



# Cystic Fibrosis Research News

## Title:

AGTR2 absence or antagonism prevents cystic fibrosis pulmonary manifestations

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## What was your research question?

We examined whether decreasing the activity of a receptor called AGTR2 would be good or bad for CF lung disease. The AGTR2 receptor is made by a gene also called AGTR2, that is expressed in lungs. Exciting data from a genetic survey of CF patients identified common genetic variations near the genetic code for the AGTR2 gene that associated with worse CF lung symptoms. Our study questioned whether intervention to decrease its expression would be good or bad for CF lung disease.

## Why is this important?

Although there has been a great deal of progress on developing new therapies for CF, some of these therapies are only useful for CF patients with a specific type of genetic mutation out of a number of possible CF mutations. Therefore, additional therapeutic options designed to benefit all CF patients are needed. The previous genetic survey identified a specific gene called AGTR2 that might be altering how severe someone's CF symptoms are, but that study did not indicate whether blocking this gene, or stimulating this gene, would be beneficial for CF patients.

## What did you do?

First we examined the AGTR2-linked genetic variation in a younger group of CF patients at Rainbow Babies and Children's Hospital in Cleveland Ohio to replicate previous genetic studies. Next, we measured the pulmonary function of CF mice with and without the AGTR2 gene. We tested this in CF mice with the F508del CF mutation, and in those with the R117H CF mutation, to ensure the results were not specific to one type of CF mutation. Finally, we treated CF mice from the time they were young until adulthood with daily injections of a drug designed to block the AGTR2 receptor, then measured their pulmonary functioning.

## What did you find?

In our local cohort of CF patients, we found the same association between the AGTR2 genetic variation and lung disease severity noted in previous studies. We measured the pulmonary function of CF mice with and without the AGTR2 gene, and found that when the AGTR2 gene was absent in CF mice, their pulmonary function was greatly improved. These results were observed in both F508del CF mice and R117H CF mice. We also wanted to know if those same results would be achievable with medications. The CF mice treated with the AGTR2 blocker also had improved pulmonary function compared to untreated CF mice.



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## **What does this mean and reasons for caution?**

Together these results indicate that using drugs to reduce AGTR2 activity is beneficial for CF mice, and may be a potential new therapy for people with CF. The AGTR2 receptor is part of the renin-angiotensin signalling pathway. Medications that act on the renin-angiotensin signalling pathway are commonly prescribed to patients with high blood pressure, and it will be interesting to see if they are helpful for CF patients. Caution is needed, as these studies were done in mice. Though CF mice do experience many of the same pulmonary challenges as CF humans, there are important differences. It is unclear whether reducing AGTR2 in humans would have similar benefits.

## **What's next?**

These results point to an exciting new avenue for improving pulmonary disease severity in all patients with CF, regardless of their specific CF mutation. Careful clinical trials will be required to evaluate the effectiveness of AGTR2 blockers in humans, and determine optimal dose, timing, and interactions with other medications.

## **Original manuscript citation in PubMed**

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