD
Ron Gibson, MD, PhD	Ella Balasa	JP Clancy, MD
John LiPuma, MD	Kirsten Kulik	Tony Durmowicz, MD
Stacey Martiniano, MD	Jennifer Spaulding	Ann Field, PhD
Eric Olson, PhD		Genevieve Maul, MS
Lisa Saiman, MD, MPH		Dara Riva, MS
Pradeep Singh, MD		

The following sections will define each of the six Areas of Research Focus, describe examples of Foundation-funded research, and outline the research priorities for the next five years. These sections will demonstrate some of the scientific approaches we are pursuing to accelerate our understanding of CF infections, improve outcomes for people with CF-associated infections, and develop new treatments. This initiative builds upon the CF Foundation's already robust infection research funding and highlights the research priorities for the future that were informed by the steering committee.

Some of these Areas of Research Focus require higher levels of investment than others to accelerate progress and make the largest impact. Therefore, spending levels across the six areas are not expected to be equal. The largest spending amounts are expected in the Developing New Treatments focus area because new treatments are a top priority and drug development is expensive.

Improving Detection and Diagnosis

Definition

Develop new ways to detect microorganisms and diagnose infection accurately, quickly, and easily for people with CF to inform patient/provider conversations about the need to treat (e.g., causing disease) and the best course of treatment.

Examples of existing research efforts

NTM infections in CF are becoming increasingly common and difficult to treat. It is, therefore, one of the Foundation's highest priority antimicrobial areas. Common NTM infections in people with CF include *Mycobacterium abscessu*s (*M. abscessus*) and *Mycobacterium avium* complex (MAC).

In 2017, the Foundation created the NTM Consortium to help standardize the diagnosis and treatment of NTM lung disease based on published clinical practice guidelines sponsored by the Foundation and the European Cystic Fibrosis Society (ECFS). The consortium is facilitating two large studies, PREDICT and PATIENCE. People with CF with at least one positive NTM culture in the past two years are eligible for PREDICT. PREDICT is an observational study of routine care of people with CF. People with CF who enroll in the study have multiple respiratory cultures

over time and routine clinical and radiologic assessment. The PREDICT protocol uses a flowchart to evaluate and treat other conditions that could be affecting the patient's health and determine whether to diagnose a patient with NTM lung disease. The determination of NTM lung disease is the trigger to discuss antimicrobial treatment.

The PATIENCE study uses consensus recommendations for treatment and follows those patients who are receiving treatment for NTM disease. The goal is to see how well the treatment plan works to reduce their symptoms from NTM disease and clear the mycobacteria from the lungs so that a standardized treatment approach can be developed. PATIENCE will be discussed in more detail in the "Optimizing Current Treatments" focus area section. The consortium of sites with expertise in NTM also creates a network of clinics where potential NTM therapies can be tested in clinical trials for future clinical trials for new therapies targeting NTM.

A separate issue is that as people with CF have overall improved health with better treatments and therapies that are becoming available, it is anticipated that a larger subset of the CF population may lose the ability to spontaneously cough up sputum for routine cultures. This may make it more difficult to detect microorganisms in the future. Research is ongoing to evaluate alternate methods of detecting microorganisms, such as using exhaled breath condensate (EBC) to scan for a microbe's "fingerprint." Additional detection technologies are also being developed.

Research priorities

There are several important areas of research to explore further as we seek ways to enhance detection and diagnosis. Over the next five years we plan to:

- Form a working group of experts to **better understand the role of fungi in CF lung infection and exacerbations**, specifically reviewing detection methods, and exploring if and when the presence of fungi constitutes a diagnosable infection that may benefit from treatment. Until the impact of fungi is better understood, it will remain difficult to test new treatments. The working group is anticipated to develop something similar to the CF Foundation's funded efforts in NTM known as the PREDICT and PATIENCE studies that are helping us to better differentiate NTM presence (without impacting the health of the person) and NTM disease (causing harm that requires treatment) as well as what treatments are most effective.
- **Support novel detection methods** beyond culture. This is increasingly important as more of the CF population becomes unable to produce sputum for culture. This includes supporting more accurate and more rapid detection methods and improving susceptibility testing methods.
- **Support research to inform updated culture guidelines in an era of highly effective modulators** to ensure that infections continue to be adequately monitored. May include monitoring of routine culture results and infection status, trying different methods for culture and comparing efficacy of methods, exploring the timing of routine cultures and which ones are done during care, etc.

