



Chronic lung inflammation: Research perspectives and priorities for drug repurposing

November 2022





LifeArc is a self-funded medical research charity. Our mission is to advance translation of early science into health care treatments or diagnostics that can be fully developed and made available to patients. We have been doing this for more than 25 years and our work has resulted in a diagnostic for antibiotic resistance and four licensed medicines. Our success allows us to explore new approaches to stimulate and fund translation. We have our own drug discovery and diagnostics development facilities, supported by experts in technology transfer and intellectual property who also provide services to other organisations. Our model is built on collaboration, and we partner with a broad range of groups including medical research charities, research organisations, industry and academic scientists. We are motivated by patient need and scientific opportunity.



The MRC funds research at the forefront of science to prevent illness, develop therapies and improve human health. Founded in 1913 to tackle tuberculosis, the MRC now invests taxpayers' money in some of the best medical research in the world across every area of health. Thirty-three MRC-funded researchers have won Nobel prizes in a wide range of disciplines, and MRC scientists have been behind such diverse discoveries as vitamins, the structure of DNA and the link between smoking and cancer, as well as achievements such as pioneering the use of randomised controlled trials, the invention of MRI scanning, and the development of a group of antibodies used in the making of some of the most successful drugs ever developed. Today, MRC-funded scientists tackle some of the greatest health problems facing humanity in the 21st century, from the rising tide of chronic diseases associated with ageing to the threats posed by rapidly mutating micro-organisms.

Glossary We have used the following terms throughout this report:

Biomarker: A biological molecule found in blood, other body fluids, or tissues that may indicate a normal or abnormal process, condition or disease.

Bronchi: The tubes that carry air into and out of the lungs.

Cilia: Cilia are slender hair-like projections found on airway epithelial cells. Their role is to protect against infection by carrying particles trapped in mucus out of the lung.

Epithelial biology: The epithelium is one of four types of body tissue. Epithelial cells have a range of functions in different parts of the body including protection, secretion and absorption.

Immunomodulation: Using therapies to adjust the immune response to infection to an effective level.

Ion channels: Protein molecules that span the cell membrane allowing ions to pass from one side of the membrane to the other.

Microbiomes: The micro-organisms found in our environment, including our body. The microbes in a microbiome may also protect us against germs, break down food to release energy and produce vitamins.

Mucociliary clearance: This is the lung's most important natural defence mechanism, the clearing of the airway. It includes the protective mucous layer, the airway surface liquid layer and the cilia on the surface of some cells responsible for moving this surface layer.

Multiomics: The combination of multiple omics datasets.

Neutrophils: A type of white blood cell which fights infection by destroying bacteria and body tissue.

Omics: High throughput, comprehensive tests measuring a particular type of molecule. Examples include genomics (genes), transcriptomics (RNA) and proteomics (proteins).

Phagocytes: Immune cells that absorb harmful bacteria and other foreign particles.

Proteome: The proteins that can be expressed by a single cell, tissue or organism.

A meeting of minds



While there have been welcome advances in the treatment of chronic lung infections in recent years, more needs to be done."

Dr Catherine Kettleborough

Challenge Leader
LifeArc Chronic Respiratory
Infection Translational Challenge



On Monday 30 May 2022, LifeArc and the Medical Research Council hosted an online workshop with stakeholders - patients, academics, charities, clinicians, policy makers, scientists and industry representatives - to discuss opportunities to repurpose existing drugs to treat chronic lung inflammation and infection in people living with bronchiectasis (BE) and cystic fibrosis (CF).

The purpose of this workshop was to gather stakeholder perspectives on current treatments, research and knowledge gaps to inform LifeArc's drug repurposing research funding call. This report provides a summary of the presentations and discussions at the workshop.

Thank you to everyone who joined the event, including our expert speakers from the respiratory, microbiology, cilia and airway epithelial research communities whose presentations feature in this report.

Thank you to Professor Alison Condliffe and other members of the steering group for your vision and practical support in organising this workshop.

A special thank you to Angelo Micciche and Daniella Richards for sharing your unique perspectives on what it's like to live with CF and bronchiectasis and the impact infections and inflammation have on your lives. Your insights galvanised everyone at the workshop to step up our efforts to develop new therapies to treat acute exacerbations and infections.

While there have been welcome advances in the treatment of chronic lung infections in recent years, more needs to be done.

The LifeArc Chronic Respiratory Infection Translational Challenge is our new £100m programme to accelerate scientific innovation for people living with bronchiectasis and cystic fibrosis.

We're partnering with patients, academics, charities, healthcare professionals and industry to fast-track scientific discoveries into new clinical solutions to transform how chronic respiratory infections are detected, treated and managed.

We'll invest up to £100m by 2030 in collaborative projects to deliver new tests, treatments and technology. Our goal is to enable people with bronchiectasis and cystic fibrosis to live longer with improved quality of life by breaking the vicious cycle of infection, inflammation, and permanent lung damage.

Repurposing existing therapies could help achieve this ambition. As this report shows, there are significant opportunities to repurpose drugs in this area.

Find out about our
**£10m drug repurposing
funding call at**
[lifearc.org/respiratory/
chronicinfections](https://lifearc.org/respiratory/chronicinfections)



SCAN ME



“There are real opportunities to repurpose and develop new therapies in this area, but we’re going to need big teams and integration across disease areas and disciplines.”

Professor Stuart Elborn,
Queen’s University Belfast



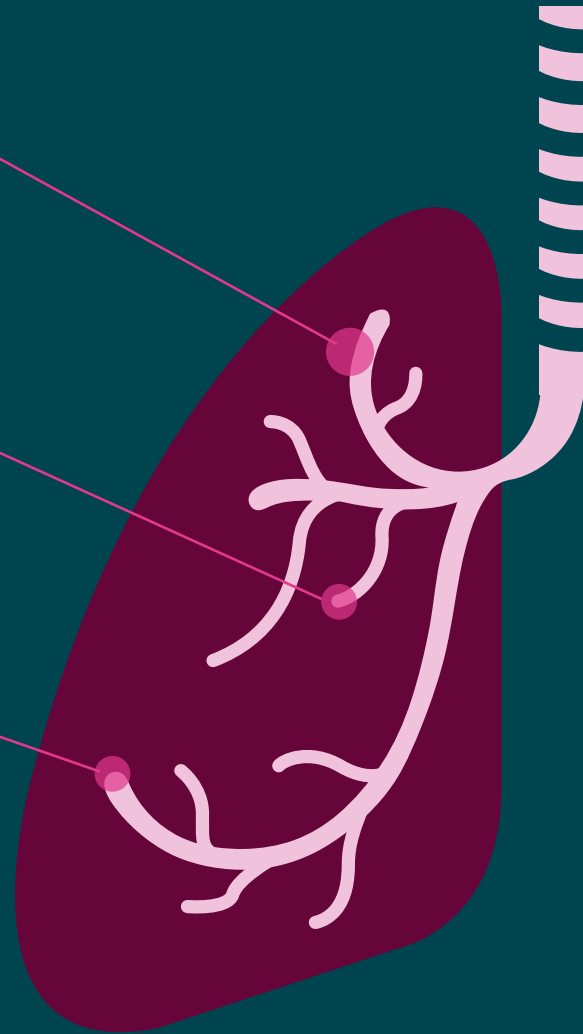
“The mainstay of treatment for most patients is antibiotics... the big opportunity is the open field we have for development of immune modulating or anti-inflammatory drugs.”

