Toward Clinical Application of the Bioartificial Pancreas

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B-cell replacement is currently the only therapy for type 1 diabetes able to restore euglycemia. It is performed in the clinical setting by transplanting the pancreas or isolated islets of Langerhans. Islet transplantation is slowly gaining standard-of-care status but has yet to demonstrate equivalent success rates as whole pancreas transplantation. Closed-loop mechanisms able to deliver insulin in real-time through a sensor-and-pump system, realizing a portable artificial pancreas, do not require immunosuppression, are showing improving results, but have not yet been able to achieve the same level of glycemic control as β-cell replacement. A bioartificial pancreas would offer the best of both worlds by combining a biological component—tissue able to deliver insulin in a regulated fashion—and an artificial container.

Efforts devoted to design and realize a bioartificial pancreas arise from the shortage of donor organs and the need for lifelong immunosuppression. The attributes of an ideal bioartificial pancreas should be biocompatibility, protection from inflammatory/immune cells and mediators, vascularity to supply oxygen and nutrients and allow insulin outflow, and ease of access for potential reloading. Most attempts at building a bioartificial pancreas have involved microencapsulation or macroencapsulation of islets of Langerhans. Overall, microencapsulation strategies have not been very successful at consistently reversing diabetes other than in rodent models. Conformal coating of islets is being explored as a way to circumvent the issues of capsule thickness and diffusion distances associated with traditional microencapsulation. More convincing results, however, have been achieved in large mammals with macroencapsulation, in the form of more or less sophisticated pouches, sheets, and devices.

The study published by Pepper et al in this issue of Transplantation provides insight into the early phases of implantation and function of islets transplanted to diabetic mice in the novel Sernova Cell Pouch, which is currently being tested in a first-in-man trial with a safety primary endpoint and an immunomodulatory properties, such as mesenchymal stem cells, Sertoli cells, regulatory T cells, or by devising localized immunosuppression release methods inside the pouch.

Additionally, macroencapsulation devices can be loaded with various kinds of unlimited sources of cells able to secrete insulin in a regulated fashion, such as xenogeneic islets or stem cell-derived tissue, potentially solving the organ shortage problem and offering a cure to all individuals diagnosed with type 1 diabetes. This approach has already reached the phase II clinical stage, with a trial from the ViaCyte company, in which a pancreatic endoderm cell product derived from human embryonic stem cells is loaded into an immune-protecting device (Encaptra) for subcutaneous implantation without immunosuppression (ClinicalTrials.gov identifier: NCT02239354).

At this point, we would like to emphasize the importance of the role played by the native pancreatic extracellular matrix (ECM) in the vitality and function of islets. This role goes far beyond mere structural properties and concerns gene expression, intracellular and intercellular signaling, differentiation, gene expression, hormone secretion, and cell survival. It is doubtful that such properties can be efficiently reproduced by biomaterial scaffolds mimicking ECM composition, and it is likely that using ECM scaffolds as a lining for the container component of a bioartificial pancreas would enhance engraftment, function, and survival of the insulin-producing cells or tissue seeded onto it. To that end, key molecular components of the ECM have been identified and can be combined to reproduce ECM composition, or, perhaps closer to physiology, ECM can be obtained from animal pancreases using decellularization technology.

Finally, for perfect biocompatibility, the containing component of a bioartificial pancreas could be made of biological tissue rather than macroencapsulating biomaterial. Such an approach was recently used by transplanting marginal quantities of allogeneic islets into isolated “venous sacs,” with excellent functional outcomes. Venous sacs are venous segments naturally vascularized by their vasa vasorum, tied at both ends and loaded with insulin-producing tissue. The above-listed strategies could be readily applied to venous sacs, in what would be a fully biocompatible bioartificial pancreas.

We are eagerly awaiting the results of the Sernova Cell Pouch clinical trial, which will be an important step in demonstrating the potential of macrodevices in the development of a clinically efficient bioartificial pancreas. In the meantime,
the present article will provide readers with an in-depth analysis of the reasons why this clinical trial has good chances to be successful.

REFERENCES