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Cystic Fibrosis Research News

Title:

Targeting *G542X CFTR* Nonsense Alleles With ELX-02 Restores CFTR Function in Human-Derived Intestinal Organoids

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What was your research question?

Does ELX-02, a small molecule capable of nonsense mutation read-through, produce functional cystic fibrosis transmembrane conductance regulator (CFTR) protein in cells with a G542X mutation, which is the most common type of nonsense mutation in people with CF ?

Why is this important?

Genetic information is translated into proteins that perform necessary tasks (like CFTR's role conducting chloride) for cells. This translation can be terminated early when a nonsense mutation introduces an early stop signal into the gene (as occurs in approximately 10% of people with CF). The truncated protein may be unable to function and is often unstable and starts to degrade leading to cell malfunction and disease. Current modulator therapies designed to improve CFTR activity are ineffective when CFTR protein is not being made. To overcome this, cells must be able to ignore (or read-through) this stop signal to produce full-length CFTR. ELX-02 is a compound that may increase read-through.

What did you do?

Previous studies indicated that G542X read-through with ELX-02 is possible, but different results can be seen when testing cells from different individuals. In some situations, these cells can be grown in a way where they group together and model a small organ, called an organoid. We used individual-derived organoids from CF donors to test cells for CFTR activity where the cell has one or two copies of the G542X mutation. Following exposure to ELX-02, we tested the cells for production of the CFTR protein, CFTR activity and for changes in the transcript that codes for the protein.

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What did you find?

Across many experiments, we observed that ELX-02 can produce active CFTR protein in organoids with G542X mutations. While no CFTR activity is found in these G542X organoids when untreated, an increase in activity was seen with increasing amounts of ELX-02. We also observed that ELX-02 increased the CFTR transcript, the molecule used to produce the protein, about 5-fold in some cases.

What does this mean and reasons for caution?

These data support that it is possible to make active CFTR protein in G542X cells using ELX-02. This is an important step for advancing a new therapy as increasing the amount of active CFTR is a direct approach to reducing CF disease burden. The data helped inform the ELX-02 clinical trials by identifying the types of CFTR genetics that should be included. We believe organoids are a useful model to help identify potential new therapies for people with CF with rare mutations. Data from the clinic are needed to understand if these laboratory results translate to an effective therapy.

What's next?

As ELX-02 advances in the clinic for people with CF due to G542X CFTR mutations, we will continue to test the molecule with other types of nonsense mutations to determine if they too may benefit from this approach.

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