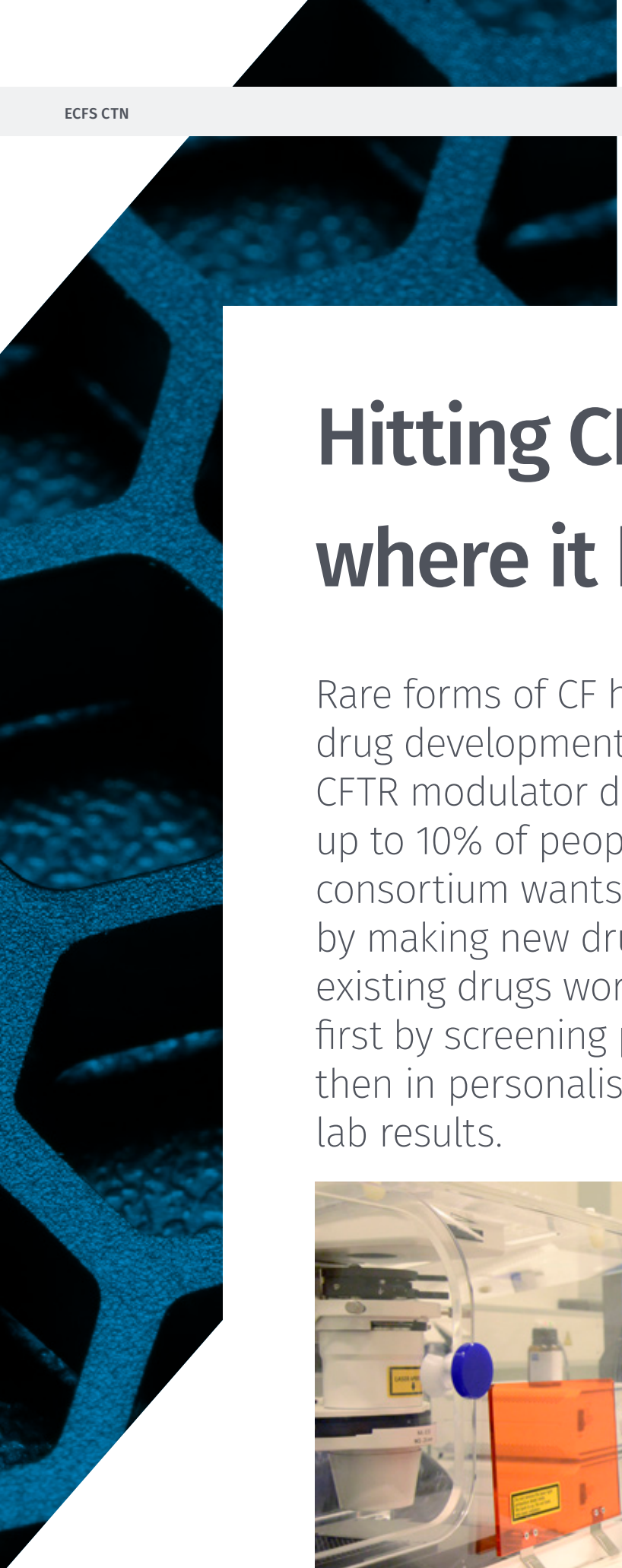
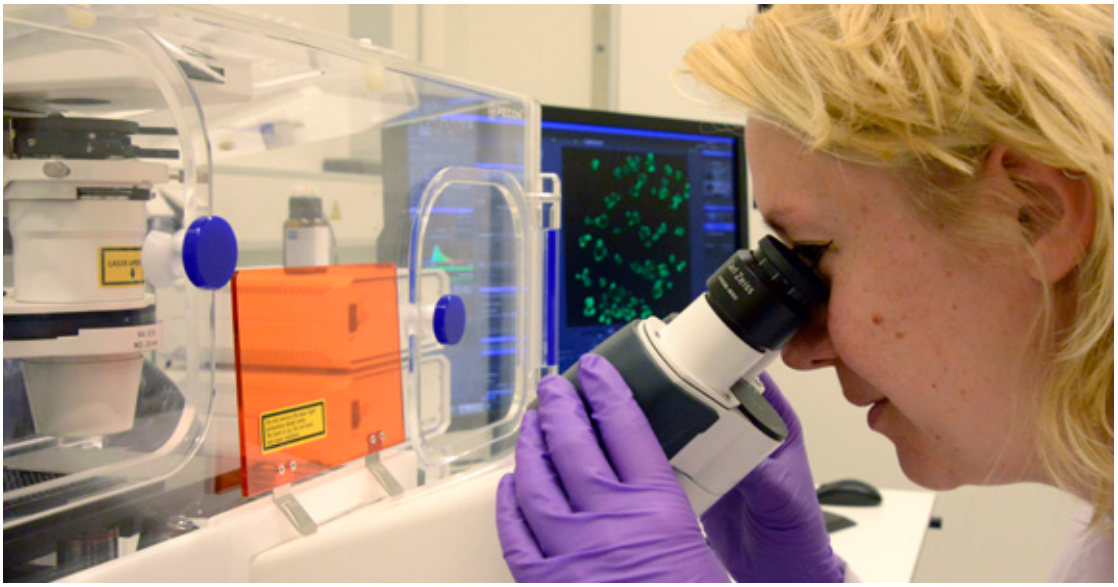
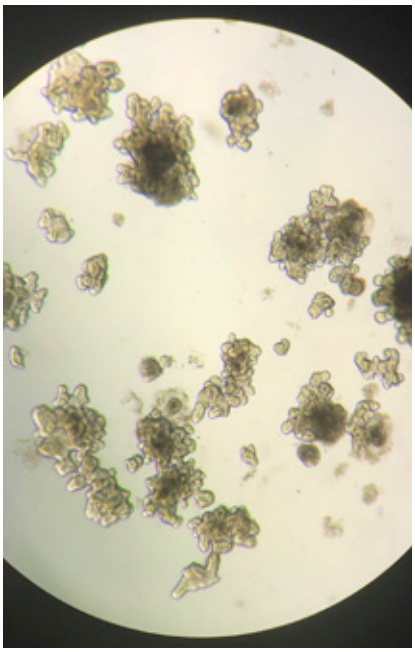


