

Improving Gene Editing in the Liver

Technique shows promise for treating genetic diseases that require correction or replacement of defective genes in the liver.

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Advances in genome editing have raised hopes for curing a wide range of disorders caused by single genetic mutations. Hundreds of such conditions could potentially be treated by correcting disease-causing genes in the liver alone.

Cells in the liver can be easily reached by gene editing tools. Early studies that used gene editing to shut down the activity of genes in the liver have shown promise. But many more disorders are caused by defective genes that need to be repaired to restore normal function. A gene editing approach called homology-directed repair can potentially replace parts or all of a defective gene. But this technique requires actively dividing cells to work.

A research team led by Drs. William Lagor from Baylor College of Medicine and Gang Bao from Rice University have been developing a homology-directed repair system called Repair Drive to give genetically edited cells a jumpstart using the liver's natural growth processes. The system uses small interfering RNA (siRNA) to temporarily shut down an essential gene called Fah in liver cells. This knock-down process can be tailored to last for specific periods of time.

To deliver a healthy version of the gene that needs repair or replacement, the team attaches it to a version of Fah that is resistant to the siRNA inhibition. This repair package is then delivered to liver cells using a modified version of a virus. In theory, this combination would let populations of gene-edited cells grow while removing unedited cells.

In a set of new studies, funded in part by NIH, the researchers tested Repair Drive in several mouse models. Their results were published on February 12, 2025, in [Science Translational Medicine](#).

The researchers observed rapid growth of cells edited with Repair Drive after siRNA administration. The mice showed signs of mild liver damage, as expected. But this damage resolved by 12 weeks after treatment.

To look at long-term safety, the team used Repair Drive to deliver a gene called FIX to adult mice. Defects in FIX cause a type of hemophilia, a bleeding disorder, in people. The team used siRNA to suppress normal Fah for 3 months, then examined the mouse livers after a year.

They found that Repair Drive mice secreted about five times more FIX after a year than they did before gene repair. The amount of FIX produced by the repaired liver cells would be enough to prevent dangerous bleeding events in people with FIX defects. By a year after treatment, the mice had normal-appearing livers and normal Fah activity, or expression.

Notably, Repair Drive did not raise liver cancer rates in the mice. Two mice in each group had small areas of abnormal growth in their livers, which are common for mice of this age, but these did not show cancerous changes.

“Think of a yard full of weeds—that is like a diseased liver. The weeds are cells that don’t express the gene that they should be expressing,” Lagor explains. “Using Repair Drive, we come in and kill off the weeds, or the unhealthy cells. In doing so, we basically create space for fresh new grass plugs (i.e. corrected cells) to grow and make a new lawn. We also spent a lot of effort making sure that the weed killing only happens for a brief period of time, and that the lawn is healthy in the long run.”

More work is needed to test the Repair Drive system in models that have other common liver diseases, such as viral infections or fatty liver disease. The technique also needs to be tested for safety in larger animal models.

This [research summary](#) was published by the National Institutes of Health on March 11, 2025.