Cystic Fibrosis Trust

Impact of CF Innovation Hub on lung health

University of Cambridge

April 2024

Uniting for a life unlimited

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Foreword

The CF Innovation Hub on lung health at the University of Cambridge was established in 2018 under the leadership of Professor Andres Floto. Thanks to the incredible generosity of our supporters, Cystic Fibrosis Trust successfully raised £5 million for the Innovation Hub, which was match-funded by the University of Cambridge.

As the programme draws to a close, we share some of the highlights of this incredible collaboration over the past six years.

The nature of the investment and the collaboration in the Innovation Hub has enabled the researchers to tackle ambitious, innovative and high-stakes programmes of work. It has brought together a truly world-leading collaboration of exceptional calibre scientists. They have been able to make rapid progress and adapt with speed and innovation as new knowledge emerges. The work in the Innovation Hub has complemented our other research activities such as our Strategic Research Centre and Venture and Innovation Award funding, as well as activities within the CF AMR Syndicate.

The last six years have been an exciting and challenging time for the CF community. Access to CFTR modulator medicines such as Kaftrio has been life-changing for so many people with CF in the UK. However, it has brought renewed anxiety for those unable to benefit. In contrast, the COVID-19 pandemic has been a worrying time for people with CF and their loved ones, spending much of it shielding in order to protect themselves. For scientists, lockdowns and social distancing brought frustrating obstacles and delays to their research.

The activities in the Innovation Hub have reflected these external changes. Knowledge gained from understanding CF lung infections has been applied to understanding the COVID-19 virus and treatments for it. Digital health studies running parallel to the Innovation Hub programme were accelerated during the pandemic to enable virtual care, and data from these have been used by Hub researchers to refine an algorithm predicting lung exacerbations.

We know that while the health of those on CFTR modulators has improved significantly, they continue to develop lung infections. This means that everyone with CF still needs access to effective medicines to treat these infections.

We are delighted with the success of the CF Innovation Hub on lung health. World-class advances in our knowledge of CF lung infections have been made. It has attracted new expertise into CF research and the leadership of the principal investigators and interdisciplinary collaboration have inspired and supported the next generation of CF researchers. It has also attracted new and exciting further funding. The Innovation Hub exemplifies what can be achieved with this level of investment and multidisciplinary collaboration. It has been the inspiration for the creation of our new Translational Innovation Hub Network in partnership with LifeArc, which we will announce later in the year.

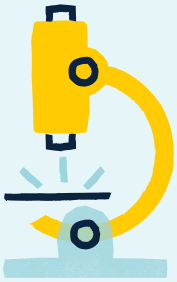
Thank you so much for your contribution to being a part of it. We hope you enjoy reading some of the success stories and the voices of those involved.

Dr Lucy Allen, Director of Research and Healthcare Data, Cystic Fibrosis Trust

Key highlights

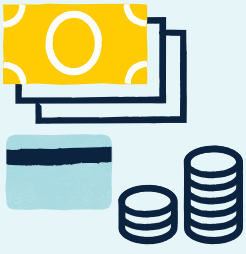
10 new targets for antibiotic drug discovery identified

19 world-class scientific reports published



Supported and developed the careers of 24 early career researchers

Attracted five world-class researchers into the field of CF research for the first time



Led to further funding from seven organisations

Introduction

CF lung infections

People with CF are particularly susceptible to developing lung infections caused by bacteria, fungi and viruses due to the build-up of thick, sticky mucus in their lungs.

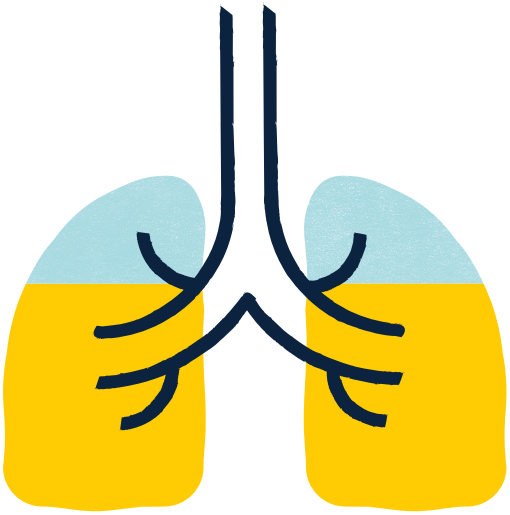
The thick mucus makes the bugs they are exposed to difficult to remove. Collectively bacteria, fungi and viruses are known as 'microbes', and the group of medicines designed to treat these infections are known as antimicrobial medicines.