Professor James Chalmers,
University of Dundee



“We have no cures and no licensed PCD drugs; we have empirical treatments, for example what cystic fibrosis patients are treated with, but they may not correctly target the problem of cilia immotility.”

Professor Hannah Mitchison,
University College London



In the UK today, there are **10,837** people living with CF and at least **300,000** living with BE*

Key themes

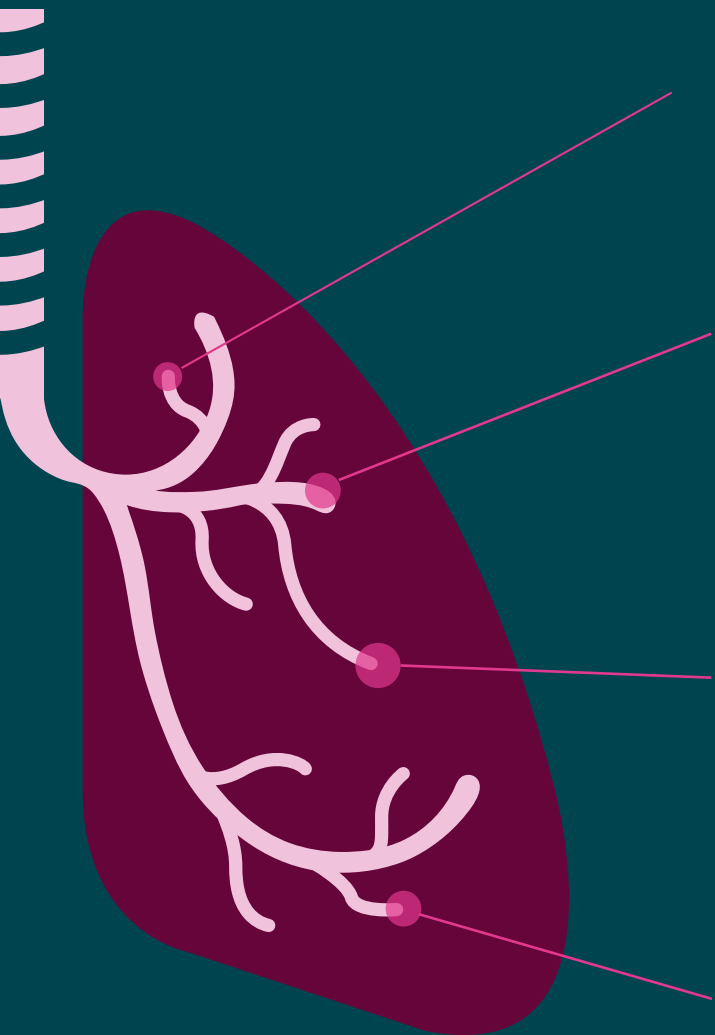
The key themes that emerged from the workshop were:

1 Patient needs underpin everything we do and, therefore, patients should direct our ambition.

2 Exacerbations have the biggest negative impact on patients' quality of life. Early detection and intervention - ideally prevention - of exacerbations is key for patients.

3 One of the most important requests from patients is to reduce treatment burden and improve formulations. We should therefore look to multi-purpose, rather than just repurpose, existing treatments.

4 We need to think beyond tackling the pathogens and understand the disease in its complexity.



“Repurposing of non-antimicrobial therapies as antimicrobials is a really exciting area of research and drug development, with significant promise yet to be delivered.”



Dr Deborah O'Neill,
NovaBiotics Ltd.

“I see an opportunity for a closer collaborative working relationship between cystic fibrosis, bronchiectasis, COPD and PCD researchers on basic mechanisms, biomarkers and model systems for testing new approaches as well as drug repurposing and trial design.”



Professor Jane Davies,
Imperial College London

“There are plenty of opportunities for intervention to prevent or reduce inflammatory lung damage, but it will require multidisciplinary funding at scale.”



Professor Andres Floto,
University of Cambridge

“We really need a widespread effect from public-private partnerships, non-profits, academic researchers and companies to successfully investigate repurposing.”



Professor Adilia Warris,
University of Exeter

* Cystic Fibrosis Trust, UK Cystic Fibrosis Registry Annual Data Report 2020 <https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources>.
British Lung Foundation 'Bronchiectasis statistics' <https://statistics.blf.org.uk/bronchiectasis>.

5 There is an urgent need to consolidate and translate insights from multiomics and other studies to develop new therapies and improved biomarkers to monitor how patients respond to treatment.

6 Repurposing drugs to better treat infections and exacerbations requires a multi-disciplinary and multi-organisation approach.

7 There is a need for better model systems to test potential repurposed therapeutics in the laboratory.

8 The research community strongly supports greater collaboration, including data sharing, to accelerate innovation for patients.

Patient perspectives

Angelo Micciche



It's the not knowing that's hardest."

"Until my mid 20s I was very well. In my mid 20s I had my first round of intravenous (IV) antibiotic treatment and since then I've had twice yearly IV courses each year. I consider myself very lucky in some respects.

"My latter years have been more challenging. I've had a lifetime of IV antibiotics now so antibiotic resistance has become quite an issue for me as well as side effects and reactions to antibiotics. I'm limited in what antibiotics I can use and I'm literally down to two or three now.

"Just before the pandemic, my health was terrible. I was having IVs every four to six weeks. It was a scary time. The IVs would stabilise me and then I'd go through two to three weeks of feeling terrible. My health was constantly zig-zagging. And then just by chance, a new drug treatment Kaftrio became available. It has stabilised me, but I haven't seen massive gains.

