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# Cystic Fibrosis Research News

## Title:
Extracellular phosphate enhances the function of F508del-CFTR rescued by CFTR correctors

## Lay Title:
Boosting the rescue of faulty CFTR with phosphate

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## What was your research question?
We investigated whether phosphate affects the function of cystic fibrosis transmembrane conductance regulator (CFTR) with the most common cystic fibrosis (CF)-causing genetic defect, F508del, after its rescue by CFTR-targeting drugs. Phosphate plays several important roles in cells, including the formation of cell borders, storage of genetic information and energy production.

## Why is this important?
Previous research has shown that after rescue by CFTR targeting drugs, the function of CFTR with CF-causing defects can vary. Variation is even seen between cells from different people with CF carrying the same genetic defect. One explanation for this variation is the activity of proteins that transport different substrates into and out of cells where CFTR is found. To optimise personalised medicine for all people with CF, it is essential to identify these different transport proteins and manipulate their activity to maximise the function of CFTR with CF-causing defects that have been rescued by CFTR targeting drugs.

## What did you do?
For this laboratory-based study, we used two types of cells. First, model cells widely used in CF research, which forms cell sheets like those that lines ducts and tubes in the body affected

by CF. Second human cells from the air passageways of people with CF and the most common CF-causing genetic defect F508del. With both cell types, we performed two studies. First, we tested whether the cells carry the gene of a phosphate transporter. Second, we studied CFTR function in cell sheets treated with CFTR-targeting drugs to learn whether phosphate boosts the rescue of CFTR with the F508del defect.

## What did you find?

We found that both model cells and human airway cells carry the gene of a phosphate transporter and there was no difference between non-CF cells and CF cells with the F508del defect. When we treated cell sheets with the clinically used CFTR-targeting drugs lumacaftor and elexacaftor-tezacaftor-ivacaftor (Trikafta), the function of CFTR with the F508del defect was greater when cell sheets were bathed in a phosphate-containing solution than when phosphate was absent. In further experiments, we found that the beneficial effect of phosphate on the function of CFTR with the F508del defect also required sodium in the solution bathing cell sheets.

## What does this mean and reasons for caution?

Our results suggest that human airway cells have a phosphate transporter that uses sodium movements to power the uptake of phosphate from the fluid lining the air passageways. They also suggest that the accumulated phosphate makes CFTR with the F508del defect work better after it has been rescued by CFTR-targeting drugs, such as Trikafta. There are several reasons why caution is necessary. First, this study is laboratory research, not a clinical trial. We therefore do not recommend dietary phosphate supplements when using Trikafta. Second, we only studied F508del. The effects of phosphate on other CF-causing genetic defects are unknown.

## What's next?

We seek to identify the phosphate transporter that mediates phosphate accumulation by human airway cells. Moreover, we are keen to learn whether phosphate boosts the function of CFTR with other CF-causing defects rescued by either Trikafta or other CFTR-targeting therapies to help optimise personalised medicine for all people with CF.

## Original manuscript citation in PubMed

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