Cystic fibrosis care is very dependent on the use of antimicrobial medicines, particularly antibiotics for the treatment of lung infections. Antibiotics are used proactively to control the extent and harmfulness of existing bacterial infections, as well as for treating flare-ups of sudden dips in lung health known as exacerbations.

Exacerbations may require long courses of treatment, at hospital or at home, with unpleasant side effects and significant disruption to day to day life. Left untreated, these infections can trigger permanent lung damage, meaning people are more breathless and have less energy for daily activities.

The bugs causing these infections are becoming resistant to existing antimicrobial medicines such as antibiotics. It means the medicines aren't as effective or no longer work as a treatment. This is known as antimicrobial resistance (AMR). New medicines to treat CF lung infections are urgently needed to overcome AMR.

Serious infections caused by the bacteria *Mycobacterium abscessus* (*M. abscessus*), that are part of the NTM group of infections, and *Pseudomonas aeruginosa* (*P. aeruginosa*) are becoming resistant to medicines, and they are a particular focus of the CF Innovation Hub on lung health.



CF Innovation Hub on lung health

The aim of the CF Innovation Hub on lung health at the University of Cambridge is to harness multidisciplinary world-class research to accelerate progress towards preventing lung damage in CF and subsequent loss of lung function.

Researchers addressed four key areas that would improve lung health for people with CF, these were:

- designing medicinal chemicals as treatments for *M. abscessus* and *P. aeuruginosa* infections
- developing better ways to manage lung health using home monitoring and machine learning data
- investigating how future medicines could be personalised to individuals with CF (which may also be applied to repairing the lungs in future)
- creating a national resource for future research

Designing medicinal chemicals

Current antibiotics work on very precise sections of specific proteins, known as 'targets', within the bug they're being used to treat. If the bug evolves and adapts to live without the targeted protein, the medicine that acts on it becomes less effective.

To develop new antibiotics researchers need to:

1. find new proteins to target, and
2. find chemicals that act on the new targets as a starting point to make new medicines.

Identifying targets

Researchers at the Innovation Hub have identified six new targets for the bacteria *M. abscessus* and four new targets for the bacteria *P. aeruginosa*. The researchers identified these targets by extracting bugs from samples from people with CF, and then analysing the bacterial DNA. For each of these protein targets, further analysis has confirmed that inactivating them is an effective strategy for developing new medicines.

Bacteria constantly adapt and change to their local environment by changing their DNA. Understanding how these bugs are changing in the lungs of people with CF is important for managing treatment of infections and developing new antibiotics.

Antibiotics are designed to work on specific 'essential' bacterial proteins, so if bacteria no longer need or use that protein, the medicine will be less effective. To design new antibiotics that are likely to be effective for strains of *M. abscessus* and *P. aeruginosa*, scientists need to identify new essential proteins.

Researchers at the Innovation Hub have successfully conducted studies to try and identify new drug targets, with access to samples from people with CF, using exciting new technologies and the expertise to analyse the results. This has included sophisticated novel gene editing techniques to identify new essential proteins, and validating their findings in the lab. Medicinal chemists have begun designing new antibiotics against these targets and their results have been reported in several high-profile research papers.

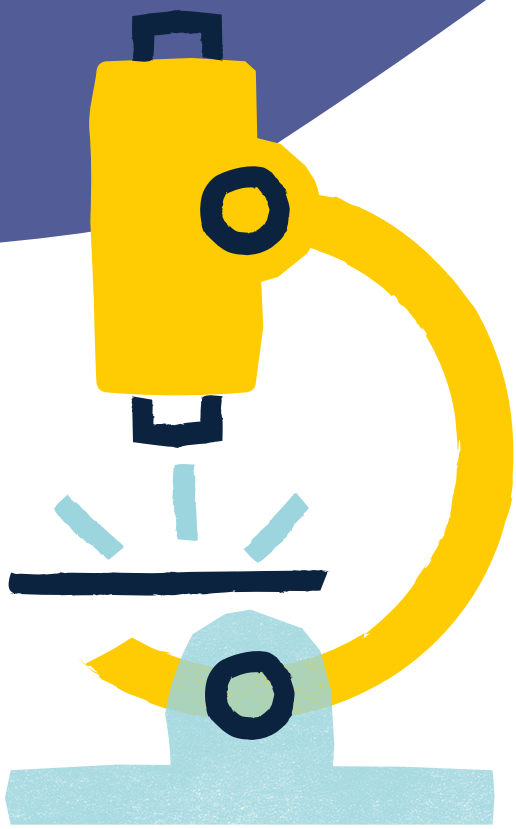
From bacterial genetics to a new clinical trial

Analysis of the DNA of the infection-causing bacteria *Mycobacterium abscessus* (*M. abscessus*) highlighted a possible new approach to treating infections. Researchers at the Innovation Hub are working with a biotech company to test this approach in an early stage clinical trial on people with CF in Cambridge.

