



# Cystic Fibrosis Research News

**Title:**

CFTR-beyond the airways: Recent findings on the role of the CFTR channel in the pancreas, the intestine and the kidneys

**Lay Title:**

CFTR in the pancreas, the intestine and the kidney: Function, dysfunction and potential future remedies

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**What was your research question?**

The authors briefly explain how the CFTR channel interacts with other transporters to regulate fluid and bicarbonate output in the pancreas, the intestine and the kidney. The spectrum of disease manifestations (signs and symptoms) that result from a dysfunctional CFTR in these organs are described. Finally, new treatment strategies are highlighted.

**Why is this important?**

More recent CF therapy including CFTR-targeted therapy has reduced the severity of lung disease and has increased lifespan. To further reduce disease burden and improve the quality of life, it is important to find new treatment strategies for managing disease in the other affected organs. For example, recent studies in patients and in animal models of pancreatitis have found that CFTR dysfunction, either by genetic mutations or by toxic substances, plays an important role in disease manifestation. Intestinal obstructive disease is also a major burden in patients with CF. Finally, CF-associated defects in the kidney and intestinal bicarbonate secretion may cause the body's pH to increase (metabolic alkalosis) which may negatively affect lung function.

**What did you do?**

The groups of Peter Hegyi and collaborators in Hungary studied the early stages of pancreatitis in animal models and tested the preventive and therapeutic effect of CFTR-targeted ther-

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apy. The group of Ursula Seidler and collaborators investigated the mechanisms of CFTR-dependent and CFTR-independent fluid and bicarbonate transport in the murine intestine. They also tested strategies to inhibit intestinal fluid absorption and acid output with the goal to prevent intestinal obstruction. The group of Karl Kunzelmann and collaborators studied the importance of a functional CFTR protein and of another anion channel in renal bicarbonate excretion into the urine of mice, and in the formation of cysts in the kidney.

## What did you find?

Laboratory studies indicate that CFTR dysfunction is a major causative factor of pancreatitis, and that CFTR-targeted therapy may alleviate its severity. The intestine has CFTR-dependent and CFTR-independent pathways for fluid and bicarbonate movement. It was shown that CFTR-targeted therapy improves the CFTR-dependent intestinal fluid and bicarbonate secretion. However, inhibition of another transported (called the  $\text{Na}^+/\text{H}^+$  exchanger 3 [NHE3]) in the small and large intestine decreases fluid absorption and increases bicarbonate output even in mice that do not express any functional CFTR. Furthermore, a twice daily oral administration of a drug which inhibits intestinal NHE3 activity reduced the incidence of intestinal obstructions, decreased mucus hyperproduction and increased gut health in CFTR-deficient mice. Finally, the oral intake of a defined dose of sodium carbonate resulted in an increase in the blood pH in mice lacking CFTR, but not in the mice with a functioning CFTR channel, which excreted more bicarbonate into the urine. A similar observation was made in patients with CF. CFTR-targeted therapy improved bicarbonate output in the kidneys after an oral intake of sodium carbonate.

## What does this mean and reasons for caution?

It is known that CF causes serious disease of the pancreas and the intestine. The mechanisms are currently being unravelled in animal models, and novel treatment options and their safety are being tested in animals. Careful observations of patients with CF that are being treated by CFTR-targeted therapies raise hope that these treatments may improve or prevent pancreatic and intestinal disease and improve bicarbonate excretion into the urine. The results also suggest that non-CFTR targeted therapy may improve intestinal health in patients that do not qualify for CFTR-targeted therapy, or as adjunctive treatment.

## What's next?

The studies in animal models will be ongoing to obtain further insight into the action of new molecules, the benefits of treatment at a cellular and organ level, as well as indicate potential



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risks. However, the real challenge is to set up study protocols and initiate clinical trials in the patient cohorts detailed above.

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