European Cystic Fibrosis Society

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

# Cystic Fibrosis Research News

**Title:**
Antisense oligonucleotide targeting of mRNAs encoding ENaC subunits α, β, and ɣ improves cystic fibrosis-like disease in mice

**Authors:**
Chenguang Zhao, Jeff Crosby, Tinghong Lv, Dong Bai, Brett P. Monia, and Shuling Guo

**Affiliations:**
Ionis Pharmaceuticals, 2855 Gazelle Court, Carlsbad, CA 92010 USA

## What was your research question?
Previous studies show that the epithelial sodium channel (ENaC) is hyper-active in CF patients and plays an important role in the pathogenesis of CF. In this study our goal was to determine if antisense oligonucleotides (ASOs) which lowers ENaC levels would potentially reduce CF lung symptoms in mouse models.

## Why is this important?
Even with improved care and new therapies available, there remains a portion of the CF population which would benefit from newly discovered drugs. Much effort over the years has tried to identify therapies that rehydrate CF airways by targeting ENaC with the goal of improving disease. This protein is composed of three subunits (α, β, and γ), all of which are required for maximum channel activity. Previously we demonstrated that ASOs specifically targeting ENaCα reduce ENaC activity, mucus production, inflammation and airway hyper-responsiveness. Further investigation targeting each of the three subunits in the same study was required to understand the contribution of each of these subunits.

## What did you do?
We first identified antisense ENaC inhibitors which were safe in both cell culture and in mouse lungs. The safe ASOs that effectively reduced levels of each of the three ENaC subunits were identified. We next demonstrated that when these ENaC subunit ASOs were delivered to mouse lung, they could penetrate through the mucus into the lung cells and reduce the corresponding ENaC subunit levels. Using a mouse model which is similar to human CF disease, we tested if ENaC subunit ASO treatment could prevent and reverse established lung disease.

# Cystic Fibrosis Research News

## What did you find?

We evaluated ENaC subunit ASOs administered directly into the lungs of mice by local delivery which resulted in decreased ENaC expression and function. We found that these inhibitors were effective at preventing lung disease and increasing survival in a mouse model of CF disease. Also, we demonstrated that delivery of ENaC subunit ASOs reversed the disease. Specifically, reduction of any of the ENaC subunits normalized sodium channel activity, mucus production, inflammation, and improved lung function. ENaC has been suggested to play an important role in asthma. We demonstrated that subunit ASOs improved lung function but not mucus clearance in a house duct mite-induced mouse asthma model.

## What does this mean and reasons for caution?

This is the first *in vivo* study demonstrating that all three subunits are potential targets for CF lung disease. An antisense ENaC inhibitor offers several important advantages including high selectivity, long half-life with less frequent administration and the majority of drug delivered specifically to the lung. In addition, ASO drugs are well suited for combination therapy and are expected to combine well with CFTR modulators. In previous studies we demonstrate the ability to effectively deliver ASOs to the lung by inhalation. These results must be received with caution as targeting ENaC with ENaC subunit ASOs for the treatment of CF or other lung diseases has yet to be conducted in humans.

## What's next?

ENaC antisense therapy may provide a novel, potent and safe treatment option for CF. We have identified the human ENaC$\alpha$ subunit drug and are initiating a phase one clinical trial later this year. We expect ASO reduction of any ENaC subunit would provide effective treatment regardless of underlying CFTR mutations.

## Original manuscript citation in PubMed

https://www.ncbi.nlm.nih.gov/pubmed/?term=Antisense+oligonucleotide+targeting+of+mRNAs+encoding+ENaC+subunits+%CE%B1%2C+%CE%B2%2C+and+%C9%A3++improves+cystic+fibrosis-like+disease+in+mice


cfresearchnews@gmail.com