European Cystic Fibrosis Society

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

Cystic Fibrosis Research News

Title:
Physiological and pharmacological characterization of the N1303K Mutant CFTR

Authors:
Samantha DeStefano[1,2], Maarten Gees[3], Tzyh-Chang Hwang[1,2]

Affiliations:
[1]Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO 65211
[2]Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, MO 65211
[3]Galapagos NV, Mechelen, Belgium

What was your research question?
In our study, we aimed to gauge the severity of the gating defect (where the CFTR protein channel reaches the cell surface but does not open correctly, if at all) caused by the N1303K mutation, to understand why this gating defect occurs, and to assess if, and to what extent, CFTR modulators (including both potentiators and correctors) can improve the gating function and transportation (trafficking) of the CFTR protein to the cell surface in people with the N1303K mutation.

Why is this important?
This is important because N1303K is the fifth most common mutation in the *CFTR* gene which causes cystic fibrosis (CF). N1303K causes a severe, pancreatic-insufficient form of CF, but effective CFTR modulators targeting the basic underlying defects of this gene mutation are being developed. N1303 is at the equivalent position, but in the opposite half of CFTR, as F508, deletion of which (F508del) constitutes the most common mutation in CF. Like F508del, N1303K is a Class II folding defect mutation, which results in a reduced number of CFTR channels in the cell surface. Both of these common, Class II folding defect mutations also show gating defects once they reach the cell surface.

What did you do?
In cells grown in the laboratory, we tested the response of CFTR channel proteins with this mutation to CFTR modulators including potentiators Ivacaftor (VX-770) and GLPG1837, as well as correctors Lumacaftor (VX-809) and Tezacaftor (VX-661).

European Cystic Fibrosis Society

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

Cystic Fibrosis Research News

What did you find?

We found that fully activated CFTR channels with the N1303K mutation assume only approximately 6% of the gating function of wild-type CFTR. Our data also showed that the gating defects in N1303K are fundamentally different from that of F508del in spite of the fact that N1303 and F508 are located at the equivalent position in the CFTR protein. More important, the gating function of N1303K mutant proteins can be improved dramatically by the CFTR potentiators tested; this reached approximately 50% of channel gating activity of wild-type CFTR with Ivacaftor and 100% of this activity with GLPG1837. We also showed that CFTR correctors Lumacaftor and Tezacaftor can lessen the magnitude of the trafficking defect caused by N1303K. However, unlike the F508del mutation, a combination of correctors and potentiators did not cancel out the effects of correctors.

What does this mean and reasons for caution?

Although more studies using human epithelial (surface layer) cells are needed to verify our observations made in non-human cells, these results support using a combination of CFTR potentiators and correctors to treat people carrying the N1303K mutation in the *CFTR* gene.

What's next?

Current studies, used together with the atomic structure of CFTR which has recently been solved, pave the way for future work that may explain the molecular basis for the gating defects associated with N1303K and F508del.

Original manuscript citation in PubMed

7 June 2018