Of the many different strains or variants of *M. abscessus* that exist, only a few cause serious, hard-to-treat infections in the lungs of people with CF. Studying how the bacteria change and adapt into infection-causing strains can provide important information on how to prevent these infections from developing, and highlight new approaches to treating them.

Studies of how bacteria adapt are conducted by analysing their DNA – their genes. Scientific research published by Dr Josie Bryant and colleagues within the Innovation Hub reported on a general process for how *M. abscessus* evolves in the lungs of people with CF.

One of their findings was that an infection-causing variant had evolved to become less sensitive to nitric oxide, a chemical produced in the body to fight off infections. The biotech company 30Technology has developed a treatment that releases nitric oxide when it comes into contact with *M. abscessus*. Researchers hope that when the nitric oxide from the body is combined with extra nitric oxide from the treatment, this will be sufficient to kill the less sensitive bacteria. This treatment is currently being assessed in a CF clinical trial at Royal Papworth Hospital.



Developing chemicals that work against these targets

Once the protein targets within a particular bug, or strain of bugs, have been identified, the next step is to design a medicine that works against these targets. This is a long process that can take many years to achieve. It requires an understanding of the shape and properties of the protein target and careful chemical design of the medicines.

To understand the shape and properties of the protein target, more traditional methods such as X-ray crystallography have been used alongside cutting-edge artificial intelligence software, such as Deep Mind's AlphaFold protein analysis software.

For the chemical design of the medicines, one of the strengths of the Innovation Hub is the diversity of approaches that have been adopted, including **fragment-based drug design** and **diversity orientated synthesis** approaches, which are explained below. Licenced medicines for other conditions have been designed using both of these approaches.

Innovation Hub researcher Professor Sir Tom Blundell has applied his **fragment-based drug design** approach to developing new antimicrobial medicines. An analogy to explain how this approach works is the design of a made-to-measure shoe. Small chemicals or 'fragments' are tested for their fit in each part of the protein target (fitting the shoe material against each part of the foot) and then the different chemical fragments are joined together to make a larger chemical that can be tested for its effectiveness as a medicine (making the shoe and trying it on).

Professor Dave Spring is a pioneer of a design approach known as **diversity oriented synthesis**. The starting point for using this method within the Innovation Hub was to test whether chemicals that have very different chemical properties to each other could kill or prevent *M. abscessus* from growing. The chemicals that work best are known as 'hit' chemicals. The second stage was to identify the bacterial proteins that the hit chemicals target.

Such a wide-ranging medicinal chemistry skillset and level of expertise was considered as "hugely impressive" by the Innovation Hub's Independent Scientific Advisory Board: **"Hugely impressive work. High-quality science and extensive expertise in drug discovery and chemistry"**.

One of the challenges of developing new antimicrobial medicines is getting the drugs into bugs themselves, and then keeping them there. Alongside the extensive research to develop new medicinal chemicals, the researchers have also developed complementary methods to increase the likelihood of the medicines staying inside the bacteria – where the antibiotic needs to be to have an effect.

Making protein models available to all

An important task in successful drug design is knowing what your protein target looks like. Proteins start off as a straight string of (amino acid) building blocks that become intricately folded to do their job. Each protein has a unique shape and chemical properties.

Innovation Hub researchers created 3D structural models of all the ~3,400 proteins made by *M. abscessus*. The models are now freely available in a protein database for researchers across the world to use. This is a phenomenal achievement! Prior to the publication of this database, information on only 53 *M. abscessus* proteins was publicly available. The creation of these models is vital to design chemicals that 'fit' the new target proteins identified in the Innovation Hub and will speed up the search for effective antibiotics against *M. abscessus* internationally.

Keeping medicines inside bacteria

Bacteria have natural defences to protect themselves from toxins. To be effective, antibiotics need to overcome these defences. A greater understanding of how to evade them would make antibiotic design significantly easier. Researchers at the Innovation Hub have developed new rules to address this problem, which could leave a huge legacy for the future design of new medicines.

An early step in the design of a new antibiotic is to test how much of it is needed to kill or stop bacteria from growing. Researchers at the Innovation Hub found that they had chemicals that were a good match for the protein targets they had identified, but they performed poorly in this test. They found that the chemicals were either not getting inside the bacteria very well – where the antibiotic needs to be to have an effect – or the medicines were quickly being pumped out of the bacteria.