"But things seem to be changing again for me. I was feeling unwell and had IV antibiotics again in December and another course in March. It seems to be a three-month pattern so I'm wondering where I'm heading.

"It's very destabilising – not just the period when you're receiving IV treatment in hospital but also the lead up when I'm exhausted all the time. You have night sweats and all of the other symptoms. I can decline, really, really quickly. In the space of six hours, I could go from really well to terrible. Really not well.

"It's a struggle. I do worry about the long term and my ability to work full time, for example, as things progress. It's the not knowing that's hardest. I would like to think my health will stay stable, but history has told me that's not going to be the case. I just want to live with a greater degree of certainty. That's just impossible at the moment."

Daniella Richards



I still get out of breath just going upstairs."

"I was diagnosed with bronchiectasis at the age of 12. I had just recovered from leukaemia. My consultant told me my lungs were like those of a 50-year-old miner who smokes 40 cigarettes a day. That came as quite a shock.

"I did manage pretty well through school and college. I had an annoying cough, lots of chest infections and coughed up green sputum. I was told to just rest a lot and keep taking my antibiotics.

"In 2009, I found out I had a bacterial infection called *Pseudomonas aeruginosa* in my lungs which is when the antibiotics didn't work so well. I started on nebulisers and other antibiotics.

"Over the next few years, I had quite a few more chest infections but carried on working. I was a beauty therapist. I really loved it. I kept working when I had chest infections. I just took tablets and my clients got used to me coughing all the time.

"I adopted my beautiful little girl in 2014, and she's kept me very busy. Unfortunately, my chest infections became more frequent, and I had to go into hospital a lot more to receive intravenous antibiotics.

"In 2019, I had to retire from work. I just couldn't do it anymore. I had lots more chest infections and my antibiotics weren't working anymore. I'm grateful to not be at the point where I need a lung transplant. I'm currently on nebulisers and steroids. I'm a lot more active. I go to pilates once a week. I do the school run with my little girl. I still get out of breath just going upstairs, getting in the washing from the garden.

"I don't how long these medications are going to last. But I hope with research and new treatments, I can keep going and keep well. I would like to control the *Pseudomonas* better as that can make me feel quite poorly."

Precision medicine

In his keynote address, Professor Stuart Elborn (Queen's University Belfast) explained why precision medicine offers untapped potential for identifying drugs that could benefit people living with CF and bronchiectasis.

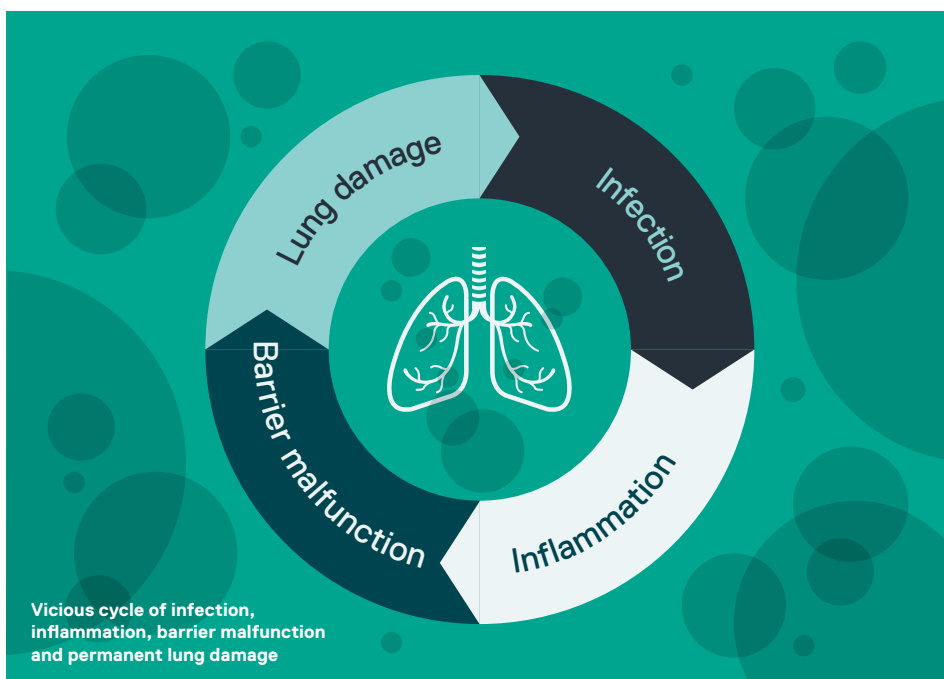


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Using ‘omics technologies’ would mean researchers no longer have to rely on a single biomarker on which to base approaches to identify potential therapies or define interventions.”

Professor Stuart Elborn

Queen's University Belfast



Professor Elborn began by outlining the importance of the lung's barrier function to good physical health. Regulated by the immune system, the barrier function protects the lungs from environmental pathogens including allergens, infectious agents and pollutants.

Chronic respiratory disease occurs when the barrier malfunctions, which can be triggered by faulty genes, problems inside the barrier function itself or environmental factors.

When the barrier malfunctions, the lung's ability to clear itself of allergens, infectious agents and pollutants – known as mucociliary clearance – is compromised. This creates a vicious cycle of infection, inflammation, permanent lung damage and ultimately lung failure.

Professor Elborn said precision or personalised medicine could transform how infection and inflammation are treated. Precision medicine uses data to tailor treatments to each individual. Using omics technologies, clinicians analyse a person's genes, for example, to identify which treatments are likely to achieve the best outcome with least side effects based on their genetic make up.

While the approach offers significant potential for people with CF and bronchiectasis, more research is needed to better understand the causes and progression of lung inflammation in patients.

Professor Elborn said combining multiple datasets – genetic, protein and microbe data – offers a potential solution. Combining datasets would enable scientists to build a more detailed profile of infection, inflammation and lung damage.

Instead of relying on targeting a single biomarker or molecule, scientists could develop treatments to target each stage of the disease cycle. Artificial intelligence technology could be used to develop 'signatures' of disease enabling treatments to be tailored to each patient depending on where they are in the disease cycle of infection, inflammation and lung damage.

Professor Elborn said precision medicine is only possible if researchers, clinicians and industry work together to pool data, knowledge and expertise.

Immunomodulation

Professors Andres Floto and James Chalmers explained how therapies that regulate the immune response to infections could help reduce CF and bronchiectasis inflammation.



There are huge opportunities in the widespread application of omics to explore specific disease pathways.”

