Novel Vector Reversed Type 1 in Early Studies

Pancreatic islet cell transplantation can result in euglycemia, but there are significant obstacles.

BY RICHARD HYER

CHICAGO — A modified gold nanoparticle vector has been used successfully to transfect pancreatic islets in a murine model, reversing type 1 diabetes in vivo, according to research conducted at the University of Illinois at Chicago.

The vector also reversed type 1 diabetes in vitro in human and mouse islet cells.

"This work shows for the first time efficient and nontoxic transfection of islets at a very high rate of over 98%, and with good homogeneous intracellular distribution," Rafael A. Vega, Ph.D., said at the annual meeting of the Central Surgical Association.

The distribution of the nanoparticle vector was nearly identical in rodent and human islet cores. "Characterization of the islet function demonstrated biocompatibility, and no functional compromise was observed with untransfected or transfected islets," said Dr. Vega, lead investigator of the study.

He and his colleagues isolated mouse

pancreatic islet cells and human islet cells, transfected them with the vector, and transplanted them into a murine model (four mice). An oligonucleotide-modified gold nanoparticle (AuNP) was used as the vector, and was chemically conjugated with a marker to quantify distribution.

Flow cytometry demonstrated 98% transfection. The vector was not found to be toxic, and no functional compromise was observed for three key parameters: mitochondrial membrane potential, glucose and KCl-stimulated Ca²⁺ influx, and glucose-stimulated insulin secretion.

Normal function was preserved in the AuNP-transfected islets. The mice maintained steady body weight as efficiently as the untransfected control mice, and all mice returned to euglycemic status, demonstrating that reversal of diabetes can be preserved even with transfected gold nanoparticles. No toxicity was observed post transplantation. AuNP-transfected human islets were found to have graft function similar to that of untransfected control

islets, as confirmed by intraperitoneal glucose tolerance testing.

"Essentially, we were able to demonstrate that in vivo functions remain intact," said Dr. Vega. He expressed interest in related uses of the nanoparticle vector, such as for direct manipulation of post-transplant factors including inflammation, apoptosis, amyloid formation, oxidative stress, and immunologic response.

'This work shows for the first time efficient and nontoxic transfection of islets at a very high rate of over 98%, and with good homogeneous intracellular distribution.'

Dr. Vega said that pancreatic islet cell transplantation is an attractive therapy for type 1 diabetes, because recipients may achieve euglycemia. There are significant obstacles, however, including the availability of donor cells and the potential for rejection post transplant.

"One of the problems of pancreatic islet cell transplantation is the effective delivery of molecular therapeutic cargos into islets," said Dr. Vega. "It is actually

difficult to achieve intracellular penetration when using a vector," at least in part because of the islet's complex multicellular architecture. The AuNP vector shows some promise for solving this problem.

The vector was found to reduce enzymatic degradation of the nucleic acid cargo and to have a strong binding affinity with complementary targets, with little or no observed toxicity, said Dr. Vega.

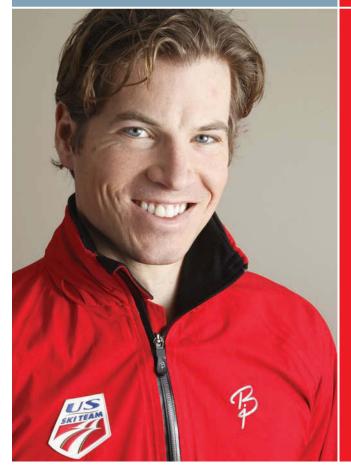
Dr. Dixon Kaufman, a professor of surgery at Northwestern University, Chicago, who attended the presentation, said, "You're onto something that's efficient and safe, and looks extremely promising."

Dr. Kaufman asked about the fate of the nanoparticles over time. "If it diffuses very efficiently, how long is it retained? Does it diffuse out of the islets as well?"

"As far as where in the cells they go, it's in the cytoplasm," said Dr. Vega. The gold nanoparticles stay in the cell, he said. "The data that we're looking at shows no functional compromise or toxicity with them in there."

The study was funded by the Chicago Diabetes Project and the University of Illinois at Chicago. Dr. Vega reported no relevant financial interests.

Lilly Diabetes



HI62552 0110 PRINTED IN USA ©2010, LILLY USA, LLC. ALL RIGHTS RESERVED.

Congratulations Kris Freeman

Lilly Diabetes congratulates United States Olympian Kris Freeman on his third Winter Olympic Games. Lilly is proud to sponsor this inspiring athlete and role model – the first ever endurance athlete with type 1 diabetes to compete for an Olympic medal. Kris is a shining example of living and achieving despite having a serious and challenging disease like diabetes. We salute him, his family, doctors and coaches on this remarkable achievement.

For more, visit www.lillydiabetes.com