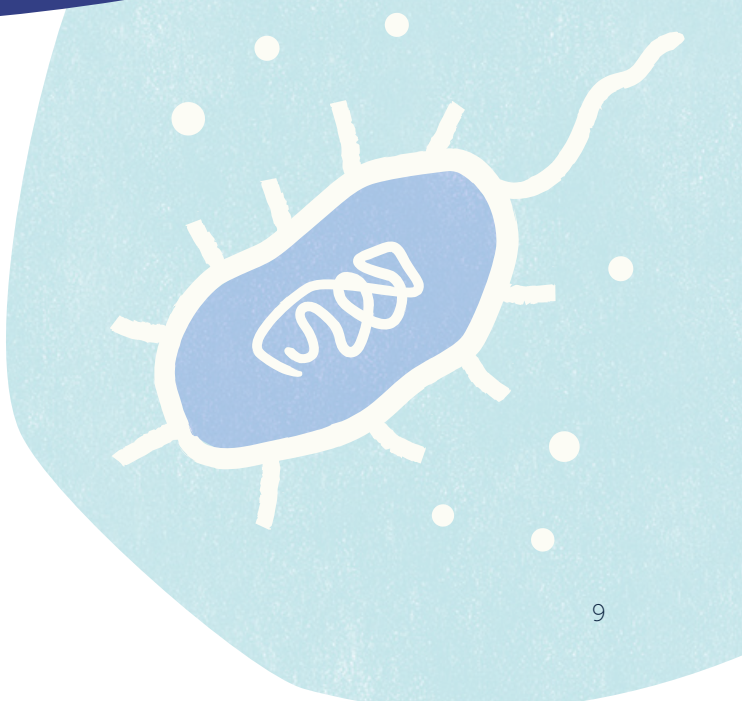
To investigate, they initially tested approximately 1,000 fragments for their ability to get inside (permeate) the bacteria. At the same time, they calculated the chemical properties of these fragments. They found that they could use the properties of the chemicals to predict their permeability into the bacteria, and saw the potential to create 'permeability rules' to assist with the design of new antibiotics.

To do this, the researchers screened tens of thousands of chemicals and developed quicker and easier methods to detect their presence inside the bacteria, a useful tool that could be used widely. The researchers also developed methods to disregard chemicals that had bound to the cell wall of the bacteria or were broken down by them. These data are currently being used to build and refine a machine-learning algorithm to predict permeability.

Prof Floto and colleagues have received support from the Bill and Melinda Gates Foundation to apply these techniques to the related bacteria *Mycobacterium tuberculosis* which causes TB (where the 'permeability rules' may be different to *M. abscessus*).

These methods have been described as 'permeability rules'. In addition to the design of new antibiotic medicines for CF-related lung infections, these 'rules' will be useful for researchers and companies who are developing new antibiotics for other infections.

"In terms of the size and breadth of the impact, I think that developing the permeability rules for new antibiotics is going to be our biggest legacy of the Innovation Hub," commented Prof Andres Floto.



Researcher profile

Dr Josie Bryant

"Working in the Innovation Hub had a direct impact on setting up my lab..."

Before becoming at team leader at the Sanger Institute in Cambridge, Dr Josie Bryant spent some time working as part of the Innovation Hub team at the University of Cambridge. Here, she tells us about her career so far and the benefits of working in a multidisciplinary research group.

"I started working on *M. abscessus* infections in people with CF as part of my PhD in collaboration with Prof Andres Floto. At the time, very little was known about the genetics of *M. abscessus* and I found it fascinating how much there was to discover. A few years later, I joined Prof Floto's lab at the University of Cambridge with funding from my Henry Wellcome Fellowship. I was directing my own research with Prof Floto as my mentor. We worked together as one team, with those funded directly from the Innovation Hub.

"The results I got when I was part of the Innovation Hub, studying the genetics of *M. abscessus* have been a highlight of my career so far.

"When you look at how a bacteria or a virus mutates, most of it is random, and it doesn't really matter to the biology of the bug. What I found was that in different people with CF, the same set of genes of *M. abscessus* kept evolving. We saw it over and over again. You rarely see a signal that strong, but it still excites me now to see that data. It tells us what the bug does to grow so well in the lungs of people with CF and become much more difficult to treat.

"I felt very lucky to be in that lab. There were clinicians, chemists, mathematicians and microbiologists all working together. Because we were so interdisciplinary, we could all come at the problem from a different angle, doing different kinds of experiments and providing experimental evidence for the observation I'd made from the genetic data.

