

Tolerance induction and reversal of diabetes in mice transplanted with human embryonic stem cell-derived pancreatic endoderm.

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Public Summary:

The CIRM Diabetes Disease Team is developing a replacement pancreatic cell therapy for type 1 diabetes that is manufactured from a single human embryonic stem cell line. As such, this cell therapy represents an allogeneic implant in recipients with diabetes, which if left unprotected would be rejected by the recipient's immune system. The Team is developing a macroencapsulation approach to protect the implanted cells from the recipient's immune system, but other approaches may be valuable to pursue as well. In this report, the Team demonstrates in animal models that the replacement pancreatic cells can be protected from the immune system by treating the recipient's immune system with specifically targeted molecules, known as co-stimulatory blockade. Because this approach has the precision to make the recipient immune system specifically tolerant to the implanted cells, and not generally immunosuppressed as commonly used pharmacological approaches do, it holds the promise of allowing for cellular replacement and transplant technologies without the well known undesirable side effects of immunosuppression.

Scientific Abstract:

Type 1 diabetes (T1D) is an autoimmune disease caused by T cell-mediated destruction of insulin-producing beta cells in the islets of Langerhans. In most cases, reversal of disease would require strategies combining islet cell replacement with immunotherapy that are currently available only for the most severely affected patients. Here, we demonstrate that immunotherapies that target T cell costimulatory pathways block the rejection of xenogeneic human embryonic-stem-cell-derived pancreatic endoderm (hESC-PE) in mice. The therapy allowed for long-term development of hESC-PE into islet-like structures capable of producing human insulin and maintaining normoglycemia. Moreover, short-term costimulation blockade led to robust immune tolerance that could be transferred independently of regulatory T cells. Importantly, costimulation blockade prevented the rejection of allogeneic hESC-PE by human PBMCs in a humanized model in vivo. These results support the clinical development of hESC-derived therapy, combined with tolerogenic treatments, as a sustainable alternative strategy for patients with T1D.

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