Professor Andres Floto
University of Cambridge

Professor Andres Floto (University of Cambridge) discussed the development of bronchiectasis. While further scientific investigation is needed to fully understand what causes bronchiectasis, the condition develops when the walls of the lung's bronchi - the tubes that carry air into and out of the lungs – weaken and become blocked (luminal obstruction).

The disease causes the airway to act like a balloon, triggering expansion of the bronchi and permanent damage to the airways. This causes excess mucus to build-up in the lungs, increasing the risk of infection, triggering inflammatory responses and permanent lung damage.

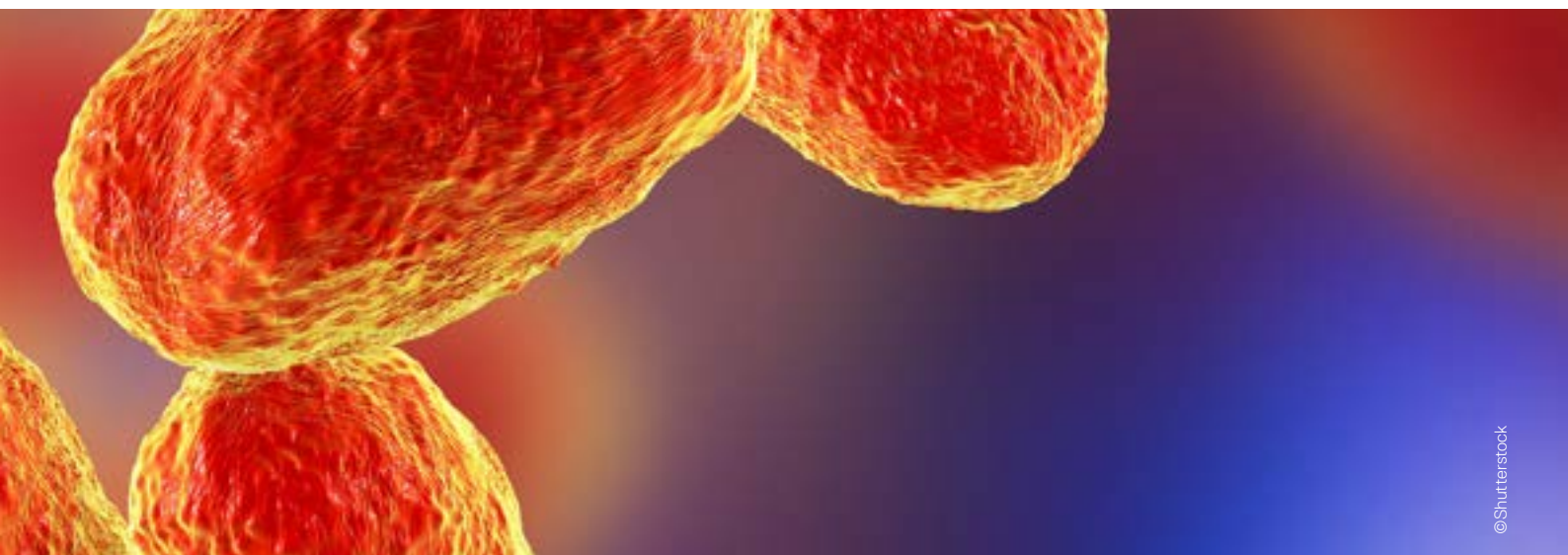
Professor Floto described one genetic study of more than 800 people with early-stage symptoms, which confirmed the stages leading to bronchiectasis and revealed potential new drug targets to treat CF and bronchiectasis. The failure of the body's immune system to respond effectively to infection was highlighted as a major cause of the acute exacerbations that cause lung damage in people living with bronchiectasis.

Another study comparing the lung cells of people with bronchiectasis with those of people without the condition found inflammation to be a key driver of the disease. It also identified new inflammatory cell types associated with bronchiectasis.

These studies suggest drugs that regulate the body's immune response offer potential targets for repurposed therapies. They include drugs that reduce inflammation of epithelial cells - the lung's surface cells - and drugs that increase the ability of phagocyte cells – a type of immune cell - to absorb bacteria and other foreign particles.

Bronchiectasis is the third most common chronic airway disease globally after asthma and chronic obstructive pulmonary disease.*

*Gao, Y-H, Chalmers, JD. Counting the cost of bronchiectasis (2020) *Respirology* (25) 1223– 1224. <https://doi.org/10.1111/resp.13888>.



Professor Floto said drug targets could be identified by conducting large population-scale studies comparing biomarkers - biological molecules found in blood, other body fluids, or tissues that may indicate a normal or abnormal process, condition or disease - of people living with CF and bronchiectasis and those without the disease.

Professor James Chalmers (University of Dundee) reminded everyone there is currently no licensed treatment for bronchiectasis, leaving patients reliant on an ever-reducing range of antibiotics to manage symptoms which are not always effective.

Professor Chalmers emphasised the importance of viewing bronchiectasis as a distinct disease. Research to date has identified five different types of bronchiectasis disease. Professor Chalmers said different drugs may be needed to treat each variation.

More research is needed to better identify the molecular signatures of the different types of bronchiectasis disease. This research could provide better targets for repurposed drugs. It would also improve how patients are matched to clinical trials, increasing the chances of success.

Professor Chalmers agreed there is significant scope to repurpose anti-inflammatory drugs to treat bronchiectasis, noting it appears to be an inflammatory disease. Bronchiectasis inflammation can be tracked by assessing levels of neutrophils – white blood cells which fight infection by destroying bacteria and body tissue. Regulating this immune response is one potential target for new therapies.

Bronsocatib, a drug that has been found to reduce levels of neutrophils in patients with bronchiectasis with a daily dose, is currently in clinical trials. Another trial is investigating if benralizumab, a drug licensed for the treatment of asthma, can reduce bronchiectasis inflammation. This drug targets levels of eosinophils – another type of white blood cells which has been linked to inflammation in around 20 per cent of bronchiectasis patients.

Other factors to consider when identifying potential new therapies are the importance of correct dosage levels and treatment regimes to understand when patients should stop taking drugs they no longer need.



Dosage, treatment duration and patient stratification will be key factors in studies of potential new and re-purposed therapies.”



Epithelial biology and mucociliary clearance

Professors Jane Davies and Hannah Mitchison explained how advances in our understanding of mucociliary clearance and epithelial tissue could offer new targets for existing drugs.



This is a really exciting area of research and drug development with significant promise yet to be delivered.”