"I'm now a team leader at the Sanger Institute in Cambridge, where I have built a research group of six scientists. Working here is very collaborative, and I've been making the most of that. It's how science should be done!

"The experience of working as part of the Innovation Hub has had a direct impact on how I've set up my lab here. I find it important to have clinical collaborators to really understand the medical condition I'm studying and to be able to sense check what the data is telling us with their clinical experience. A huge part of my research still focuses on cystic fibrosis."

Researcher profile

Dr Aaron Weimann

"The Innovation Hub has given me a springboard for the rest of my career..."

Computer scientist Dr Aaron Weimann become a postdoctoral fellow at the University of Cambridge at the beginning of the Innovation Hub programme. Here, he tells us more about his career so far.

"I have been fascinated by the world of microbes since my undergraduate studies. It's astounding to think about the diversity of microbial life that exists, mostly invisible to the naked eye. My journey into the world of infection-causing bugs and the global challenge of antimicrobial resistance began at the Helmholtz Center of Infection Research in Braunschweig, Germany. This is where I developed methods to predict antimicrobial resistance to treatment directly from the DNA of the bacteria.

"For my postdoctoral research, I looked for a place where I could bridge the gap between fundamental academic research and having a practical impact on patient care. Joining Professor Floto's lab felt like the perfect fit! Cambridge is an exciting and busy place to do research, with so much great science underway. The Centre for AI in Medicine, where I'm based, gives me access to an inspiring peer network who are working on cutting-edge research. I collaborate with global leaders in microbial evolution, such as Professor Julian Parkhill. Here, I've found an ideal environment to explore the interface of computer science, microbiology, and infection research.

"My passion for research is the thrill of exploration – being the first to uncover new insights and sharing them with the world. A defining moment in my career has been a ground-breaking discovery about *P. aeruginosa* that has just been published: we have found fundamental differences in bacteria infecting people with CF and those without CF, offering real-world implications for infection control of vulnerable patient groups.

"Long-term funding from the Innovation Hub has empowered me to pursue impactful research with tangible benefits for people with CF, and collaborate with like-minded researchers in Cambridge and beyond – an ideal springboard for the rest of my academic career."

Developing better ways to manage lung health

Early prediction of lung exacerbations

Separately funded to the Innovation Hub, Prof Floto and colleagues have been working with people with CF in the initial SMARTCARE and subsequent Project Breathe research programmes. The aim is to develop ways for people with CF to monitor their health at home and help to maintain stability of health.

"For those who took part, it was liberating because they could see on a daily basis from the graphs how their health was," commented Judy Ryan, lead research nurse of SMARTCARE and Project Breathe.

"It's easy to forget how quickly technology has developed and progressed. For teenagers with CF, their whole life has been about using technology and obtaining information 24/7 – whether that info is good or bad. It's wonderful to see that we have managed to use technology for the benefit of people with CF and that they are able to track their health in a positive way."

Using data from these studies, which was generously shared by the participants, Dr John Winn and Professor Andres Floto at the Innovation Hub have successfully developed and tested computer programs (algorithms) to predict flare-ups of infection (known as exacerbations), more than a week before people experience these symptoms.

The algorithm was initially developed using data from the SMARTCARE study of 147 participants with six months of home monitoring data. It was further refined using data from the subsequent home monitoring study Project Breathe.

The Innovation Hub team were recently awarded funding from NIHR and LifeArc to test the program in a clinical trial known as ACE-CF. The aim of ACE-CF is to test whether it is possible to predict an exacerbation using real-time data, as people with CF use a specially developed home monitoring app (called BREATHE RM) on their smartphones alongside their normal CF care.

"For me, one of the most exciting programmes within the Innovation Hub are the studies underway to predict exacerbations," explained Jade, who has CF and sits on the Hub's Independent Scientific Advisory Board.

"Like many people on Kaftrio, I have fewer exacerbations than I used to, but they do still occur. They're a lot harder for us to detect because we don't have the symptoms we're used to. It means that the symptoms can become more advanced before they're treated. Being able to detect early changes using an app would be super helpful in treating them sooner."

A match made in Cambridge

One of the ways Cystic Fibrosis Trust can enable research is to identify overlaps and synergies in the CF research community's interests.

Professor Mihaela van der Schaar, Professor of Machine Learning and AI at the University of Cambridge, is investigating whether analysis of data collected over a longer period of time (taken from the UK CF Registry) could identify when key changes in the health of someone with CF are likely to take place. For example, is it possible to predict whether someone is likely to develop a specific complication of CF and if so, at what age?

