European Cystic Fibrosis Society

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

# Cystic Fibrosis Research News

## Title:

R560S: a class II CFTR mutation that is not rescued by current modulators

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## What was your research question?

We wanted to know what are the defects that the rare cystic fibrosis-causing mutation R560S causes on the amount and function of CFTR protein in the cell and whether the existing drugs (Kalydeco, Orkambi, Symdeko and also cysteamine) are able to correct these defects.

## Why is this important?

Given the very high number of variants described to occur in the CFTR gene, it is very important, especially for the rare ones, to assess how each of them specifically affects the amount and function of CFTR protein so as to determine whether these changes are disease-causing mutations or not. Furthermore, it is very relevant to test whether these rare mutations respond to the existing drugs, preferably in patient-derived materials, as these are likely to be the best predictors of the clinical response to those drugs.

## What did you do?

We used "miniguts" (intestinal organoids) from one individual with CF who is homozygous for the rare mutation R560S and in parallel, we produced a novel cell line containing CFTR protein with this mutation, so as to study the cellular defects of this mutation in the laboratory. Firstly, we assessed whether CFTR protein with R560S is correctly located at the cell surface and whether it functions as expected. Secondly, we also assessed its response to modulators.

## What did you find?

Firstly, we found that CFTR protein with the R560S mutation fails to be correctly located in the cell (similarly to F508del), being thus a class II mutation which may be directly linked to the severe CF symptoms (phenotype). Secondly, we found that contrarily to F508del, the R560S mutation does not positively respond to the available modulators (Orkambi, Symdeko). Thirdly, we also assessed whether cysteamine corrects this mutation, but found no ability to correct R560S. Moreover, we did not detect any effect of cysteamine on the rescue of F508del (either in organoids or in cell lines).

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

The results obtained here show that, despite that R560S is classified as class II similarly to F508del, the response of these mutations to CFTR modulators is distinct. This example illustrates how difficult it is to rescue all 2,000 CFTR mutations.

### What's next?

Our work reinforces that in order not to leave anyone behind there is a strong need for a continuous effort in searching for elucidating the cellular consequences of rare CFTR mutations in order to find modulator drugs or alternative therapeutic strategies particularly for patients bearing such rare mutations.

### Original manuscript citation in PubMed

https://www.ncbi.nlm.nih.gov/pubmed/?term=R560S%3A+a+class+II+CFTR+mutation+that+is+not+rescued+by+current+modulators



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