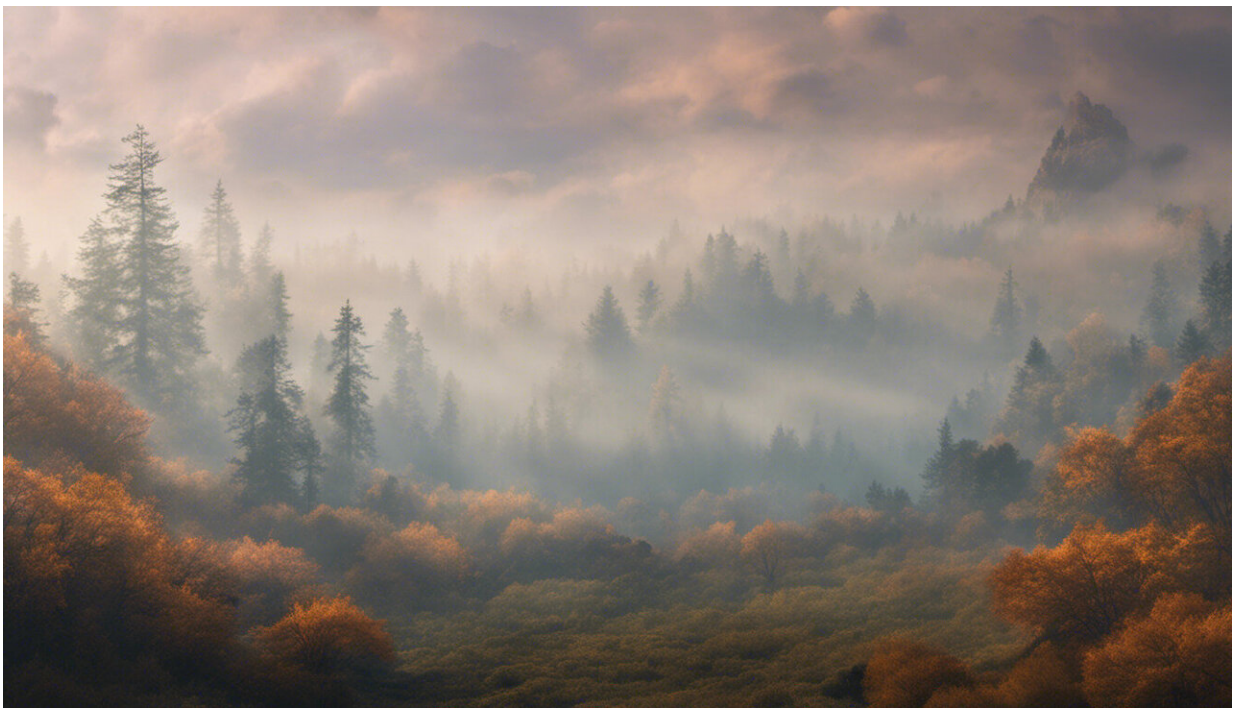
There's no cure for rare types of cystic fibrosis, but researchers are making significant advances

February 2 2022, by Vittoria D'alessio



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Current treatments for cystic fibrosis are not suitable for all patients. The lack of treatment options is distressing for people suffering from a rare type of this degenerative and life-threatening disease. But researchers are making major advances.

A decade ago, few cystic fibrosis patients lived beyond their teens. Thanks to a breakthrough in treatment options, for most patients with access to modern medicines, cystic fibrosis (CF) is no longer the catastrophic disease it once was. However, for 15 percent of people with CF, the cellular defect that causes their disease remains untreatable. For these patients, drugs are available to treat some of the symptoms of CF, but the condition continues to wreak havoc with their organs, resulting in premature death.

An EU-funded research project HIT-CF aims to change this by improving both the quality of life and the disease prognosis for people with ultra-rare varieties of CF. In Europe, there are an estimated 5,250 people who fall into this category.

The project, launched in January 2018, brings together researchers, doctors, pharmaceutical companies and patient representatives, with the aim of developing drugs and drug combinations that are matched with a high degree of precision to a patient, regardless of the rarity of their form of the disease. Such personalized medicine is possible thanks to a new approach to drug testing involving the creation of mini-organs in the lab using a patient's own stem cells. These 'organoids' are genetic replicas of organs found inside the patient's body and can be used to test how responsive a person's cells are to specific pharmaceutical compounds.

"We're effectively shifting therapeutic trials from patients to the laboratory," explained Kors van der Ent, professor in pediatric pulmonology at the University Medical Centre, Utrecht in the Netherlands, and coordinator of the multi-disciplinary HIT-CF project.