Professor Jane Davies
Imperial College London

The lung's ability to clear itself of allergens, infectious agents and pollutants – mucociliary clearance - is its primary defence mechanism. Professor Jane Davies (Imperial College London) said our understanding of this process and the role the immune system plays regulating this process and the impact of environmental factors has advanced significantly in recent years.

A defect in the CF transmembrane conductor (CFTR) - an ion channel which acts as a cell gate for salts - underpins our understanding of how the lung functions in people living with CF. For example, an imbalance in levels of sodium and as a consequence water, prevent the cilia, which are slender thread-like projections on cell surfaces which help clear the airways – from working properly. This creates thick mucus which further restricts the cilia from working effectively and clearing pathogens from the lungs.

Professor Davies said a recent study found low pH levels on the airway surface of the lungs may increase the risk of infection. The acidic environment caused by the CFTR defect, appears to prevent the immune system from eliminating bacteria, which then leads to infection and inflammation.

Knowledge of how mucociliary clearance works in people living with CF is likely to be relevant for people with other respiratory diseases including bronchiectasis. While we know therapies developed to treat CF lung infections have not always been effective in bronchiectasis patients, there are opportunities to identify and potentially repurpose drugs to target different stages common to both diseases.

As well as the potential to use CFTR modulators to treat bronchiectasis, Professor Davies cited other ion channels, as targets to be explored. Further options to consider include anti-inflammatories and anti-microbials.

*Cystic Fibrosis Trust, UK Cystic Fibrosis Registry Annual Data Report 2020.



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Professor Davies concluded by saying much has been learnt from understanding the epithelial biology in CF and that some aspects of this will have a broad applicability to other chronic inflammatory airway disease such as bronchiectasis. This could lead to identifying new therapeutic targets as well as biomarkers which could be used to design more effective clinical trials of treatments.

Professor Hannah Mitchison (University College London) explained how advances in genetic testing are increasingly helping to diagnose people with primary ciliary dyskinesia (PCD) - an inherited disease currently known to affect one in 7,500 people.

In PCD, gene mutations prevent the cilia from developing properly. The cilia are unable to move, leading to mucus build up which increases the risk of infection and inflammation and results in bronchiectasis.

NHS genetic services now routinely screen for inherited respiratory conditions. This includes identifying people who may have any number of 61 genes associated with conditions affecting the cilia.

Professor Mitchison said information gleaned from screening people with PCD for genetic mutations has helped to improve understanding of which genes affect different aspects of cilia performance. She said this information offers a fantastic toolbox for identifying new treatments to improve ciliary performance and mucociliary clearance including by repurposing existing therapies.



Scientists have largely depended on cultured human cells and organoids (artificial cells or tissue) in the search for potential therapies.”

Professor Hannah Mitchison
UCL

One in three people with cystic fibrosis have a chronic *Pseudomonas aeruginosa* infection.*

Infection and antimicrobials

Professor Adilia Warris and Dr Deborah O’Neil explained why existing antimicrobial and antifungal treatments, as well as repurposed non-antibiotic drugs, could provide new treatments for people living with bronchiectasis and cystic fibrosis.



Host-targeted approaches for regulating inflammation could be key.”

Professor Adilia Warris
University of Exeter

Fungal infection is one of the drivers of chronic lung inflammation. Professor Adilia Warris (University of Exeter) said prolonged use of antibiotics, resistance to those antibiotics and an impaired immune system can all contribute to fungal infections.

There are currently limited treatment options for fungal lung infections and resistance to the four available classes of drugs is growing. Potential new treatments are being explored, with three drugs currently in clinical trials working differently to existing therapies which could provide important alternatives to patients who are resistant to existing treatments.

Successfully repurposing existing drugs would enable patients to access new treatments much sooner. The approval process to repurpose existing drugs takes between three and 12 years compared with up to 17 years for entirely new therapies. The process is faster because existing drugs have already been shown to be safe and can be manufactured at scale quickly without additional set up costs.

Professor Warris said funding is key to increasing the number of drug repurposing clinical trials. Running trials to test different dosage levels, for example, can be costly and doesn’t typically attract industry funding. She said researchers also need better access to clinical samples and isolates taken from people with inflammatory lung disease, as well as libraries of existing compounds ideally approved for clinical use or with clinical data available.

Dr Deborah O’Neill (NovaBiotics) said there are significant opportunities to repurpose existing drugs to treat lung inflammation. Novabiotics recently repurposed cysteamine – a drug used to treat a rare genetic disorder – as a treatment for people living with CF. The company is now exploring the drug’s potential for treating bronchiectasis inflammation and pneumonia (*see case study, page 14*).



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Dr O'Neill said antibiotics can be repurposed by changing how they are administered, adapting dosage levels and combining them with other drugs. However, the most significant opportunities are with non-antibiotics that directly target the pathogen or regulate the body's response to infection and inflammation. Identifying new non-antibiotics would also help tackle the growing challenge of antibiotic resistance.

Potential repurposing opportunities include anti-virulence and anti-biofilm compounds to regulate the pathogen causing infection and inflammation and therapies that regulate the body's immune response.

Dr O'Neill stressed the importance of being able to explain how changes in formulation and dosage or drug combinations affect patients, given these drugs have typically been licensed for other purposes. Patient safety is paramount, for example, patients may be taking multiple medicines. When repurposing drugs, it's important to focus on the impact on the patient's overall health rather than bacteria levels, for instance.

When seeking to repurpose existing therapies, Dr O'Neill said identifying new intellectual property was vital as this provides commercial incentives to seek regulatory approval and invest in manufacturing. Regulators are keen to work with manufacturers to license genuinely repurposed therapies.

Dr O'Neil concluded that the future for repurposing for treatments for intractable respiratory infections in CF and bronchiectasis is bright. She said there is a real opportunity to deliver benefits for patients and commercial barriers that may have existed in the past are now surmountable.



The exciting space here is repurposing the therapeutic classes that have direct antimicrobial functionality.”

There is currently no licensed treatment for bronchiectasis.

A potentially game-changing treatment

Deborah O’Neil, Chief Executive Officer at NovaBiotics, shares the progress towards repurposing cysteamine (or NM001) as a treatment for cystic fibrosis and bronchiectasis.

What is cystic fibrosis?

Cystic fibrosis (CF) is an inherited condition that causes sticky mucus to build up in the lungs, digestive system, and other organs, causing lung infections and other symptoms. People with CF have a faulty gene called CFTR, which encodes a protein that helps to control the movement of salt and water in and out of cells.

