

## Gene therapy reverses type 1 diabetes in mice

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An experimental cure for Type 1 diabetes has a nearly 80 percent success rate in curing diabetic mice. The results, to be presented Saturday at The Endocrine Society's 93rd Annual Meeting in Boston, offer possible hope of curing a disease that affects 3 million Americans.

"With just one injection of this <u>gene therapy</u>, the mice remain diabetesfree long term and have a return of normal <u>insulin levels</u> in the body," said Vijay Yechoor, MD, the principal investigator and an assistant professor at Baylor College of Medicine in Houston.

Yechoor and his co-workers used their new gene therapy in a nonobese <u>mouse model</u> of <u>Type 1 diabetes</u>. The therapy attempts to counter the two defects that cause this autoimmune form of diabetes: autoimmune attack and destruction of the insulin-producing <u>beta cells</u> by <u>T cells</u>. First, the researchers genetically engineer the formation of new beta cells in the liver using neurogenin3. This gene defines the development of pancreatic islets, which are clusters of beta cells and other cells. Along with neurogenin3, they give an islet growth factor gene called betacellulin to stimulate growth of these new islets.

The second part of the therapy aims to prevent the mouse's immune system from killing the newly formed islets and beta cells. Previously the research team combined neurogenin3 with the gene for interleukin-10, which regulates the immune system. However, with that gene, they achieved only a 50 percent cure rate in <u>diabetic mice</u>, Yechoor said.

In the new study, the investigators added a gene called CD274 or PD-L1



(programmed cell death 1 ligand-1). It inhibits activity of the T cells only around the new islets in the liver and not in the rest of the body, he explained.

"We want the gene to inactivate T cells only when they come to the new <u>islet cells</u>. Otherwise, the whole body would become immunocompromised," Yechoor said.

This treatment reversed diabetes in 17 of 22 mice, or 78 percent. Diabetic mice that otherwise live only six to eight weeks were growing normally and were free of diabetes as long as 18 weeks after injection of the gene therapy, Yechoor said.

This treatment approach, he said, "has the potential to be a curative therapy for Type 1 diabetes."

The other mice reportedly responded to the gene therapy initially but then became diabetic again. There are two possibilities, according to Yechoor, why the therapy did not achieve a 100 percent cure rate.

"T cells are the predominant part of islet destruction, but other pathways, including beta cells could also contribute, meaning we would need to target those pathways as well," Yechoor said. "Or maybe the efficiency of this new protective gene is not sufficient, and we need to give a larger dose."

Provided by The Endocrine Society

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