# Hope for preventative treatment for cystic fibrosis lung disease

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Heidelberg researchers have succeeded in preventing cystic fibrosis lung disease in an animal model by spraying amiloride into the lungs of young mice. This is the first therapy to successfully attack the root cause of the widespread hereditary disease in a living organism.

When mice are given inhalation treatment with the drug in the first days of life, no thick mucus forms in the lungs and airway inflammation and chronic lung damage can be prevented. The researchers at Department of Pediatrics at Heidelberg University Hospital have demonstrated for the first time that preventative therapy of lung disease is possible for cystic fibrosis. Their study was published in the *American Journal of Respiratory and Critical Care Medicine*.

Cystic fibrosis (CF) or mucosviscidosis or is the most common life-shortening genetic disease in Western Europe and North America. In Germany, some 8,000 people suffer from this disease; another five percent of the population - i.e. some four million people - are healthy carriers who can pass on the disease, usually without knowing.

The cause of all symptoms of cystic fibrosis are defects at a certain locations in the genetic makeup - a mutation in what is called the CFTR ("Cystic Fibrosis Transmembrane Conductance Regulator" gene) leads to loss of salt and water and thus dehydration of the surfaces of the mucous membranes in the lungs, intestines, and other organs. Thick, sticky mucus forms clumps that cannot be easily cleared. This leads to chronic airway inflammation and other serious respiratory and digestive

disorders. There is currently no treatment available that targets airway surface dehydration, i.e. the root cause of the disease; so far it is only possible to treat symptoms such as pneumonia, respiratory distress, and lack of oxygen.

Using the mouse model he developed, Dr. Marcus Mall, physician scientist and head of the Cystic Fibrosis Center at the Department of Pediatrics has shown that certain "hyperactive" sodium channels in airway cells are responsible for the increased absorption of salt and water from airway surfaces.

In this study which has now been published, Dr. Mall's team tested whether inhibiting these hyperactive sodium channels with amiloride could improve hydration of the airway surfaces and prevent lung damage. They found that in a mouse model, amiloride administered in the first few days of life prevents the typical symptoms of cystic fibrosis and the development of chronic lung disease. However, if the symptoms were already present, the treatment brought no improvement. Chronic lung damage apparently prevents the amiloride from being effective. "This indicates that the lung damage caused by the disease may be irreversible", stated Dr. Mall.

"With amiloride, preventative therapy of cystic fibrosis that attacks the basic defect directly could be possible for the first time. But the children affected would have to be identified at a very early stage", said Dr. Mall. However, the affected children often do not show the first symptoms until the age of several months or years. It is then too late for preventative therapy. In close cooperation with the Center for Metabolic Diseases in Heidelberg, a pilot project for newborn screening for cystic fibrosis was initiated in May 2008, similar to the screening programs that have already been implemented in the US and a few European countries. The test can be done as part of the routine screening for metabolic disease using blood from the infant's heel and enables the

diagnosis to be made in the first weeks of life, i.e. before the first symptoms develop.

Even with conventional methods, early treatment improves the quality and length of life for the affected patients. In addition, the patients identified by newborn screening could now benefit from the prophylactic inhalation therapy with amiloride. The physicians at the Cystic Fibrosis Center plan to study the therapeutic effects of preventive amiloride inhalation in future clinical trials.

Reference: Zhou Z, Treis D, Schubert SC, Harm M, Schatterny J, Hirtz S, Duerr J, Boucher RC, Mall MA. Preventive but not late amiloride therapy reduces morbidity and mortality of lung disease in ENaC-overexpressing mice. *Am J Respir Crit Care Med* 2008;178:1245-1256

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