Capturing Islet Stem Cells for a Bio-Artificial Pancreas

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Introduction

Encapsulation cell therapy, allows for embryonic pancreatic islet cells to differentiate into functional alpha, beta, and delta cells, mimicking the normal composition of the islets (“bio-artificial endocrine pancreas”) would be ideal for the treatment of diabetes. The use of immunosuppressive medications in allo-islet or pancreatic transplant has been associated with increased infections and malignancy. The goal of encapsulation technology is to safely protect the transplanted islets from both allo-rejection and autoimmunity without immunosuppression. The device prevents rejection by encapsulating the progenitor cells in a semi-permeable membrane that allows smaller molecules, such as oxygen, insulin, glucose and albumin to freely pass through the membrane. At the same time, the membrane prevents larger molecules, such as immune cells and antibodies, from entering the capsule, thereby preventing rejection of the differentiating and developing islet cells.

The advent of encapsulation products that could cure Type 1 diabetes raises many questions. A few of those questions on the encapsulation cell therapy are reviewed in this article.

How Does the Islet Cell Encapsulation Function?

Currently there are several models of islet encapsulation therapy under investigation. The capsule functions as a medical drug delivery system that consists of a selectively porous cell membrane that encapsulates pancreatic islet stem cells or mature islet cells that are collected from human embryonic stem cells.1 The device is designed to protect the implanted cells from immune rejection, provide a platform for vascularization, and prevent the islet cells from leaving the implantation site. It also allows for nutrients, oxygen, and insulin to freely diffuse through the membrane. The semi-permeable membrane does not allow immune cells or infectious agents to penetrate it. Furthermore, since the pancreatic progenitor cells represent a cell type present in developing embryos, they have capacity to regenerate, differentiate, and evolve to function in a hypoxic environment, thereby promoting survival until vascularization has completed.

The devices can be implanted as a thin membranous pouch of islet stem cells under the skin or infused as tiny pellets into peritoneal cavity.1,2 Assuming the stem cells survive the implant, it takes 2–3 months for the progenitor cells to vascularize and mature into insulin-producing beta cells, based on data from the mouse models. Insulin is released from the capsule in a glucose-responsive manner. In addition to insulin-producing beta cells, the capsule is infused with mixed islet cell populations, including those that differentiate into glucagon-producing alpha cells and somatostatin-producing delta cells, all of which are critical in the fine regulation of blood glucose levels.

Current Clinical Trial Involving the Islet Encapsulation in Human

Currently there is a Phase I/II clinical trial in human subjects, started in September 2014 at the Sanford Stem Cell Clinical Center at the University of California, San Diego, California, USA (ClinicalTrials.gov (ID: NCT02239354): a safety, tolerability, and efficacy Study of VC-01 combination product in subjects with Type I diabetes mellitus). The initial phase of the study involves adults with Type 1 diabetes mainly for safety and efficacy of the islet encapsulation treatment. The second phase will consist of patients from 6 different centers in the United States and Canada. In addition to the primary outcome of a stimulated C-peptide measurement,
the study will track the patients’ exogenous insulin usage, glucose levels, hypoglycemia, safety, and tolerability. Preliminary data from the clinical trial is yet to be released.

What Are the Limitations of the Islet Encapsulation Therapy?

Beta cells require high oxygen levels to function properly and they receive the highest oxygen gradients within the pancreas. When taken out of the pancreas and transplanted to the liver as in auto-islet transplant, a drop in oxygen gradient can lead to early death of the beta islet cells. Similarly, since it can take up to 3 months for vascularization to occur within the membranous pouch, there is concern that the islet cells will not survive such a period of decreased oxygenation. The use of embryonic progenitor cells instead of differentiated beta islet cells shows significant advantage as the stem cells are able to develop in a low oxygen environment much better than the encapsulation devices that have used mature beta islet cells.3,4

The advance in biocompatible encapsulation drug delivery system provides hope for large-scale islet replacement therapy using encapsulated islets derived from embryonic pancreatic stem cells without immunosuppression. If the system performs well in the clinic as it has in pre-clinical studies, then it might be used as an alternative to insulin therapy or whole pancreas transplant in the future to manage, if not cure, Type 1 diabetes and insulin-requiring Type 2 diabetes mellitus.

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