



# Cystic Fibrosis Research News

## **Title:**

ISOGENIC CELL MODELS OF CYSTIC FIBROSIS-CAUSING VARIANTS IN NATIVELY EXPRESSING PULMONARY EPITHELIAL CELLS

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## **What was your research question?**

Several hundred changes in the CFTR gene, referred to as mutations or variants, are known to cause cystic fibrosis (CF). We sought to develop cell models of rare, CF-causing CFTR variants for drug discovery and development.

## **Why is this important?**

CFTR modulators have successfully been developed to treat some of the most common CF-causing variants. Unlike other types of CF treatments, such as antibiotics, these CFTR modulators may not be effective for people who carry two of the many rare CFTR variants. Cells with rare, CF-causing CFTR variants in the right genetic context are very limited and these cells are needed to develop new treatments. Cells from people with CF are critically important for drug development, but are of limited quantity, especially for rare CF-causing variants. Other types of cells can also be used, but all have limitations.

## **What did you do?**

We developed a process using gene editing technology to create cells with specific CFTR variants. These cells are an essentially inexhaustible supply and can be used in drug discovery, including in experiments that measure the function of the CFTR protein. As proof of concept, we first created cells with the most common CFTR variant, F508del, and demonstrated that these cells are responsive to approved CFTR modulators. Next, we created and characterized cells with the CFTR variants G542X or W1282X. Both are so-called nonsense variants and

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belong to the most common class of CF-causing variants without approved CFTR modulating therapies.

## **What did you find?**

The process we developed is versatile and efficient and we successfully created and characterized cells for several CFTR variants. The cells with the F508del CFTR variant responded as expected to approved CFTR modulators, which validated the usefulness of these cell models for drug development. Encouraged by these findings we made the cells with the rare CF-causing mutation G542X or W1282X, and we found they also have similar characteristics to what is seen in cells from people with CF that carry these variants.

## **What does this mean and reasons for caution?**

These newly created cells can model aspects of the CF disease and can contribute to the development of therapies that address the currently unmet medical need of those people with CF with rare mutations. The cells are available to the CF research community and have already been shared with many researchers. The cell model of F508del responds as expected to approved therapies. However, the usefulness of the G542X and W1282X cells for drug development cannot be fully evaluated until more and better potential treatments are identified.

## **What's next?**

We are continuing to create and characterize cells with other rare, CF-causing CFTR variants. All these cells are available to the CF research community and will continue to be used by our group and others to learn more about CF disease and to develop new therapies.

## **Original manuscript citation in PubMed**

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