Most people with CF will require several tablets and/or treatments every day – including different medicines to treat and prevent lung problems. These include antibiotics to treat chest infections, inhaled medications to promote mucus clearance, and anti-inflammatory drugs to widen the airways and make breathing easier.

More recently, CFTR modulator therapies have been approved that are designed to correct the faulty protein made by the CFTR gene. But these medications are only effective in a subset of CF patients with specific mutations.

What is bronchiectasis?

Bronchiectasis is a long-term condition where the airways of the lung become widened, leading to a build-up of excess mucus that can make the lung more vulnerable to infection.

What problem are you trying to address?

When a person with CF or bronchiectasis has a chest infection that becomes severe, it is called an exacerbation or flare-up. Repeated exacerbations can lead to progressive lung damage that can seriously impact a person’s quality of life and even shorten their life expectancy. There is an urgent need for new treatments that can prevent or reduce lung exacerbations from occurring – and clear them more effectively. In particular, there is currently a lack of treatments that can be used during exacerbations to lessen the impact and reduce the length of these episodes – as CFTR modulators and most other existing treatments for CF are instead designed to reduce their frequency.

How did this repurposing project come about?

We initially set out to look for 'biofilm busting' compounds with activity against problematic bacteria associated with CF which exist in structures called biofilms that make them harder to treat. Through this work, we identified cysteamine, which is the active compound in candidate treatments we called NM001. This compound is also present in an existing medicine used to treat an unrelated rare genetic condition called cystinosis, which particularly affects the eyes and kidneys.

Through further laboratory experiments, we then realised that NM001 had several promising properties as a potential candidate for treating CF and bronchiectasis-associated lung disease. These included anti-inflammatory effects, potent mucolytic activity (the ability to break down mucus), antimicrobial, anti-virulence, and antibiotic-potentiating effects.

Importantly, NM001 is not a mutation-specific CFTR-targeting intervention – so it has the potential to benefit all CF patients.

What happened next?

The existing forms of cysteamine that were approved for treating cystinosis were oral capsules, which have a very distinct smell and aftertaste - so they can be unpleasant to take. When planning more palatable formulations of cysteamine for patients experiencing acute exacerbations and those with more stable disease, we engaged with CF patients. They surprised us by saying they’d much prefer to take the drug as an oral formulation when they were unwell – and would be ok with an inhaled (dry powder) version for maintenance when they were well.

That led us to develop two forms of NM001 – an oral (tablet) form for patients with CF experiencing lung exacerbations, and an inhaled (dry powder) formulation with no odour and a pleasant taste as a maintenance treatment for patients with stable disease.



Scientists at NovaBiotics working on NM001.



Our inhaled formulation of NM001 has shown very encouraging data in laboratory studies, and we’re working towards initiating phase 1 clinical studies in CF and bronchiectasis patients.



What stage has it reached?

We recently completed an exploratory phase 2b global clinical study of NM001 in oral form in CF patients, following the encouraging results from an earlier phase 2a trial which was part-funded by the Cystic Fibrosis Trust. These studies have provided data confirming that the drug is safe, as well as determining the best dose and how we should measure its effectiveness in patients in a larger trial. We now plan to progress the tablet form of NM001 in registrational studies that will include both CF and bronchiectasis patients – and we've also sought patient input when developing the protocols for these studies.

Our inhaled formulation of NM001 has shown very encouraging data in laboratory studies, and we're working towards initiating phase 1 clinical studies in CF and bronchiectasis patients as soon as possible.

What advice do you have for others?

Our project is an example of repurposing a compound rather than a drug, so it's more complex than using an existing drug to treat a new condition, but it gives you the scope to make changes – such as improving the formulation and changing the route of administration.

But in any repurposing project, you will need to consider whether it's going to be feasible to repurpose a compound or existing drug from a clinical and patient perspective – and not just because of even the most encouraging activity data you might have seen in the laboratory. First and foremost, it has got to be safe for patients – and you will also need to think carefully about the dose required for benefit in the new patient population and how you're going to administer it.

You should also consider the specifics of their health condition and other medications they take, which all be very different from the patients and condition the drug or a compound was initially used to treat. There will already be a lot of safety data available, which is a big advantage of a drug repurposing project compared to developing a new molecule from scratch.

However, you should be aware that this may not necessarily be for the dose you need to use it at in the new group of patients, your new formulation and the route of administration you are intending to develop it for.

It is also absolutely critical to engage with patients at every stage of the project. You can think something is a great direction – and then they can just blow that out of the water. They will provide you with absolute gold dust.

Speaker profiles

Professor Stuart Elborn

Professor and Faculty Pro-Vice-Chancellor,
Queens University Belfast

Professor Elborn's main focus is Cystic Fibrosis focused on understanding pathophysiology of infection and inflammation and the translation of new therapies into clinical practice. This programme of work is undertaken with laboratory and clinical collaborators in QUB. This includes a significant commitment from the NICRN (Respiratory Health) where he is PI on 6 current clinical trials. Professor Elborn has smaller programmes with others in COPD, bronchiectasis, lung cancer including clinical trials. Professor Elborn's research is funded by grants from government agencies, charitable bodies, industry and money raised from clinical trials. Professor Elborn has developed a clinical trials network for Respiratory Health funded by the Northern Ireland Research and Development Office. Professor Elborn endeavours to bring scientists and clinicians together to promote inter-disciplinary collaboration. Professor Elborn has been successful in developing programmes of research across disciplines, hospitals and universities in Northern Ireland and across the UK and Europe.

Professor Andres Floto

Professor of Respiratory Biology,
University of Cambridge

Andres Floto is Professor of Respiratory Biology at the University of Cambridge, a Wellcome Trust Senior Investigator, and Research Director of the Cambridge Centre for Lung Infection at Papworth Hospital, Cambridge. His research is focused on understanding how immune cells interact with bacteria, how intracellular killing and inflammation are regulated and sometimes subverted during infection, how population-level whole genome sequencing can be used to reveal biology of bacterial infection, and how therapeutic enhancement of cell-autonomous immunity may provide novel strategies to treat multi drug resistant pathogens. Clinically, he specialises in the treatment of patients with Cystic Fibrosis (CF), non-CF bronchiectasis, and infections with Nontuberculous Mycobacteria (NTM). He is co-chair of the British Thoracic Society NTM guidelines committee, the joint US CF Foundation-European CF Society (ECFS) NTM Guidelines Group and the ECFS working group on NTM.

