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****UT Southwestern diabetes researchers produce glucose-responsive artificial beta cells

DALLAS -- Diabetes researchers at The University of Texas Southwestern Medical Center at Dallas have taken the first step toward creation of a genetically engineered "artificial beta cell," according to the Jan. 15 issue of The Proceedings of the National Academy of Sciences, U.S.A.

The UT Southwestern researchers say that future development of this artificial beta cell could offer a potential alternative to human islet-cell transplantation, currently being tested for people with diabetes. The engineered cells were created by adding a piece of DNA to cells derived from the pituitary gland, conferring the function of insulin release in response to changes in the external concentration of glucose (blood sugar).

Insulin-dependent diabetes mellitus (IDDM)--a disease expected to affect more than 1 million Americans by the year 2,000--is caused by the body's own immune system's attacking the beta cells, which control insulin production. Lack of insulin leads to serious disability and, ultimately, death. Treatment of the disease requires replacement of the insulin by injection, by automatic insulin-infusion pump or by

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transplantation of insulin-secreting tissue (i.e., the islets of Langerhans, which are clusters of beta cells found in the pancreas).

Principal author of the Proceedings report is Dr. Christopher Newgard, assistant professor of biochemistry and researcher in the Gifford Laboratories for Diabetes Research at UT Southwestern. Other members of the team are Steven Hughes and Christian Quaade, graduate students in the Newgard laboratory, and Dr. John H. Johnson, associate professor of internal medicine and researcher at the Dallas Department of Veterans Affairs Medical Center, a UT Southwestern teaching hospital. Director of the Gifford Laboratories is Dr. Roger Unger, holder of the Touchstone/West Distinguished Chair in Diabetes Research. Among other research advances, Unger is internationally recognized for describing the role of glucagon in diabetes.

The engineered cells have not yet been tested in animals or humans with diabetes. To do so will require protection of the artificial cells from attack by the body's immune system. Recent reports have indicated that islet cells can be encapsulated in a semi-permeable "jacket" that allows entry of glucose and exit of insulin, but prevents attack by the immune system. Such protected islets have been shown to be capable of curing diabetes for periods of several months in experimental animals. The hope is that the new engineered cells will serve in a similar capacity.

While much progress has been made in the transplantation of islet cells, Unger said that there would never be enough human beta cells available to help the thousands of diabetics needing treatment. In addition, whether the transplanted islet cells are human or from another source, the process of obtaining them is expensive. "On the other hand, there could be an endless supply of the biologically

engineered non-islet cells capable of glucose-stimulated insulin secretion," said Unger.

Researchers explained that potential uses for the artificial beta cells include not only treating diabetes but also developing a diagnostic test for persons at risk for Type I (IDDM) diabetes.

Newgard explained that UT researchers are using an insulin-secreting clonal cell line (AtT-20ins) originally developed by Dr. Regis Kelly and coworkers at the University of California, San Francisco. Kelly inserted the human insulin gene into AtT-20ins cells and found that cells manipulated in this way were capable of secreting normal human insulin. Newgard and his team received those cells from Kelly and demonstrated that they did not respond to changes in extracellular glucose as normal islets must.

The reason for the lack of response became apparent when the Dallas workers discovered that AtT-20ins cells lack the expression of a glucose transporter protein, known as GLUT-2, which allows glucose to enter the cell and is thought to be of central importance in the control of glucose-stimulated insulin release in islets. When the Dallas workers introduced the gene for GLUT-2 into AtT-20ins cells, the cells gained the capacity to respond to changes in external glucose.

"Although insulin expression previously has been achieved in a wide variety of clonal cell lines, this is the first demonstration that genetic engineering can be used to produce a cell line that releases insulin in response to changes in glucose concentration," said Newgard. "This type of control is essential if clonal cells are to be considered as an alternative therapeutic strategy for patients with insulin-dependent diabetes."

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Newgard also pointed out that one of the remaining problems to be solved involves the relatively low levels of glucose needed to stimulate insulin production in the bioengineered cell line. "Recent work on the engineered cells tells us that insulin is released very rapidly and with a pattern that is quite similar to that of normal islets in response to glucose," said Newgard. "This insulin release occurs, however, at glucose concentrations that are less than concentrations normally seen in human blood." The Dallas team believes that this overzealous response to low glucose concentrations can be corrected by further molecular manipulations, involving genes thought to play a role in glucose metabolism in the cells under study.

Unger said he is very excited about the work. "Engineering an artificial beta cell that can replicate very rapidly is a dream for bioengineers," he commented.

The study on the artificial beta cells was supported by a grant from the National Institutes of Health and a Research and Development Award from the American Diabetes Association.

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NOTE: The University of Texas Southwestern Medical Center at Dallas comprises Southwestern Medical School, Southwestern Graduate School of Biomedical Sciences, Southwestern Allied Health Sciences School, affiliated teaching hospitals and outpatient clinics.