Antifungal drug improves key cystic fibrosis biomarkers in clinical study

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Dr. Martin D. Burke led a clinical study that found that an antifungal drug improves a key biomarker in the noses of patients with cystic fibrosis. Credit: L. Brian Stauffer

A drug widely used to treat fungal infections improved key biomarkers

in lung tissue cultures as well as in the noses of patients with cystic fibrosis, a clinical study by researchers at the University of Illinois Urbana-Champaign and the University of Iowa found.

Cystic fibrosis is caused by a missing or defective ion channel in the lining of the lungs, called CFTR. This leaves patients vulnerable to lung infections. Treatments called modulators can help some but not all patients, based on which type of genetic mutation causes the symptoms.

The patients who participated in the clinical study were among the 10% of patients who cannot respond to modulator treatments, suggesting the antifungal drug, amphotericin B, could benefit all patients regardless of their mutation, said study leader Dr. Martin D. Burke. Burke is a professor of chemistry at Illinois and the associate dean for research for the Carle Illinois College of Medicine, as well as a medical doctor. The study was published in the *Journal of Cystic Fibrosis*.

In previous work, Burke's group demonstrated that amphotericin forms ion channels in cell membranes that perform similarly to the missing protein, acting as a prosthetic on the molecular scale to restore function on a cellular level.

"This is the first clinical study," Burke said. "We have a long way to go, but this has increased our optimism that a molecular prosthetics approach could provide a new way to treat all people with cystic fibrosis, including those who cannot benefit from modulators. The mechanism should work the same for everyone, regardless of mutation."

In the new study, Burke's group, in collaboration with Dr. Michael J. Welsh at Iowa, tested the drug in cultures of lung tissue from patients with cystic fibrosis. They confirmed that the drug increased ion secretion in the cultures. Then, in experiments designed to replicate the first clinical studies of the modulator drugs, they tested it in patients'

noses.

Patients with cystic fibrosis lack the CFTR channel in the airway cells in their nose as well as in their lungs, so testing the drug in the nose is the first step to demonstrating that it could be effective in the rest of the airway as well, Burke said.

The researchers assessed whether the drug increased ion flow in the nose cells by measuring a biomarker known as nasal potential difference. In the study, the nasal form of amphotericin B changed the nasal potential difference in a way that suggested that amphotericin was performing the job of the missing CFTR channels.

"Though amphotericin B is an imperfect surrogate for the CFTR protein, these results provide the first evidence that small-molecule ion channels can impact physiology in people with cystic fibrosis," said Rajeev Chorghade, the first author of the study, who was a graduate student in Burke's group at the time of the study and is now a postdoctoral fellow at the Massachusetts Institute of Technology. "These results encourage further clinical trials to determine whether inhaled amphotericin B can improve lung function and health-related quality of life in people with CF, especially those not on modulators."

Next, the researchers plan to perform a clinical study to determine whether amphotericin inhaled directly to the lungs would improve lung function and immune response in patients with cystic fibrosis. To accomplish this, they have started a new company, cystetic Medicines, with the goal of developing a powder-based inhaler. The company has already raised $25 million in initial investments.

"One of the big advantages of amphotericin B is that it's already clinically approved. That's why we've been able to move so fast," Burke said. "We used a form of amphotericin that has been used widely to treat

fungal infections in the nose, so it was a nice opportunity for us to better understand the potential for cystic fibrosis applications quickly and safely. Now we need to develop a safe and effective mechanism to deliver it to the lungs."

More information: Rajeev S. Chorghade et al, Amphotericin B induces epithelial voltage responses in people with cystic fibrosis, *Journal of Cystic Fibrosis* (2020). DOI: 10.1016/j.jcf.2020.11.018

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