European Cystic Fibrosis Society

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

Cystic Fibrosis Research News

Title:

A small molecule neutrophil elastase inhibitor, KRP-109, inhibits cystic fibrosis mucin degradation

Authors:

Shashi Chillappagari[1,2,3,8], Christian Müller[3], Poornima Mahavadi[2,8] , Andreas Guenther[2,8,9], Lutz Nährlich[1,8], Jonathan Rosenblum[4], Bruce K. Rubin[5], Markus O. Henke[3,6,7]

Affiliations:

[1]Department of Pediatrics Justus Liebig University Giessen, Feulgenstrasse 12, 35392 Giessen, Germany.
[2]Department of Internal Medicine, Justus-Liebig-University Giessen, Klinikstrasse-36, 35392, Giessen, Germany.
[3]Department of Pulmonary Medicine, Philipps-University Marburg, Baldingerstrasse 1, 35043 Marburg, Germany.
[4]ActivX Biosciences, Inc., 11025 North Torrey Pines Road, Suite 120, La Jolla 92037, CA, USA.
[5]Department of Pediatrics, Virginia Commonwealth University 14 School of Medicine, 1001 East Marshall Street, Richmond 23298, VA, USA.
[6]Asklepios Fachkliniken München-Gauting, Germany;
[7]Member of the Comprehensive Pneumology Center (CPC), Helmholtz Zentrum, Munich, Germany.
[8]Member of the German Centre for Lung Research (DZL), Giessen, Germany.
[9]Member of the European IPF Registry/Biobank, Lung Clinic Waldhof-Elgershausen, Greifenstein, Germany.

What was your research question?

In cystic fibrosis (CF), the protective airway mucus layer is mostly destroyed by enzymes such as proteases from bacteria and cells. We studied a drug that blocked these enzymes to see if it would prevent breaking down the mucus layer.

Why is this important?

Mucus normally protects the airway (bronchial) lining from infection and irritation. Persons with CF have persistent infection by bacteria that produces an enzyme, called “protease” that breaks mucus and attacks the airway cells. The cells that the body uses to fight the

infection produce a similar protease. These proteases destroy the protective mucus coating and leaves the airway vulnerable to chronic infection. This is normally controlled by antiproteases, but in CF the proteases overwhelm the capacity of antiproteases to stop this destruction. We hypothesized that adding an experimental antiprotease drug, KRP-109, to sputum might inhibit this mucus breakdown.

What did you do?

We first tested KRP-109 in phlegm (sputum) from people with CF, by adding increasing amounts to the sputum to see if it blocked the bacterial proteases, or the protease from the body's inflammatory cells; "neutrophil elastase" or NE. We evaluated this by examining mucus breakdown. We also tested to see if KRP-109 inhibited neutrophil elastase that was in the sputum, and if KRP-109 would decrease the protease activity from different strains of Pseudomonas; one of the most important bacteria that infect the CF lung. For all of these studies we compared KRP-109 with the body's natural antiprotease; "alpha-1 protease inhibitor" or A1PI.

What did you find?

We showed that KRP-109 was indeed able to block the breakdown of mucus, that this depended on the amount of protease already in the sputum and on the amount of KRP-109 that we added, and that the effect was similar to the body's normal antiprotease; A1PI. Of the 2 forms of mucin that make up the mucus layer, MUC5AC from surface mucous cells and MUC5B mostly from mucous glands, KRP-109 was somewhat better at protecting MUC5B. To our surprise, KRP-109 did not seem to inhibit the bacterial protease.

What does this mean and reasons for caution?

It appears that KPR-109 can block neutrophil elastase when there is not enough A1PI to stop proteases from destroying mucus. This is the normal way that body stops excessive inflammation and suggests that this could be a promising new therapy for CF.

What's next?

We next need to test if animals with CF-type lung disease can be protected by inhaling an aerosol of KRP-109 and if long term inhalation is safe and does not damage the airway. If these studies are promising, we can then start testing KRP-109 in persons with CF.

Cystic Fibrosis Research News

Original manuscript citation in PubMed

http://www.ncbi.nlm.nih.gov/pubmed/?term=A+small+molecule+neutrophil+elastase+inhibitor%2C+KRP-109%2C+inhibits+cystic+fibrosis+mucin+degradation