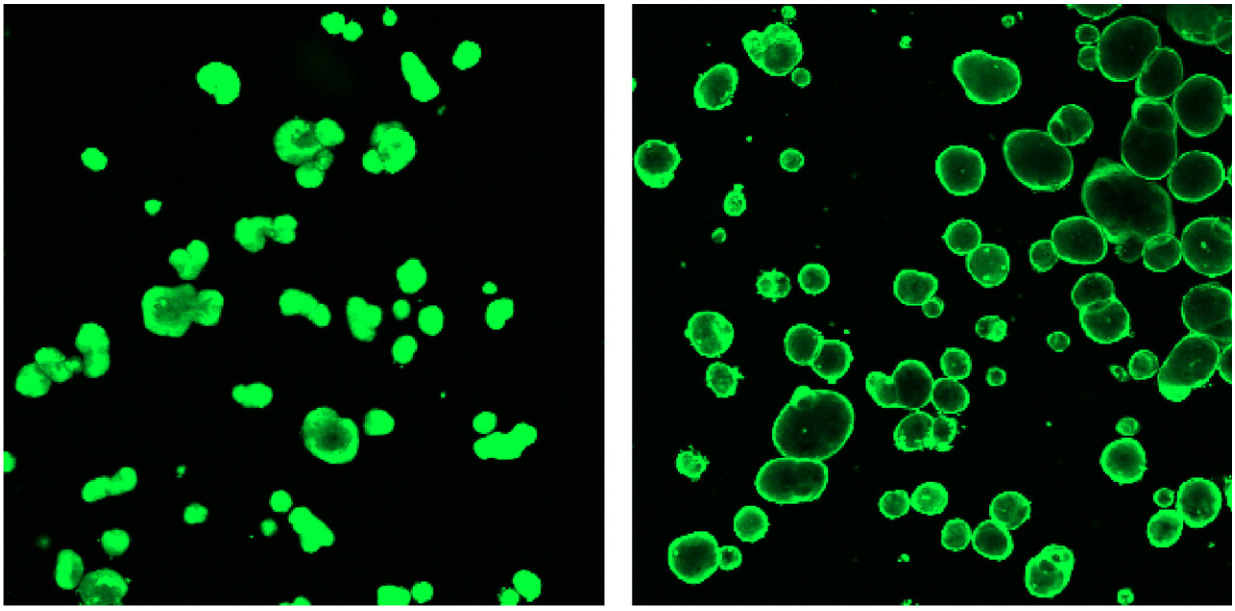
Curing genetic disease in human cells

February 20 2020



Organoids with cystic fibrosis (left) that do not swell due to a mutation in the CFTR-gene and organoids in which this mutation is repaired (right) that do swell because the CFTR-gene is functional again. Credit: Eyleen de Poel en Maarten Geurts, copyright UMC Utrecht and Hubrecht Institute

While the genome editing tool CRISPR/Cas9, developed in 2012, cuts a mutation out of a gene and replaces it with a gene-piece, a newer type of CRISPR, called base-editing, can repair a mutation without cutting the DNA. Therefore, genome editing using base-editor is considered safer. Scientists from the research groups of Hans Clevers (Hubrecht Institute) and Jeffrey Beekman (UMC Utrecht) show for the first time that this

base-editing can safely cure cystic fibrosis in stem cells derived from patients. The results of this study were published in *Cell Stem Cell* on the 20th of February.

In 2018, a new CRISPR enzyme was developed that makes the CRISPR technique more precise and less error-prone, according to biologists Maarten Geurts (Hubrecht Institute) and Eyleen de Poel (UMC Utrecht).

Maarten says, "In traditional CRISPR/Cas9 genome editing a specific piece of the DNA is cut out resulting in DNA damage. This is done with the aim that the cell repairs this cut using a lab-made piece of 'healthy' DNA. However, in the new CRISPR-technique, called base editing, the Cas-part is altered in such a way that it no longer creates a cut, but still detects the mutation. So, instead of creating a cut and replacing the faulty DNA, the mutation is directly repaired on site, making this a more effective genome editing tool."

The current research shows that this new version of CRISPR/Cas9 can be safely and effectively applied in human stem cells.

Miniguts

The Hubrecht Organoid Technology foundation and the UMC Utrecht have generated a biobank consisting of intestinal organoids. These are tiny versions of the gut, that are established in the lab using the stem cells of cystic fibrosis (CF) patients. The miniguts are used for disease modeling and the development of new therapies. The biobank was set up together with many CF centers across Europe and the Dutch CF Foundation (NCFS). In this study, the miniguts were used to test whether the new base-editing technique can be applied in human stem cells. Maarten explains how this exactly works: "CF is caused by a mistake, a mutation, in the CFTR-gene leading to malfunctioning of the gene. As a consequence, the mucus in many organs, including the lungs, is less

hydrated, resulting in mucus build-up and organ failure. With the new base-editing technique the mutation in the CFTR-gene can be detected and repaired without creating further damage in the genome."

Even though this research shows that this novel CRISPR tool is effective in the lab, this does not mean that patients can already benefit from it. Eyleen: "This research represents a big step towards genetic repair of diseases in patients. However, a big question that remains is how to deliver the CRISPR-enzyme to the appropriate organs in the patient. Cystic fibrosis might also not be the most suitable disease to treat with CRISPR, as many organs are affected by the disease. Currently, the first medical applications with CRISPR gene editing are showing impressive clinical effects in diseases that affect a single organ or tissue such as sickle cell anemia. Further research is needed before the base-editor can be used for clinical application. However, in part due to this study, the first clinical applications may already happen in the coming five years.

More information: CRISPR-based adenine editors correct nonsense mutations in a cystic fibrosis organoid biobank. *Cell Stem Cell* 2020. DOI: 10.1016/j.stem.2020.01.019

Provided by Hubrecht Institute