

Cystic Fibrosis Research News

Title:

Inhaled ENaC Antisense Oligonucleotide Ameliorates Cystic Fibrosis-Like Lung Disease in Mice

Authors:

Jeff R. Crosby^a, Chenguang Zhao^a, Chong Jiang^b, Dong Bai^a, Melanie Katz^a, Sarah Greenlee^a, Hiroshi Kawabe^c, Michael McCaleb^a, Daniela Rotin^b, Shuling Guo^a, and Brett P. Monia^a

Affiliations:

^a Ionis Pharmaceuticals, 2855 Gazelle Court, Carlsbad, CA 92010 USA

^b The Hospital for Sick Children, 686 Bay Street, Toronto, Ontario, M5G 0A4 Canada

^c Max Planck Institute of Experimental Medicine, Göttingen, Germany

What was your research question?

It is reported that the epithelial sodium channel (ENaC) is hyper-active in CF patients which causes the airway dehydration, defective clearance, and persistent infection and inflammation. Our goal is to test if antisense oligonucleotides (ASOs) can reduce ENaC in the lung and improve cystic fibrosis lung symptoms in mouse models.

Why is this important?

Even with improved care and new therapies available, CF remains a significant unmet medical need. Although ENaC has been proposed to be a good drug target for CF, the ability of ENaC inhibitors to improve CF disease has yet to be demonstrated. Trials with previous ENaC inhibitors have failed due to short half-life or undesirable systemic side effects such as ENaC inhibition in kidneys which resulted in high levels of potassium in the blood. Inhaled ASO drugs have a long tissue half-life and minimal systemic exposure representing a novel and safe therapeutic approach for CF lung disease.

What did you do?

We first identified safe ASOs that effectively reduced ENaC in cell culture and normal mouse lungs. We next demonstrated that when these ENaC ASOs were delivered by aerosol in mice, they could penetrate mucus and reduce ENaC levels. The ENaC ASOs were evaluated in three CF-like lung disease mouse models which have increased ENaC levels, the Nedd4L knockout mice, β ENaC transgenic mice, and the Nedd4L ASO induced CF mouse model



Cystic Fibrosis Research News

which we developed as an adult-onset CF model. With the Nedd4L ASO induced model, we also tested if ENaC ASO treatment could reverse established lung disease.

What did you find?

We demonstrated that ASOs delivered by aerosol distributed into the lung and decreased ENaC expression and function. We found that ENaC ASOs delivered by aerosol were effective at preventing lung disease in multiple CF-like mouse models. In a more clinically relevant setting, we demonstrated that delivery of ENaC ASOs reversed the disease. Specifically, ENaC ASOs normalized sodium channel activity, mucus production, inflammation, and improved lung function. In addition, delivery of ENaC ASOs to the lung did not affect ENaC in the kidney and therefore had no effect on potassium levels in blood.

What does this mean and reasons for caution?

An antisense ENaC inhibitor offers several important advantages over other ENaC therapeutic approaches currently in development. First of all, antisense drugs offer high selectivity. ASO drugs can be delivered to the lungs at low doses and low volumes in simple water-based solutions. Dosing can be as infrequent as monthly due to the long tissue half-life and duration of action. In addition, lack of systemic exposure and the ease to combine with other classes of drugs are additional advantages of this approach. However, targeting ENaC for the treatment of CF has not been clinically proven.

What's next?

Our data demonstrate that ENaC antisense therapy may provide a novel potent and safe treatment option for CF. We have identified the human ENaC drug and are in the process of getting ready to test this compound in the clinic. This treatment approach is applicable to all CFTR mutations.

Original manuscript citation in PubMed

<https://www.ncbi.nlm.nih.gov/pubmed/?term=Inhaled+ENaC+Antisense+Oligonucleotide+Ameliorates+Cystic+Fibrosis-Like+Lung+Disease+in+Mice>

Cystic Fibrosis Research News

cfresearchnews@gmail.com