Following introductions by Cystic Fibrosis Trust, Professor Andres Floto and Professor van der Schaar have developed an exciting and fruitful collaboration, securing several joint research funding grants and establishing the Cambridge Centre for AI in Medicine, of which they are co-directors.

They have also received follow-on funding from the Cystic Fibrosis Foundation to apply advanced machine learning methods to analyse UK CF Registry data to find ways to better personalise treatment and create tools to help in clinical decision-making.

"My collaboration with Prof Andres Floto is all about innovation and novel approaches," commented Professor van der Schaar.

"By harnessing the power of data, we can predict the trajectories of disease and optimise treatments for individuals with CF – paving the way for a future where personalised healthcare is a reality. Thanks to the Trust and its pioneering patient database, the UK CF Registry, our partnership is fuelling progress, one project at a time."

Professor Andres Floto

Professor Mihaela van der Schaar

Developing regenerative medicine approaches for treatment

Stem cells are a special type of cell that can serve as a repair system in many different places in the body.

In the last few decades, researchers have been using them to understand the root causes of many different conditions, as well as developing methods to repair or replace cells damaged or lost due to disease. Treatments that work by repairing or replacing cells are known as regenerative medicines.

Stem cells can be created from cells in the blood, and then these stem cells can be converted into many different types of lung cells that are important for keeping the surface of the lungs clean, hydrated, and infection-free.

Researchers at the Innovation Hub have made excellent progress in two specific areas:

1. creating, understanding and testing the use of stem-cell grown lung cells as a potential method for future regenerative therapy
2. understanding more about how and why individuals with CF with the same CF mutations have different experiences of the condition by studying variations in non-CF genes in stem cell-grown lung cells.

Researcher profile

Dr Marta Vila Gonzalez

> "A great opportunity for me to broaden my knowledge and make my research more multidisciplinary..."

Working in research is a competitive career path. After completing a PhD, it can be increasingly difficult to obtain further funding and secure a permanent research position. Ultimately, researchers must be able to demonstrate their independence to further their careers and continue to contribute to CF research.

Dr Marta Vila Gonzalez is a postdoctoral research fellow at the University of the Balearic Islands and the Health Research Institute of the Balearic Islands (IdISBa). From 2018 to the end of 2023, she worked at the Stem Cell Institute, University of Cambridge as part of the Innovation Hub. Initially funded directly from the Innovation Hub as a post doctoral research assistant.

In 2020 Dr Vila Gonzalez was awarded a prestigious Sir Henry Wellcome Postdoctoral Fellowship, giving her financial independence to continue her CF research. The award recognises her potential as a future leader in this field, and the opportunity to set the direction of her CF research.

Dr Vila Gonzalez has been pioneering the use of cutting-edge induced pluripotent stem cell technology to derive ionocytes to study in the lab. Ionocytes are a new type of lung cell and were only very recently characterised. They have been shown to contain large amounts of CFTR, the protein affected in CF, and are therefore an important cell type to understand to develop effective treatments for CF.

"Receiving the Sir Henry Wellcome Fellowship was a very important milestone in my career. It has been a great opportunity for me to broaden my knowledge and make my research more multidisciplinary by establishing exciting collaborations that will be maintained through my scientific career. Ultimately, obtaining this award is a key step to become an independent scientist and is helping me establish myself in the field of CF research in my home country."

Creating a national resource for future research

At the outset of the programme, one aim of the Innovation Hub was to create a national research infrastructure to accelerate the progress of CF research across the UK. This has been established in the form of the CF BioResource project as part of the National Institute for Health and Care Research (NIHR)'s Rare Disease BioResource.

The CF BioResource was created by Professor Andres Floto, Director of the Innovation Hub and Professor Alex Horsley, Director of Manchester Adults CF service, with the support of Dr Lucy Allen, Director of Research and Healthcare Data at the Trust.

Supported by the clinical trial network within the Trust's Clinical Trial Accelerator Platform (CTAP), around 900 participants have been recruited into the CF BioResource project so far. Talks have recently begun to establish the processes for researchers to gain access to the resource.

Resources for developing personalised medicines for CF

The availability of treatments that are tailored or personalised to individuals with CF is a long-term goal to improve the lives of everyone with CF. Progress towards this goal has been accelerated due to work at the Innovation Hub, through lab-based research and by leading an infrastructure project to make clinical studies more feasible.

CF affects everyone differently. Even two children with the same parents may have different symptoms, numbers of infections, or longevity, despite similar treatment options. Some of those differences may be caused by natural, small differences in other (non-CF) genes. But we don't know enough about which genes these are or how or when they exert their effects.