Understanding CF Microorganisms

Definition

Support research to better understand CF microorganisms (e.g., bacteria, viruses, and fungi), how they are acquired, and how the body responds in order to improve treatment.

Examples of existing research efforts

This is an area with a large number of projects, as understanding CF microorganisms is fundamental to progress in the other research focus areas. Nearly 100 projects are currently being funded, the majority of which are academic basic research projects to enhance our understanding of CF microorganisms. Research is being funded on individual microbes, including *P. aeruginosa*, *Burkholderia*, NTM, *Staphylococcus*, *Stenotrophomonas*, and rhinovirus. In addition, studies are being conducted to evaluate the microbiome, interactions between microbes, and host-pathogen interactions. The Foundation is also funding research into potential novel treatments, including phage therapy (the use of bacteriophage – a type of virus that targets bacteria - to fight infections).

Research that uses clinical isolates from patients is critical to our understanding as these microbes evolve within the host over time. We support biorepositories of clinical isolates from people with CF that can be used by researchers to ensure that they are looking at the most relevant strains in their experiments.

Research priorities:

A lot of work has been done to understand CF microorganisms in isolation. With improved technologies and tools that have become available in recent years, researchers are starting to better understand how microbes interact with each other and with their human hosts in more complex environments. Over the next five years we plan to:

- **Support further research on microbial communities** in systems where the **host response** can be included to better understand how microbes change and how treatments may need to overcome barriers present in complex systems to be efficacious. This area of study includes viral, polymicrobial studies, host-pathogen interactions, and the microbiome.
- **Develop and evaluate novel model systems** (e.g., lung on a chip, chronic in vivo infection models) that can allow researchers to explore more complex interactions and chronic infection states.
- **Support research to better understand how microbes are acquired** to improve our understanding of how to minimize the risk of infection. For these studies to be successful, they will need to be linked to the patient, ideally with a companion clinical or epidemiological study to match environmental samples to infection status of an individual.
- **Standardize the methods used to collect and analyze airway microbiome** to ensure appropriate controls to mitigate contamination from mouth/upper respiratory tract or

reagents used in testing and agree on a pipeline for microbiome analysis to allow for improved cross-study comparisons.

Developing New Treatments

Definition

Support the development of safe and effective treatments for infections, including antibiotics, antivirals, and antifungals for people with CF.

Examples of existing research efforts

The Foundation's efforts to develop new treatments extend far beyond direct funding for research projects. We interacted with 71 infection-related biopharmaceutical companies in 2018 to discuss their development plans, evaluate their science and approach, provide advice, link them to resources, and in some cases, provide direct funding for their drug development efforts. We are constantly scanning the landscape for new and cutting-edge treatments that could benefit the CF community.

The Foundation is working with more companies on the development of new treatments for infections than in any other area of our research portfolio, including modulators. This includes funding for more than 12 industry antimicrobial programs, many of which are in early-stage clinical trials.

As mentioned above, NTM is one of the Foundation's highest priority antimicrobial areas. In 2019, the Foundation awarded up to $5.1 million to the TB Alliance and Johns Hopkins University to identify new treatments for the two most common NTM strains seen in people with CF (*M. abscessus* and MAC), as well as to identify a preclinical model that can accelerate testing of new drug combinations.

There are several novel antimicrobial approaches in development that are not traditional antibiotics. One innovative approach involves using gallium, a metal similar 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 was completed to see if gallium (which has already been approved by the FDA for intravenous use) is safe and effective at controlling *P. aeruginosa* in people with CF. A second trial studying if gallium is effective in treating NTM will start in 2019.

Another unique approach is exploring the use of inhaled nitric oxide (NO), a natural antibiotic that is produced by the immune system. An early stage clinical trial is underway to determine the effectiveness of this potential therapy in 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 has been supporting several studies exploring the best way to fight these bacteria.

This funding includes a Phase 3 clinical trial that started in late 2017 to test the use of inhaled vancomycin.

