THE HARTWELL FOUNDATION

2007 Individual Biomedical Research Award

M. Michael Wolfe, MD

Professor
Department of Medicine

Boston University

Peptide Replacement Therapy Using Transgenic Stem Cells Delivered to the Small Intestinal Mucosa

Dr. Wolfe proposes to develop a remarkably innovative therapy for type-1 diabetes that will obviate the need for insulin injections. His plan is to program transgenic stem cells derived from skin fibroblasts to express insulin after their placement in the small intestine. His novel approach combines cutting-edge stem cell technology, gene transgenics, and contemporary clinical endoscopy as the means of gene delivery. Once transformed, the stem cells will act like pancreatic β-cells, which produce and regulate insulin secretion in response to ingestion of carbohydrates. Using endoscopy, he will inject the transformed cells into the gastrointestinal cells of the upper small intestine, which overcomes two major shortcomings of current technology: the need to inject live viruses and the permanent nature of gene delivery, which does not provide the means for termination if deemed potentially harmful. The relocation of insulin production to the intestine will "hide" the insulin-producing cells from the autoimmune response that ordinarily destroys pancreatic β-cells. A feasible 3-step plan will be used to demonstrate the effectiveness of meeting the goal of peptide replacement therapy for diabetes: 1) successful expression of a protein that requires transfection, but no post-translation processing or regulation (i.e., interferon alpha for treating viral hepatitis, including hepatitis B and C); 2) successful expression of a protein that requires transfection and translation, but no regulation (i.e., human growth hormone for treating clinical deficiency states); and finally, 3) successful expression of insulin, which requires transfection, translation and regulation. A critical aspect of this plan also includes is a demonstration of the safety of the technology, with intent to engineer the stem cells so that they can "on-demand" be specifically eliminated if it should become desirable. If Wolfe is successful in implementation, the bonus in his research plan will be replacement therapy for three different disease states by virtue of generating three different biomolecules along the way to developing insulin replacement therapy. Ultimately, numerous deficiency states may eventually be addressed using a similar approach, including Gaucher's Disease, Hurler Syndrome, Sly Disease, anemia, hemophilia, short bowel syndrome, osteoporosis, obesity, and secretory diarrhea syndromes.