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New simple test could help cystic fibrosis patients find best treatment

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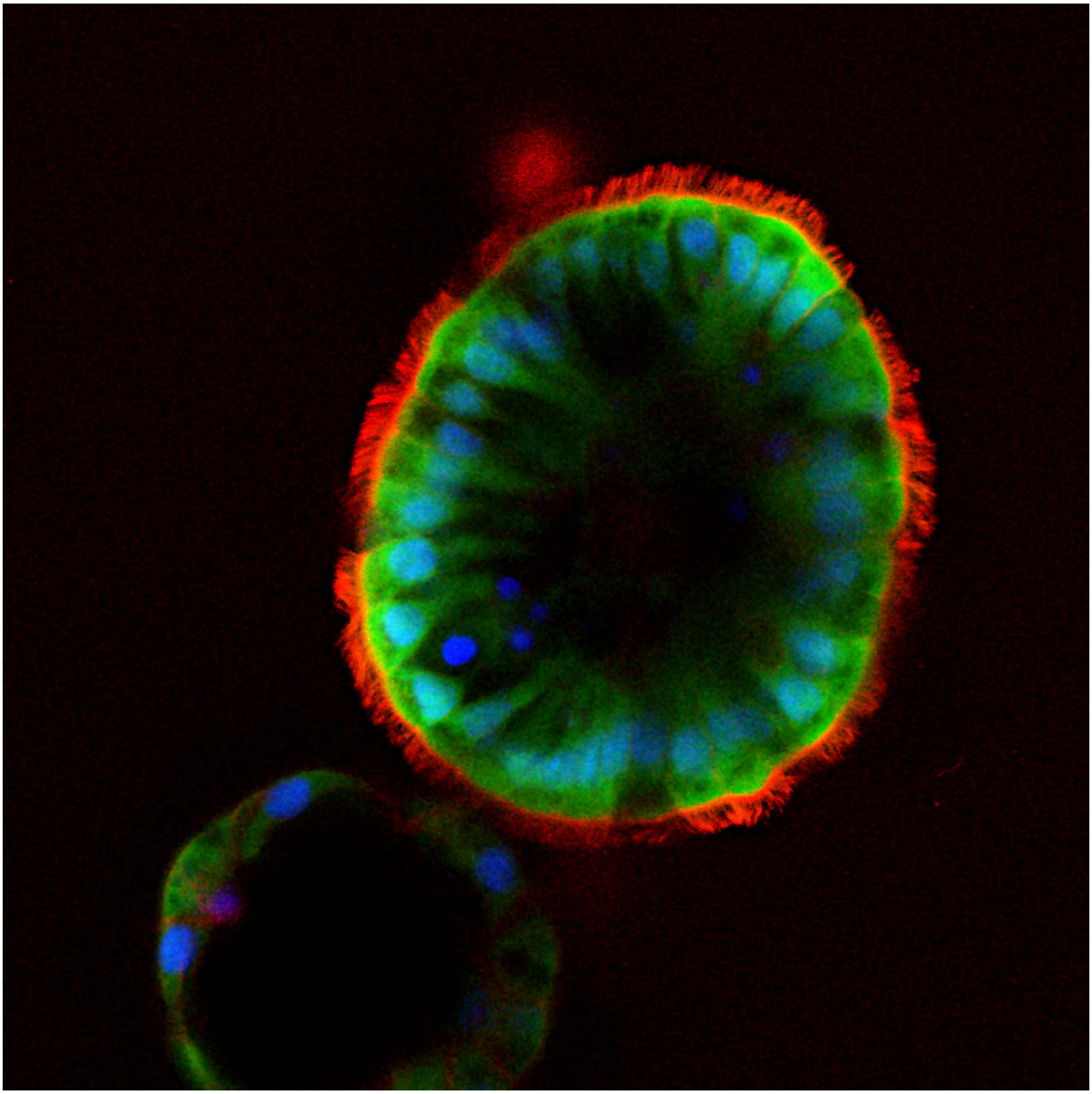

Nasospheroids that developed from a CF patient's nasal tissue in a dish. UNC researchers are using them to screen the effectiveness of CF treatments. Credit: Gentzsch Lab, UNC School of Medicine

Several cutting-edge treatments have become available in recent years to correct the debilitating chronic lung congestion associated with cystic fibrosis. While the new drugs are life-changing for some patients, they do not work for everyone. In a study published today in the *Journal of Clinical Investigation Insight*, a team led by UNC researchers presented a simple test that aims to predict which treatment is most likely to work for each patient, an approach known as personalized or precision medicine.

