Cross-species transplant in rhesus macaques is step toward diabetes cure for humans

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With an eye on curing diabetes, scientists at Washington University School of Medicine in St. Louis have successfully transplanted embryonic pig pancreatic cells destined to produce insulin into diabetic macaque monkeys – all without the need for risky immune suppression drugs that prevent rejection.

The transplanted cells, known as primordia, are in the earliest stages of developing into pancreatic tissues. Within several weeks of the transplants, the cells became engrafted, or established, within the three rhesus macaque monkeys that received them. The cells also released pig insulin in response to rising blood glucose levels, as would be expected in healthy animals and humans.

"The approach reduced the animals' need for insulin injections and has promise for curing diabetes in humans," says senior investigator Marc Hammerman, M.D., the Chromalloy Professor of Renal Diseases in Medicine. "The transplants worked without a need for immune suppression and that is a major obstacle we have overcome."

The researchers' results appear online and will be published in the journal *Xenotransplantation* in November.

Although the transplants fell short of producing sufficient insulin to cure the macaques' diabetes, Hammerman predicts that with additional research, including the transplantation of additional embryonic pig cells into the animals, he will be able to reduce their need for insulin

injections entirely.

The new research follows on the heels of reports by Hammerman and his colleagues demonstrating that transplanted pig pancreatic primordia can cure both type 1 and type 2 diabetes in rats, without using immune suppression drugs. Other scientists have tried different types of pancreatic cell transplants – in animals and humans – as a stepping stone to curing diabetes, but they all require anti-rejection drugs. These drugs must be taken daily to stave off rejection and have adverse effects of their own that limit the success of the transplants.

As a treatment for diabetes in people, pig insulin typically works as well as the human form. Before recombinant DNA technology enabled pharmaceutical companies to manufacture human insulin in the 1980s, pig and cow insulin were routinely given to diabetic patients.

The primates in the current study had type 1 diabetes, the form that occurs when islet cells in the pancreas stop producing insulin all together. The Washington University researchers transplanted 19 embryonic pig pancreatic primordia into each diabetic monkey. Each primordium is smaller than the diameter of a period that ends a sentence and is transplanted into a membrane that envelops the intestines and other digestive organs.

The transplanted cells were retrieved from the pig embryos early in their development, which is believed to render them "invisible" to the primates' immune system or induce a state of tolerance, either of which eliminates the need for immune suppression.

The researchers determined by multiple methods that the transplanted cells became established within the primates. And as the cells matured, they began to release pig insulin. "We found using every method that the cells engraft long-term and, thus, are not rejected by the animals'

immune systems," Hammerman says. "It's been more than two years since our first transplant was carried out. That particular primate doesn't produce any primate insulin, but has pig insulin circulating in its bloodstream that has reduced by more than 50 percent the amount of injected insulin the animal needs, compared to levels before the transplant. The animals have never received immune suppression drugs."

Two of the macaques remain healthy. One, however, became anemic about six weeks post-transplant and was euthanized a month later after developing acute respiratory distress. The researchers could not find a link between this animal's illness and the pancreatic cell transplants.

The two remaining macaques have each received two transplants of embryonic pancreatic cells. One of the animals has been followed for 23 months after his first transplant, and the amount of insulin he needs to have injected has declined by some 55 percent over baseline levels. The other macaque has been followed for 10 months after his initial transplant, and his need for injected insulin continues to decline over time.

Hammerman and his colleague Sharon Rogers, research instructor in medicine, are leaders in the emerging field of organogenesis, which focuses on growing organs from transplanted embryonic organ precursors known as primordia. Unlike embryonic stem cells, which can become virtually any cell type, primordia are locked into becoming cells of a particular organ.

"We are encouraged by these results," Rogers says. "The absence of a need for immune suppression in diabetic rats gave us hope that we were on the right track. But many findings in rats do not hold true for species that are more closely related to humans, such as non-human primates. This one did."

The team will now determine how best to eliminate the need for injected insulin in the diabetic macaques that receive transplants, thus demonstrating long-term effectiveness of the technique, and establish the absolute safety of pancreatic primordia transplants. If these experiments succeed, the researchers plan to conduct clinical trials in humans with diabetes.

"We hope to find out how to apply our findings to human type 1 and type 2 diabetics because the embryonic pig primordia would represent an unlimited source of tissue for transplantation," Hammerman says.

Source: Washington University in St. Louis