Hitting CF where it hurts

Rare forms of CF have been neglected by drug development programmes, with no CFTR modulator drugs on the horizon for up to 10% of people with CF. The HIT-CF consortium wants to fill this gap. Not by making new drugs, but by checking if existing drugs work for rare CF mutations – first by screening patient tissue in the lab, then in personalised clinical trials based on lab results.





CF organoids under the microscope
after 7 days culture in the lab

Annelotte Vonk dims the lights, draws her chair up to the microscope and lines the dish up under the lens. Since the courier delivered the rectal biopsy tissue to her lab in Utrecht, Annelotte has been coaxing stem cells in the tissue to grow into mini-replicas of the intestine with the same rare type of CF as the patient who gave the rectal biopsy. These "organoids" could hold the key to finding a drug that treats this patient's rare version of CF. The previous morning, Annelotte had pipetted a tiny dose of an experimental CF drug onto the organoids. Now, she's ready to see if the drug has managed to fix the faulty CFTR protein. With a steady hand, she pipettes in a few drops of an agent to stimulate the organoids. "We tell the microscope to take a picture every 10 minutes and we do that for an hour," says Annelotte, "then you have a mini-video of what happens to the organoids over that hour."

Organoids – the first success

Researchers have identified over 2000 CF-causing mutations, but to date, drug development has focused only on the most common mutations, such as dF508.

Around 10% of patients have mutations so rare that they are sometimes shared by only one or two other patients worldwide.

Few pharma companies have the resources or the economic motivation to develop drugs specifically for these patients.

In 2015, the CF team in Utrecht, Netherlands treating a very ill teenage boy with an ultra-rare form of CF were running out of treatment options. Using newly developed organoid technology, they showed that a recently licensed CF drug successfully activated intestinal organoids grown from the boy's rectal biopsy. The drug proved to be just as effective in real life, and the Dutch insurance company agreed to pay for the drug, based on the combination of organoid and real-life results.

The HIT-CF project was put together to capitalise on this success, and launched just a few years later in 2018, with over €6 million of funding from the EU Horizon 2020 research programme.