To date, scientists involved in the project have grown organoids from 500 European patients with ultra-rare forms of CF. Ultra-rare can mean that just one or two people worldwide share the same form of the

disease.

Describing his team's work with organoids, Professor van der Ent said: "We've asked pharmaceutical companies to hand over drugs from their development pipelines so we can test these compounds against the organoids. These drug candidates target the basic protein defect involved in cystic fibrosis.

"What is special about this work is that it means we can create highly personalized treatments for patients with rare mutations. What's also special is that we can mix and match compounds from different companies to see if patients are responsive to a certain combination of drugs."

From April, the project's clinicians will start testing compounds that have proven to be effective on organoids on real-life patients. "We expect these patients to respond well," said Professor van der Ent. "We hope that within five years, these patients will have new drugs."

Targeting the cystic fibrosis gene

One in 35 people carries the faulty gene that causes CF—usually without knowing. Two people carrying the faulty gene have a 25 percent chance of having a child born with the disease. Without modern treatment, most people born with CF do not live long beyond their thirties.

Until recently, the only way to treat CF was with antibiotics to fight infection, steroids to reduce inflammation, physiotherapy to clear airways, exercise, nutrition and transplants (of the lungs, liver and sometimes other organs). Although the disease still remains incurable, since 2012, a new class of drugs called modulators has transformed treatment for many.

CFTR modulators target specific defects in the CFTR protein, thereby restoring healthy function of the protein so that chloride (which is present in salt) can flow across the cell surface. To date, four such modulators have reached the market, and these drugs are both transforming the quality of patients' lives and lengthening their lifespan substantially.

"Thanks to these drugs, in some patients there's a lung-function improvement of 30–40 percent and life expectancy can increase from the age of 30–40 to 60–80," said Professor van der Ent. "In other words, there can be a normal life expectancy."

One significant downside of CFTR modulators is their price: treatment costs up to €200,000 per patient per year. As a result, only patients in countries with a well-funded health service can access medication. Meanwhile, many patients in Eastern Europe, along with other less developed parts of the world, are missing out.

Another drawback—and one that HIT-CF aims to address—is that CFTR modulators are only being clinically tested in patients with well-described, common mutations of CF. There are up to 2,000 genetic mutations that lead to CF, but just 120 of these are responsible for 80-85 percent of disease occurrence. It is patients with these common forms of the condition who are able to benefit from the CFTR modulators currently on the market.

So why are patients with rare mutations being left behind? The high cost of clinical trials means it simply does not make commercial sense for drug companies to focus their efforts on this sub-group of CF patients.

Step in organoid technology

Scientists involved in the HIT-CF project are taking tissue samples from

the rectum of patients with rare forms of CF, isolating stem cells, and growing these to form mini-intestines.

There are two major advantages of using organoids to screen potential drugs: there are no safety considerations for the patient, and the screening process is highly efficient (any number of compounds from a library of potential drug candidates can be thrown at an organoid, and at speed). As a result, the potential cost savings are vast. For participants of the HIT-CF project, this is great news.

"This study is giving people who have been excluded from clinical studies the chance to be recruited for a study and to find medicines that will tackle the causes of their disease," said Dr. Elise Lammertyn, head of research at the European federation of national CF patient organizations Cystic Fibrosis Europe, a partner in the HIT-CF project.

"There are quite a few (conventional) clinical trials going on in Europe for cystic fibrosis, but most of these are only open to those with the most common mutations of the disease, and the 10–15 percent of people with ultra-rare mutations are left out in the cold. This new study is about personalized medicine at its most innovative."

Universal access to treatment

Prof. van der Ent, in partnership with other scientists involved in CF research, is set to launch Fair Therapeutics—a company that will set out to use organoid technology to bring CF drugs to market for patients with both common and rare mutations, at affordable prices.

"In a sense we'll be competitors to big pharma but actually we will all be working towards the same goal of reaching all CF patients," said Professor van der Ent.

First, however, the project scientists must acquire permission from the European Medicines Agency (EMA) to approve organoid testing so it can be used beyond the current study. "It will be very helpful to have a test in the lab that can be used in conjunction with less lengthy clinical trials to prove the effectiveness of drugs in small groups of people," said Professor van der Ent. "It will highly speed up the pipeline of new drugs for all kinds of diseases, not just CF. It could even be used as a predictive tool for cancer treatment: you do a biopsy of a tumor, add chemotherapy and other drugs to the organoid, and then use the most sensitive treatment on the tumor."

Provided by Horizon: The EU Research & Innovation Magazine

Citation: There's no cure for rare types of cystic fibrosis, but researchers are making significant advances (2022, February 2) retrieved 26 April 2024 from https://medicalxpress.com/news/2022-02-rare-cystic-fibrosis-significant-advances.html

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