Research priorities

We recognize that addressing infection is not our fight alone — there has been an increase in global awareness of the need for new antimicrobial treatments across a wide range of infections. Partnering with other organizations committed to combatting infection will be critical to our success. Over the next five years we plan to:

- **Link with other organizations committed to combatting infection.** The Foundation has connected with CARB-X -- a public-private partnership dedicated to accelerating the development of antibacterial treatments – to identify companies interested in developing treatments for people with CF. In addition, the Foundation is participating in a cross-functional working group led by the Infectious Diseases Society of America and The Pew Charitable Trusts to identify policy solutions to the market failures that make antibiotic development less attractive to industry sponsors than other areas of drug development.
- **Identify promising antimicrobials that could be applied to CF infections.** This effort includes an emphasis on products already approved or in development for other indications that may also be successful in treating CF infections. Investment in developing new treatments will focus on key CF pathogens, including *P. aeruginosa*, *S. aureus*/MRSA, NTM, *Burkholderia, Stenotrophomonas*, and *Achromobacter*. As progress is made in understanding the role of fungi in the CF lung, investment in fungal treatments may be increased. Investment in antivirals also may be considered.
- **Continue to support and accelerate progress on the development of novel approaches and products that can treat multiple organisms**. We are seeing an increase in new approaches (e.g., phage, immunotherapy, toxin neutralization, prevention/vaccination strategies, etc.) as alternatives or adjuncts to traditional antibiotics. The Foundation will continue to encourage unique approaches to infection treatment and support strong science in this area. Approaches that can be developed through established regulatory pathways to commercialization making therapies widely available will be prioritized.
- **Enhance the preclinical platform and develop a clinical platform for difficult-to-treat organisms.** A large part of developing new treatments is understanding the clinical path to approval of a final product (e.g., study design, clinical endpoints, etc.). The Foundation will work with experts to develop clinical development plan options for difficult-to-treat organisms that industry can use as a model for their clinical development plans.

Optimizing Current Treatments

Definition

Identify better ways to treat infections that maximize effectiveness and minimize the overall treatment burden for people with CF.

Examples of existing research efforts

CF care has changed substantially over the years, benefiting in part from studies aimed at discovering the best treatment regimens and combinations for patients. Evidence for the success of a particular treatment plan is needed to support inclusion in treatment guidelines and improve outcomes for people with CF. Research in this area aims to optimize available treatments to ensure that they are used in the best way possible for CF care.

Sometimes there isn't a clear treatment plan, particularly for difficult-to-treat infections. This was the case a few years ago with NTM. To address this issue, the PREDICT and PATIENCE studies were designed to implement consensus guidelines for diagnosing NTM disease, standardizing treatment, and exploring the effectiveness of this approach. The PATIENCE study follows patients identified with NTM disease in the PREDICT study (discussed above in Detection and Diagnosis) who are receiving treatment to see how successful the treatment plan is. The goal is to develop a standardized effective treatment plan for NTM disease. The researchers follow a specific treatment algorithm to combine antibiotics into a treatment plan. By doing so, they can evaluate how well existing treatments clear NTM infection and use these results as a baseline for testing new treatments for NTM.

Exacerbations are complex, and treatment plans may vary from care center to care center. 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.

Research priorities

The Infection Research Steering Committee recommended that the Foundation focus first on defining standard therapy approaches, before expanding into personalization of treatments. Over the next five years we plan to:

- **Form a working group to advance our understanding of exacerbations and exacerbation phenotypes**. Currently, we treat all exacerbations in a similar way without differentiating the potential cause (bacterial, viral, etc.). We hypothesize that exacerbations likely have multiple different causes. If we could differentiate exacerbation phenotypes, we could explore treatment options to determine which ones are the most appropriate for certain types of exacerbations.
- Expand on success of PREDICT/PATIENCE approach to **standardize treatment for other difficult-to-treat infections** (e.g., fungi).

- **Continue STOP studies.** Leverage data from existing STOP studies to see what additional questions can be answered in retrospect. Utilize this platform for future exacerbation studies.
- **Fine-tune dosing of drugs** for multi-drug-resistant gram-negative organisms. Consider pharmacokinetics (the study of how drugs move into, through, and out of the body) and drug-drug interactions of FDA-approved antimicrobials with each other and with other concurrent medications to optimize dosing in people with CF.

Evaluating Long-Term Antimicrobial Use

Definition

Understand how long-term or frequent, intermittent antimicrobial use affects people with CF to optimize benefits and reduce risks.