"I've always been quite well; however, a lot of other people with same mutations as me haven't been. I'd like to know why there's that difference. If it's behavioural, I can keep doing it, but if it's genetic, it opens up a huge avenue for different treatment options," said Jade, a member of the Innovation Hub's Independent Scientific Advisory Board.

Professor Alex Horsley

Alongside the important ways of understanding the contribution of non-CF genes to CF in the lab, using stem-cell-derived lung cells (see page 14 'Developing regenerative medicine'), research studies in people with CF can also help scientists to increase their knowledge in this area. However, identifying participants who have specific non-CF gene variants is extremely difficult. The NIHR BioResource programme is designed to address this.

"Information about non-CF gene variations is not easily available to clinical researchers, and this can slow down studies or prevent them from happening. The CF BioResource is creating a register of people with CF who have agreed to be contacted about research, based on their genetic make-up. We hope that this will provide a strong incentive for researchers to work in this area," said Dr Lucy Allen, Director of Research and Healthcare Data at the Trust.

"Selecting people with CF to take part in research studies based on their non-CF genetic profile is a very powerful tool. This isn't possible in other countries, so it will attract researchers to conduct their studies in the UK," said Prof Alex Horsley.

So far, the CF BioResource has recruited around 900 people with CF to give a sample for research and join a registry of people who are willing to take part in future research.

"Deciding to take part was a no-brainer, really. It required virtually no effort on my part. I had to give a blood sample, which is done routinely anyway. Research is vital, and I would definitely encourage others to participate," said Alan, who has provided their genetic information to the CF BioResource.

Wider reach of CF Innovation Hub on lung health

Research within the Innovation Hub has massively accelerated the pace of progress in improving lung health in cystic fibrosis. In addition, the new knowledge gained and methodologies created will accelerate progress in other areas of medical research, beyond CF.

People living with CF are particularly vulnerable to antimicrobial-resistant lung infections. However, in a wider context, antimicrobial medicines are the cornerstone of modern medicine. The emergence and spread of drug-resistant bugs affects the ability of medical teams around the world to treat common infections and to perform life-saving procedures, including cancer treatments, organ transplantation and many other types of surgery. In addition, drug-resistant infections impact the health of animals and plants, reduce productivity in farms, and threaten food security.

New knowledge gained about how to prevent CF infection-causing bacteria *M. abscessus* and *P. aeruginosa* from being passed on and how to develop more effective treatments for them can be adapted and applied to other infections caused by these bacteria in other conditions. These include research databases and toolkits, such as the Mabellini database of the shape and properties of all of the proteins within the *M. abscessus* bacteria (page 8 of this report), which can be used by all researchers working to prevent and more effectively treat this infection; and a database that allows easier comparison and analysis of the genetics of infection-causing bugs known as 'Panaroo'.

New methods for developing better and more effective antimicrobials against *M. abscessus* and *P. aeruginosa* have established principles that can be applied to developing medicines against other infection-causing bugs, such as the medicinal chemistry methods applied (page 8) and the 'permeability rules' for keeping medicines inside bacteria (page 9).

Collaboration across medical disciplines is key to advancing science. We were delighted that funding for the Innovation Hub helped secure matched funding from Government to build the new Heart and Lung Research Institute (HLRI) on Cambridge's prestigious Biomedical Campus. Multidisciplinary working has been an essential component of advances made within the Innovation Hub. The HLRI will allow researchers to develop further collaborations from different disciplines and other disease areas.

Pioneering new methods to understand how infections are passed on

Understanding how people become infected with *M. abscessus* and *P. aeruginosa* can help prevent more people from becoming infected in the future.

Researchers at the Innovation Hub have used 'mutation signatures', a method used in cancer research, to understand how infection-causing bugs are passed on. This is the first time this method has been used to study infections.

Their research has answered important questions in CF research, led to an increased understanding of COVID-19 infections and treatments for them, and has the potential to be applied to help understand many other infectious diseases.

Location-tracking bacteria

Each time a bug is exposed to a new local environment or stress, it leaves a trail of changes in the DNA (mutations). The mutations that occur in each new environment are unique and these changes are known as a 'mutation signature'.

Although *M. abscessus* infection is mainly reported in people with CF, doctors have found that people with smoking-related lung damage are also susceptible to *M. abscessus* infections. Strains of *M. abscessus* found in the lungs of smokers acquired a specific mutation signature due to smoking-related damage.

