European Cystic Fibrosis Society

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

Cystic Fibrosis Research News

Title: Functional Restoration of CFTR Nonsense Mutations in Intestinal Organoids

Lay Title: Exploring new treatment options for people with cystic fibrosis with severe stop mutations

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What was your research question?

For people carrying so-called stop mutations in the CFTR gene (which cause the production of the CFTR protein to stop prematurely) (approximately 10% of the people with CF (PwCF) there is currently no drug available, while these PwCF are very ill. Instead of focusing on a single golden bullet, we aimed to research if a specific combination of 5 already existing compounds would be able to restore CFTR function.

Why is this important?

This project is important as it enables us to understand how we can more effectively restore CFTR function even when CFTR is severely dysfunctional due to a stop mutation. We found that it is important to combine different types of drugs. This allows us to suggest how more effective drugs for people carrying stop mutations can be developed. This is important for pwCF, but also for others who have diseases caused by a stop mutation.

What did you do?

We tested which combinations of drugs derived from various pharmaceutical companies and with varying working mechanisms were most effective in restoring CFTR function. To study whether CFTR function was restored, we used a patient-derived intestinal cell model (so-called organoids or mini-guts) carrying the most frequent stop mutations. To interpret the degree of CFTR stop mutation repair by the drug combinations, we compared effects with CFTR restoration by current drugs on the market with established clinical effects.

What did you find?

We found what type of drugs can be combined to maximize their efficacy for function repair of CFTR stop mutations. We can use a cooking analogy for explanation. Stop mutations can be seen as incomplete recipes which cannot be used to produce a complete CFTR cake (aka protein). Specific (readthrough) agents (e.g. ELX-02) instruct the cellular cooks to fill in the missing piece of the recipe. This is not very effective, but leads to some CFTR cakes. Drugs that increase the number of recipes (e.g. Smg1i) work with ELX-02 to further increase the number of CFTR cakes as more cooks can fill in the missing piece. This still not fully repairs the stop defect. By adding extra seasoning (clinically available CFTR modulators e.g. Trikafta/Kaftrio), we found optimal repair, and we observed strong CFTR repair, within the range of other clinically approved CFTR modulators.

What does this mean and reasons for caution?

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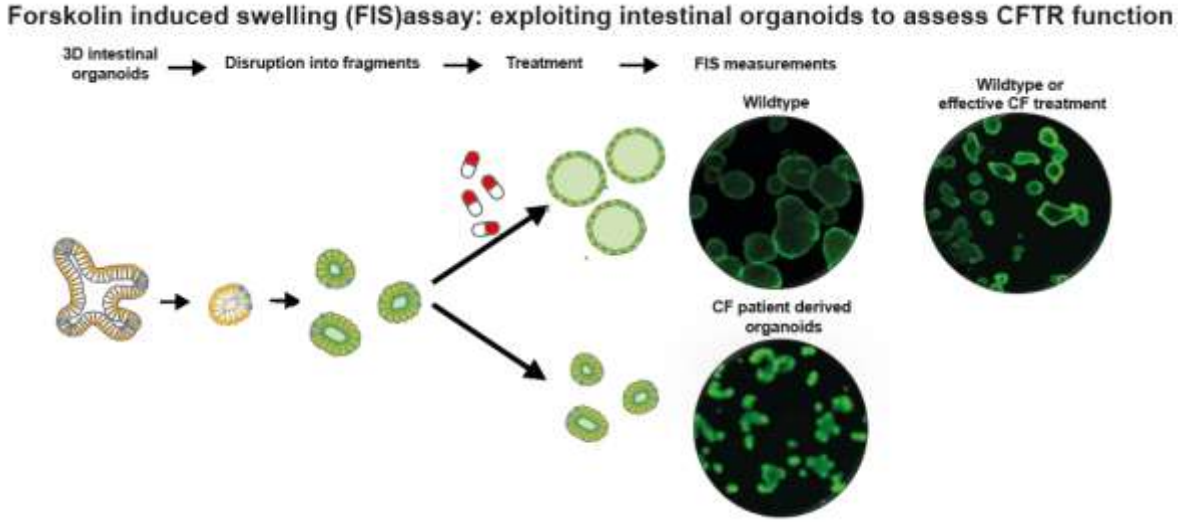
Whilst our results are promising, results in the lab are not always representative of real life situations. Whilst some of the compounds we tested are already used for PwCF in the clinic (Kaftrio/Trikafta®), others are still being investigated in clinical trials (RT agents) or at a preclinical stage are thus not readily available. The study results will help to define the avenues by which more effective treatments for people with stop mutations can be explored.

What's next?

The observations in intestinal cells are being studied now in CF airway cells. Additionally, we aim to develop a toolbox to further help in evaluating the efficacy of compounds in development for stop mutations. As we show that substantial CFTR rescue is possible by drug combinations, we hope that safe and efficacious drugs are being developed that enable treatment of stop mutations.

Potential Figure:



Original manuscript citation in PubMed

https://pubmed.ncbi.nlm.nih.gov/34666947/