Professor James Chalmers*

British Lung Foundation Chair of Respiratory
Research, University of Dundee and honorary
consultant physician, Ninewells Hospital

Professor James Chalmers is Asthma and Lung UK Chair and Consultant Respiratory Physician at the School of Medicine, University of Dundee. His laboratory works primarily on the interaction between neutrophils and bacteria during acute and chronic airway infections, particularly bronchiectasis. He chairs EMBARC, the European Bronchiectasis Network, and chaired the 2017 European Bronchiectasis Guidelines. He is chief investigator for multiple phase 1 to phase 3 international clinical trials in bronchiectasis. He is the incoming chief editor of the European Respiratory Journal and chairs the Science and Research Committee of the British Thoracic Society.

Professor Adilia Warris

Deputy Centre Director MRC CMM
University of Exeter

Adilia Warris is a professor in paediatric infectious diseases with a specific interest in medical mycology. Professor Warris is a co-director of the MRC Centre for Medical Mycology at the University of Exeter and a consultant in paediatric infectious diseases in Great Ormond Street Hospital, London. Professor Warris' research profile has a strong translational focus and specific areas of interest include the host-fungus interaction in specific patient groups with an emphasis on *Aspergillus* species; the unique interaction of *A. nidulans* and the CGD host, *Aspergillus* infections in people with cystic fibrosis, the development of new management strategies for invasive fungal disease in children, the epidemiology of invasive fungal infections in children, and the pharmacology of antifungals in paediatrics. Professor Warris chairs the European Paediatric Mycology Network (EPMyn) through which post-graduate courses in Paediatric Mycology are coordinated as well as multi-centre European studies to obtain a better insight in the fungal and clinical epidemiology of fungal infections in neonates and children. Ongoing studies are focussing on the fungal and clinical epidemiology of invasive fungal diseases in neonates and children (EPMyn-EUROCANDY study), and paediatric antifungal stewardship (PASOAP study). Professor Warris leads the Fungal Infection Scientific Content Area within PENTA Child Health.

Dr Deborah O'Neil OBE, FRSE

Chief Executive Officer and Scientific Officer,
Novabiotics

A biotechnology entrepreneur and immunologist by training, Deborah has thirty years of research experience; twenty of those in drug discovery and development. Deborah studied at University College London and then worked in postdoctoral positions in internationally acclaimed laboratories in San Diego and Ghent before moving to Aberdeen (to the Rowett Research Institute, now part of the University of Aberdeen) where she founded NovaBiotics in 2004. The business has since become a leading global biotechnology business, developing a portfolio of first-in-class therapy candidates for a number of life-threatening and life-limiting conditions including treatments for inflammatory, infectious and respiratory disease. The company's lead candidate, NM002, is currently in a phase 3 clinical trial for community acquired pneumonia caused by COVID-19, influenza and bacterial infections. Deborah is a Board member of the UK's BioIndustry Association, a Director and founding member of the BEAM Alliance (Biotechs of Europe innovating in Anti-Microbial Resistance). Deborah also chairs the UK's Medicines Discovery Catapult-Cystic fibrosis (CF) Trust's AMR Syndicate, was a member of the Scottish Life Sciences Industry Leadership Group and is a board member of the Scottish Life Sciences Association. Closer to home, she is Chair of the Life Science Board of Opportunity Northeast. Deborah is a Fellow of the Royal Society of Edinburgh and a Fellow of the Royal Society of Medicine. Named as one of the 20 women leaders in European biotech in 2019, one of the 30 top female leaders in UK Healthcare in 2018. In 2020, Deborah was made Obronchiectasis in the Queen's Birthday Honours list, for services to biotechnology, industry and charity.

Professor Alison Condliffe*

(Workshop Organising Committee Chair)

Professor of Respiratory Medicine,
University of Sheffield

Professor Alison Condliffe is a clinician scientist with an interest in bronchiectasis and respiratory infection, immune deficiency and inflammation. She studied medicine in Cambridge and London and undertook her clinical training in London and Edinburgh. During her PhD (supervised by Professor Chris Haslett and Professor Edwin Chilvers in Edinburgh) and a subsequent Wellcome Intermediate Fellowship at the Babraham Institute in Cambridge, she studied innate immune inflammatory cells called neutrophils, looking at their role in defence against infection but also their ability to cause collateral damage to lung cells. Alison's subsequent appointment as a University Lecturer in Cambridge in 2007 enabled a more translational research focus, in particular studying the impact of hypoxia (low oxygen levels) on neutrophil function and establishing novel imaging techniques. She worked for several years in the Lung Defence clinic at Papworth Hospital caring for patients with bronchiectasis and chronic lung infection and worked closely with the Clinical Immunology and Haematology services. Alison was appointed as Professor of Respiratory Medicine at the University of Sheffield in 2015. She continues to research lung infection and inflammation and to care for patients with bronchiectasis and complex lung infections.

Professor Jane Davies*

Professor of Paediatric Respiriology & Experimental Medicine, Imperial College London

Jane Davies is a Professor in Paediatric Respiriology & Experimental Medicine at the National Heart and Lung Institute and an Honorary Consultant in Paediatric Respiratory Medicine at the Royal Brompton & Harefield NHS Foundation Trust. Professor Davies focusses on translational research in the field of CF, in particular chronic bacterial infection and trial design for new drugs. She leads on the of CF Trust's Strategic Research Centres, A Personalised Approach to *Pseudomonas aeruginosa* (PAPA); this comprises a multicentre group of clinicians, microbiologists and respiratory physiologists seeking to improve detection, understanding and treatment of this common pathogen. She is the deputy chair of the steering committee of the Medicines Discovery Catapult/ CFT Syndicate for antimicrobial resistance, a member of the NIHR Respiratory TRC and chairs the R-TRC CF National Research Strategy Group. She has led a programme of research utilising opportunistic bronchoscopic sampling in children which shed light on early infection, inflammatory and host defence mechanisms in CF and other lung diseases. She co-leads an NIHR-award winning CF clinical trials team at the Royal Brompton Hospital, working as part of both the European CF Society's Clinical Trials Network and the UK Clinical Trial Accelerator Platform; within the latter, she established a pan-London network of tertiary CF centres working in harmony to delivery high quality clinical trials. She has been national and global chief investigator on multiple trials of CFTR modulators, focussing most recently on study design for infants and young children. On behalf of the ECFS, she directs the Core Facility for Lung Clearance Index, a sensitive pulmonary function test which has become established as a major efficacy outcome in such trials. She sits on the Strategy Group of the UK Respiratory Gene Therapy Consortium, which aims to develop clinically relevant CFTR gene therapy, of particular value to people with rarer mutations who cannot benefit from CFTR modulator drugs.

