Two-pronged model could help foil tough cystic fibrosis infections

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Dartmouth Medical School researchers have devised a novel approach for thwarting the relentless bacterial infections that thrive in the lungs of people with cystic fibrosis (CF), unlocking new possibilities against a tenacious and toxic hallmark of the common genetic disease.

Combining a mainstay antibiotic with drugs to deprive the bacteria of iron, which facilitates their persistent growth, appears to boost infection killing, they found.

Their research, reported in the *American Journal of Respiratory Cell and Molecular Biology* online and scheduled for publication, builds on the collaborative expertise of DMS microbiology and lung physiology labs studying cystic fibrosis infections.

Cystic fibrosis patients are plagued by infections of the bacteria Pseudomonas aeruginosa. Their mucous-clogged lungs are fertile incubators for the bacteria to breed and cluster in slimy communities called biofilms that become increasingly drug resistant and damaging. Tobramycin, the antibiotic routinely used against the microbes, can control, but not efficiently eliminate Pseudomonas established on CF airway cells.

Last year, the DMS researchers reported that it took far more tobramycin to destroy
biofilm pockets than can be delivered to the lungs. Using a surrogate tissue culture system they created to simulate human airways, they

determined that up to 10 times the maximum tobramycin dosage was needed. They were also studying iron overload in CF lungs. Airway cells with the CF gene mutation release more iron, and the bacteria depend on that iron to form their resilient biofilms, the investigators discovered.

Now, applying their findings to the clinical front, the team demonstrated that two agents already approved by the Federal Drug Administration to treat acute iron poisoning or overload can enhance the ability of tobramycin against Pseudomonas infection.

"The beauty is that we are mixing FDA-approved drugs-- antibiotics and iron chelators-- to potentiate the effect of tobramycin on biofilm formation," said lead author Dr. Sophie Moreau-Marquis, a research associate. "It's an exciting translational framework that opens the door to potentially treating CF patients, taking the novel model we developed from the lab hopefully to the clinic."

Co-authors of the study are DMS professors Dr. Bruce Stanton of physiology, who heads the laboratory where Moreau-Marquis works, and Dr. George O'Toole of microbiology and immunology.

The research combines two results: "We were first to show iron is definitive for biofilms forming on live human airway cells. And the highest concentration of tobramycin that can reach CF lungs is below what we've shown to be barely enough to eradicate biofilms on airway cells," Moreau-Marquis said.

The team used two FDA-approved iron chelators, deferoxamine and deferasirox, that can remove excess iron from the system by binding to the metal in a process called chelation. To mimic the clinical environment, they stuck to the maximum possible tobramycin dose of 1,000 micrograms per milliliter, mixed with a chelator.

The combination had a dramatic effect: it disrupted the mass of established and highly resistant bacteria in human airway cells by 90 percent and it also prevented formation of damaging biofilms. In contrast, neither an iron chelator nor tobramycin alone had such success.

"We built on the idea that if more iron helps bacteria to grow, maybe taking iron away will help kill them," said O'Toole. "The concept is to reformulate one of these iron chelators to be inhaled with tobramycin, which is already inhalable, to treat the bacteria locally in the lungs."

Still, the team found evidence that a chelator can get into lungs from the bloodstream. Using a permeable support in the lab, they mimicked giving tobramycin to the lung side and a chelator to the blood side and showed that the iron chelator is able to work its way through to lungs.

Source: Dartmouth College