Dr Peter van Mourik
Doctor and CF researcher at UMC Utrecht and HIT-CF study coordinator

Leave no patient behind

"The goal of HIT-CF is to focus on patients who are currently left out of the major drug development programmes and to help them get access to new treatments," says Dr Peter van Mourik, a doctor and CF researcher at UMC Utrecht and HIT-CF study coordinator. Four pharmaceutical companies will provide candidate drugs to be tested, first on organoids and later in personalised clinical trials on patients themselves. The more pharma companies participating, the better, according to van Mourik, because "patients will have a better chance to respond to one of the drugs being tested."

2018 - a busy year of set-up

In the first phase of HIT-CF, organoids will be grown from 500 patients and screened to see how they respond to various CF drugs. It takes a lot of paperwork and logistical planning to get CF centres ready to participate in HIT-CF. "At the moment [in april] we have at least 5 countries with approval," says van Mourik, "but we're setting up in at least 12 countries. We want to be able to include patients all over Europe." The biopsies taken at local CF clinics are sent on ice to the specialist lab in Utrecht to be grown into organoids. "At this point it's about growing the organoids and freezing them down," explains van Mourik, "then we will send them out in batches to the different labs for drug screening."

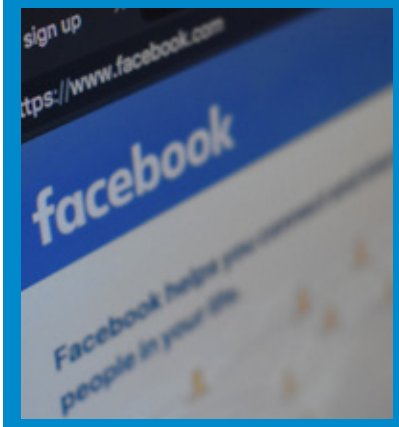
"We want to include patients all over Europe"

Preparing for the clinical trials

In phase 2 of HIT-CF, due to start in 2020, patients whose organoids had a strong response will receive that drug in a real life clinical trial. These personalised trials are very different to traditional clinical trials that test drugs in groups of patients. Designing such an innovative trial involving multiple pharma partners is a big challenge. "The ECFS-CTN is important here to give input into the protocol - seeing what's reasonable, what is wise to do," says van Mourik, "having patients involved in this to see what they think is feasible is also important."

"The ECFS-CTN is important here to give input into the protocol. Seeing what patients think is feasible is also important."

Keeping patients updated



CF Europe, the umbrella European patient organisation, is the partner in charge of communicating about project progress. “Informing and communicating with people with CF is one of the top priorities of the consortium,” says Elise Lammertyn, head of research at CF Europe.

“We regularly post updates about HIT-CF on our Facebook page, and there is a page on the HIT-CF website dedicated to the latest news. Every six months, we add a newsletter to the website which is disseminated to the national patient organizations. We also invest in educating patient representatives on HIT-CF; we dedicated a workshop to HIT-CF during the 2018 CF Europe annual general meeting.”

www.hitcf.org

All on-board

Leaving nobody behind means getting everybody on board, including regulatory authorities, such as the European Medicines Agency (EMA). This is especially important for personalised medicines for rare diseases, where the gold standard randomised clinical trials are simply impossible due to limited numbers of patients. “One of the major advances in 2018 was that we started talking to the EMA about what we need to have in place to have the drugs approved,” says van Mourik.

Medicine’s last mile

Many projects claim to be “bench to bedside” – that they bring new drugs from the laboratory bench through trials and all the way to the patient’s bedside. HIT-CF plans to live up to the “bench to bedside” claim by helping drugs jump the last big hurdle – reimbursement by national payment agencies. EMA and other regulators want to know if the drug is safe and effective, but payers need extra evidence showing that the drug represents good value for money – often demonstrated using patient-reported outcomes.

Designing trials that provide the evidence needed by both the regulators and the payers can speed up the arrival of drugs from the bench to the bedside. The HIT-CF team have started talking with reimbursement agencies “from them we will hear what’s needed to reimburse the drugs,” says van Mourik, “we’ve also been talking to the European working group MOCA - the mechanism of coordinated access to orphan medicinal products - who have payers on their committee.”

Next steps

The HIT-CF team are working hard to obtain biopsies from the 500 patients needed in the first phase of the project. If you have a rare CF mutation, and would like to participate in the project, please contact your local CF care team, or your national patient organisation. You can visit the project website to find out more: www.hitcf.org