Professor Mark Sutton*

Professor of Antimicrobial Therapy UKHSA and Kings College London

Mark Sutton obtained a PhD in Molecular Microbiology working at the John Innes Institute, Norwich in 1994. During his PhD, he developed a range of expertise in molecular genetics, molecular biology, protein chemistry, recombinant protein purification and microbiology. His PhD was followed by BBSRC-funded post-doctoral fellowships at John Innes and the University of Leeds (1994-1997), working on the generation of disease resistant transgenic plants. Mark joined the Centre for Applied Microbiology and Research (CAMR), Porton Down in 1997 (which became part of the Health Protection Agency in 2003 and Public Health England in 2013 and is now the UK Health and Security Agency) and worked on a series of commercially funded studies aiming to develop new medicines derived from the properties of botulinum neurotoxin and other bacterial toxins. The work contributed to a spin out company, Syntaxin Ltd (now acquired by Ipsen Pharmaceuticals). He spent 10 years leading a series of projects focussed on preventing the transmission of variant Creutzfeldt Jakob Disease (vCJD). These studies led to presentations to UK government advisory groups, with work cited in risks assessments and guidance documents. Dr Sutton became a Scientific Leader for Healthcare Biotechnology in 2009 and manages the Technology Development Group, an interdisciplinary research group now part of UKHSA - Research and Evaluation. The group focusses on developing and evaluating new interventions for the treatment of healthcare associated infections (HCAs) and antimicrobial resistance. The group developed models to assess applied infection control methods (decontamination, disinfection) and to evaluate new antimicrobial agents, working with a number of chemistry, pharmacy, physical science, electrical engineering and microbiology groups worldwide. The group established a screening and evaluation pathway for assessing the efficacy of new antimicrobials, especially non-traditional therapeutics and to enable analysis of resistance that emerges during exposure to antibiotics. This "Open Innovation" programme uses a range of in vitro assays, in vivo infection models, with molecular genetics and embedded whole genome sequencing used to understand susceptibility and the emergence of resistance. Mark is a Professor for Antimicrobial Therapy at King's College London and represents UKHSA on a number of advisory boards and committees, nationally and internationally. He is author on more than 100 peer-reviewed publications and a named inventor on 19 patent families, filed internationally.

Professor Hannah Mitchison

Professor of Molecular Medicine UCL

Hannah Mitchison is a biologist and Professor of Molecular Medicine at the University College London Great Ormond Street Institute of Child Health. Her group use human genetics and functional studies in cells, ciliate organisms and other in vivo models to understand the molecular genetic basis of ciliopathies with a special focus on disorders of motile cilia linked to chronic airway disease. This work has helped elucidate a cellular network of over 50 proteins essential for ciliated airway epithelium differentiation and host defence through mucociliary clearance. This has characterized the disruption in disease of multiciliogenesis master regulators, essential cilia structural proteins, ciliary transport and a cytosolic chaperone-mediated network of dynein assembly factors essential to power and regulate axonemal motor activity. Hannah is founder and current chair of the Ciliopathy Alliance and a lead in the UK Cilia Network. Her group are currently engaged in an EU-funded clinical programme to document all human variants causing motile ciliopathies, aiming to reveal the genotype-phenotype correlations that can determine how a patient's underlying genetics affect their clinical disease expression. This work will help to improve disease understanding and guide future clinical management and interventions, including new genetic medicines.

Professor Elaine Bignell*

Professor of Medical Mycology, University of Exeter

Professor Elaine Bignell is an internationally recognised leader in the field of human fungal pathogen research and a Co-Director (Research) for the MRC Centre for Medical Mycology at the University of Exeter. Her work addresses the mechanistic basis of lung diseases caused by the major mould pathogen of humans, *Aspergillus fumigatus*. Major contributions to the field have included pioneering work on the role of *Aspergillus* pH sensing in pathogenicity, transcriptional regulation of host adaptation, and the mechanistic basis of tissue invasion during invasive fungal lung disease. A molecular geneticist by training, Elaine began her independent research career as an MRC New Investigator, and by securing a fast-track to Lectureship Award at Imperial College London. She later played a major role in establishing the Manchester Fungal Infection Group (MFIG) and in securing its success as a leading International Centre of Excellence for fungal diseases research, having served as a Director of this unit for 5 years (2015 – 2020). Elaine's research seeks a mechanistic understanding of fungal lung disease with a view to developing novel diagnostics and antifungal therapies. Her approach integrates infection models which transcend multiple experimental scales to address disease outcomes at the molecular, cellular, tissue, organ and whole animal levels. Most recently, via iterative MRC funding awards, Elaine has applied a systems level approach to define pathogenicity in *Aspergillus fumigatus* and is now developing inhibitors of fungal pH signalling as novel antifungal drugs, and studying secreted fungal proteins as novel vaccine candidates and diagnostic tools.

*Workshop organising committee member

LifeArc Translational Challenge

Chronic Respiratory Infection



The LifeArc Chronic Respiratory Infection Translational Challenge is our new £100m programme to accelerate scientific innovation for people living with bronchiectasis and cystic fibrosis.

We're partnering with patients, academics, charities, healthcare professionals and industry to fast-track scientific discoveries into new clinical solutions to transform how chronic infections are detected, treated and managed.

We'll invest up to £100m by 2030 in collaborative projects to deliver new tests, treatments and technology – improved diagnostics to detect infection earlier and monitor treatment response; better treatments to reduce the burden of care with fewer side effects; and innovative devices to enable patients to manage their condition more easily at home.

Our team of in-house scientists, technology transfer and other specialists will guide partners through the commercial, legal, regulatory and other issues that can sometimes prevent scientific discoveries reaching patients.

Our goal is to enable people with bronchiectasis and cystic fibrosis to live longer with improved quality of life by breaking the vicious cycle of infection, exacerbation, and permanent lung damage.



Scan to find out more about the LifeArc Chronic Respiratory Infection Translational Challenge

Accelerating innovation for people living with bronchiectasis and cystic fibrosis



Early detection

New digital tools to predict exacerbations much earlier, enabling patients to receive the right treatment sooner, stay out of hospital and avoid permanent lung damage.



Right diagnosis

New diagnostics to better detect and quantify infectious pathogens and monitor how patients respond to treatment, reducing the risk of antibiotic resistance and ineffective care.



Better treatment

New therapies, including repurposed drugs, to expand the range of treatment options available to patients, whilst aiming to reduce side-effects and overall burden of care.

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