"Any given drug may not be the drug that works best for a given patient, because there's so much variation from person to person," said Jennifer Guimbellot, MD, who conducted the research at UNC and is now assistant professor of pediatrics at the University of Alabama at Birmingham. "We still have a long way to go to get a really optimized therapy for most cystic fibrosis patients, and the only way we can do that is to have a model like ours, where we can take cells from each individual patient and test them with each individual drug to find out which one is the best match."

From a drug-design perspective, cystic fibrosis is an enormous challenge. People develop CF because they do not have a functioning version of the CFTR gene. But the condition, which involves the buildup of thick, sticky mucus in the lungs, is tied to more than 2,000 genetic mutations. A person's specific combination of mutations affects both the severity of the disease and how well the patient responds to treatment.

Recent years have brought hope in the form of several drugs known as

CFTR modulators that counteract the effects of mutations in certain cystic fibrosis-linked genes. Rather than just treating the symptoms, the drugs get to the root cause of cystic fibrosis by helping the body's cells maintain the proper level of hydration. This, in turn, allows mucus to move freely in the lungs and other organs, preventing the buildup of sticky mucus that leaves cystic fibrosis patients prone to infections and other complications.

A trial-and-error approach for each patient - simply giving each available drug to every patient - is not feasible because the drugs cost hundreds of thousands of dollars, can take several months to work, and come with a risk of side effects. Currently, the only test available to predict how a patient will respond to CFTR drugs requires a rectal biopsy, followed by complicated laboratory manipulation of the sample to determine the drug's likely effectiveness.

Guimbellot found another approach. She was working with lead study author Martina Gentzsch, PhD, associate professor of cell biology and physiology at UNC, on an unrelated research project when she noticed some funny little balls forming from cells taken from the inside of the nose. The two scientists soon realized that the balls, which are called nasospheroids, were filled with fluid.

This gave them an idea. Maybe these nasospheroids could help to study essential parts of the CF hydration problem.

Fluid is at the heart of cystic fibrosis, since hydration of nasal and lung surfaces is what determines whether mucus is slippery or sticky. Guimbellot and Gentzsch learned how to grow nasospheroids from cells taken from the inside of the noses of cystic fibrosis patients. The researchers then exposed the nasospheroids to various CFTR drugs to see what would happen.

"When CFTR is turned on, the balls shrink down - mediated by the transport of salt and water - and we can quantify that by measuring the size of the balls," said Guimbellot.

The results suggest growing nasospheroids from nasal samples could provide a quick screening method to determine how a patient's cells react to different CFTR drugs.

"It is a relatively simple procedure that doesn't require any anesthesia and uses a brush that costs a few dollars," said Gentzsch, a member of the UNC Marsico Lung Institute. "The spheroids form quickly in just a few days without much manipulation."

Gentzsch said the testing approach could offer patients a welcome alternative to rectal biopsy. It might even be more reliable from a screening standpoint because the drugs are able to interact directly with the right parts on the outside of the nasospheroids, rather than having to enter the spheroids as required with the rectal biopsy method.

"It has many advantages, not only because patients should be able to get results really quickly, but also because our model is much more accessible to drugs for testing than the other existing models," said Gentzsch.

The results represent a proof of concept, and the researchers noted there is still much more work to do to validate the approach for clinical application.

"We have to establish how well this model can discriminate between small changes, and then do studies to see if it will predict for individual patients what their actual clinical outcomes would be," said Guimbellot.

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