Researchers from the Innovation Hub looked at these mutation signatures to answer an intriguing question of how CF infection-causing variants of *M. abscessus* were able to travel around the world. The question arose when the same infection-causing strain of the bacteria was found in the lungs of people with CF who live in the UK and Australia among other places, who had never met.

"Our analysis is the first time these mutation signatures have been used in bacteria to study their past environmental exposures. It allowed us to demonstrate a connection between *M. abscessus* infection in smokers and people with CF, but we need much more research to find out more," explained Professor Julian Parkhill, Innovation Hub Principal Investigator.

Applying new techniques to understand COVID-19 infection and treatments

The principle of using mutation signatures to track the environment and locations of strains of *M. abscessus* can be applied to other bacteria and viruses. During the pandemic, Innovation Hub researcher Dr Chris Ruis spent time helping to analyse the genetics of the COVID-19 virus.

Together with an international team of researchers, he looked at the mutation signatures in variants of the COVID-19 virus. They found a specific signature related to an antiviral medicine used to treat the infection. Their results highlighted the need for increased risk assessment when using this medicine, and flagged a caution for the development of future medicines that work in a similar way.

Dr Ruis and other members of the Innovation Hub were also able to use mutation signatures to identify the severity of infection of variants of COVID-19. Variants that infect both the upper and lower respiratory tract can result in more severe infections than those that only infect the upper respiratory tract. They found specific mutation signatures for each part of the respiratory tract. In future, analysing the mutation signatures of emerging COVID-19 variants could give an early indication of their likely severity.

New tool to investigate mutation signatures

Next, the team looked at patterns of many mutation signatures (collectively known as 'mutational spectra') from many different infection-causing bacteria (e.g. *M. abscessus*, *P. aeruginosa* and many others). Across all the bacteria they looked at, they identified a specific mutational signature that was always associated with lung infection. This allowed them to say that the bacteria showing these signatures transmit between people rather than being acquired from the environment.

"This is the strongest evidence we have that the source of *M. abscessus* infection, and other pathogens in people's lungs, is from other people with the same lung infection, rather than developing the infection from the environment," said Prof Julian Parkhill.

As part of this work, the researchers developed a freely available database which will enable all researchers to study the mutational spectra of the bugs they are investigating.

"We hope our MuTui database will be used by other researchers so we can learn together how the analysis of mutational spectra can help us tackle new and existing infections," commented Dr Chris Ruis.

Researcher profile

Dr Chris Ruis

"It's very exciting to be at the start of something new..."

Dr Chris Ruis is a post doctoral research fellow funded through the Innovation Hub. His research on mutation signatures has led to three important research papers in prestigious journals, advancing our understanding of lung infections in CF, and a wider group of infections including the COVID-19 virus. We asked him about his research and working in the Innovation Hub.

"My research focuses on where bacteria and viruses live and how people pick them up. This knowledge is really important in understanding how to prevent infections, particularly when antimicrobial resistance is such a growing problem, making treatment more difficult.

"When I first started working in this area, there was a big debate on how people with CF picked up infections caused by *M. abscessus*. Research by Dr Josie Bryant showed transmission between people in hospitals. We found that people with CF were infected with nearly identical bacteria genetically, but these people lived in quite distant places – how could this happen?

"We were able to use mutation signatures to show that these bacteria were transmitting from one person to another, and people were moving them over large distances.

"During my PhD at UCL in London, I studied viral evolution inspired by some excellent lectures in my undergraduate degree there. I moved up to the University of Cambridge six years ago to take up a post doc position. I joined Prof Andres Floto's group because of the really exciting work underway in the lab; the atmosphere and team here is mind-blowing. One of the things that is so cool about working here is how multidisciplinary it is. There's such a diverse range of expertise.

"If I had to pick a highlight of my research so far, it would be developing the methods to analyse mutation signatures. It is a whole new way of trying to understand transmission of bacteria and viruses, and it's very exciting to be at the start of something new that has the potential to translate into real-world clinical benefits.

"Prof Floto has been incredibly supportive of me developing my own research interests. There are still huge questions to answer about how people with CF are becoming infected with a range of bacteria and viruses. My aim is to stay in Cambridge and continue to provide new insights into this transmission to prevent infections."

Thank you

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Cystic Fibrosis Trust

About us

Cystic Fibrosis Trust is the charity uniting people to stop cystic fibrosis. Our community will improve care, speak out, support each other and fund vital research as we race towards effective treatments for all.

We won't stop until everyone can live without the limits of cystic fibrosis.

For more information:

visit **cysticfibrosis.org.uk/research**

or contact **research@cysticfibrosis.org.uk**