Examples of ongoing research

Long-term or frequent use of antimicrobials can be associated with side effects in addition to the expected benefits of infection control. Research that seeks to understand and mitigate known risks is ongoing.

Long-term antibiotic use (e.g., aminoglycosides, such as tobramycin) can cause acute and/or chronic kidney injury. If we could predict who is at risk of developing kidney problems, we could potentially adjust dosing or length of treatment to help lessen this risk. We are funding a pilot study that is looking for biomarkers to help identify individuals who may be at higher risk of kidney injury.

Hearing loss (ototoxicity) from aminoglycoside antibiotic use is a concern for people with CF. The Foundation is funding multiple projects to better understand ototoxicity including new treatments to prevent or mitigate aminoglycoside-related hearing loss.

Frequently, antibiotics are prescribed to young children presenting with a cough, even when the cause is due to a virus. The Foundation is funding a study to examine the impacts of prescribing antibiotics for viral infections in very young children with CF.

Research priorities

A key to understanding the impact of long-term antimicrobial use is the ability to identify emerging risks and benefits of antimicrobial use. Large datasets are needed to identify events that may occur with low frequency. Over the next five years we plan to:

- **Review databases available and develop a strategy to monitor** for emergent risks over time.
- **Gather data to demonstrate evidence for sustained effects** (benefit, neutral, or detriment) of antimicrobials used chronically.

- **Investigate the mechanisms behind known toxicities** with the goal of identifying targets for therapeutics for treatment or prevention. Improve our understanding of drug-drug interactions.
- **Support companies developing mitigation treatments and prevention strategies** for known toxicities (e.g., ototoxicity)
- **Support studies looking at ways to identify those at higher risk of developing complications** from frequent or long-term antimicrobial use, such as kidney injury, to help physicians determine the best treatment approach for that individual.

The Future of CF Infection

Definition

Understand how infections are influenced by treatments that address the underlying cause of CF.

Examples of existing research efforts

When the first CFTR modulator was approved, researchers began to study how restoring CFTR function would affect the lives of people with CF. GOAL was a prospective study of people with CF aged 6 years and older who were starting ivacaftor (Kalydeco®). It showed that over the course of a year, the number of positive *P. aeruginosa* cultures decreased in participants who tested positive in the year before they started taking ivacaftor. Similarly, another longer-term study looking at a small cohort of Irish adults with chronic *P. aeruginosa* infections showed that their *P. aeruginosa* levels decreased during their first year on ivacaftor; however, over the next 4 years, their levels appeared to rebound.

Other researchers are studying the impact of modulators on the body's response to infection. For example, one study has demonstrated that macrophages (one of the body's immune cells responsible for clearing bacteria) respond differently to *Burkholderia* infection when treated with some CFTR modulators.

Much work remains to be done to understand how CFTR modulators and other therapies that address the underlying CFTR defect will affect patients with existing infections, as well as those who have yet to be infected. We are committed to further studies to determine how things change for people with CF after starting modulators as this will be important for improving future care.

A large prospective study is being planned called "PROMISE" that will evaluate the impact of the new triple-modulator therapy on many different outcome measures if the therapy is approved. This study would incorporate multiple substudies, including one focused on assessing the impact of highly effective modulators on infections.

Research priorities

With highly effective modulator therapy on the horizon, this is a critical time to gain knowledge about what may change in the face of treatments that could have a substantial impact on the underlying cause of CF in a significant portion of the CF population. Over the next five years we plan to:

- **Support PROMISE** and other studies to gather baseline samples for future study to **evaluate the impact of modulators on participants' current infection status, their response to infection, and future infection risk.**
- **Ensure there is an infection focus** within the larger body of work for understanding the impact of highly effective modulators including **identifying patient phenotypes and exploring extreme phenotypes thoroughly.**
- **Fully explore available prospective ivacaftor data** to aid in identifying patient phenotypes and how responses to therapy may impact existing CF infections and future CF infection risk.
- **Evaluate the CF Foundation Patient Registry data over time in the younger ivacaftor-treated population** to start to understand the impact of starting CFTR modulator treatments in a younger, healthier population on infection status and infection risk.

For More Information

We are committed to transparency regarding our research efforts for infection and will launch a special section of the website dedicated to the Infection Research Initiative. This section will have the latest updates on funding and progress in each of the research focus areas.

For questions, please contact Genevieve Maul, Director of Research Communications, at gmaul@cff.org.