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Human Pancreatic Islet Production: From Research Protocols to Standardized Multicenter Manufacturing

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Transient function following human pancreatic islet allotransplantation in a subject with type 1 diabetes was first reported over 25 years ago (1). Since then, clinical outcomes have been progressively improving, and nowadays islet transplantation represents a largely applied procedure that in experienced centers has a success rate similar to that of whole-pancreas transplantation (2,3). It might appear of little interest to discuss again the technical aspects of human islet manufacturing and to ask, is it justified to spend much time and many resources to further improve these procedures?

The answer is yes, of course. Islet isolation and purification, that is islet manufacturing, are key elements in any islet transplant program. The ability to retrieve most of the islets from a human pancreas is the obvious prerequisite for the success of an islet transplant, as in vivo islet graft function significantly correlates with the number of transplanted islets (4). In addition, islet isolation procedures greatly affect islet quality in terms of viability, function, and proinflammatory conditions, all factors associated with in vivo islet graft function (5,6). The optimization of islet production will also lead to an improved cost efficacy of the overall islet transplant programs, which is now among the major limiting factors for the wider application of this procedure. A detailed protocol that could be used as a reference document for islet manufacturing could be of significant assistance to rationalize the work from the laboratory personnel involved in islet isolation, an activity that lasts usually 7–8 h, often during the night and weekends. Finally, the standardization of procedures is now absolutely required by the current regulations for cell production for human use with the aim of guaranteeing the quality of the cell and tissue products and hence the safety of the recipients. Despite these premises, a standardized method for islet manufacturing that could be used as a reference in the field was not yet available, resulting in significant heterogeneity in the clinical results among centers using different isolation methods and in a significant challenge in the comparison of data coming from different centers especially within multicenter trials.

Islet isolation procedures have been the subject of several landmark publications with very high impact factor, beginning with the original description of the automated method (7). This method was the first that appeared to be feasible and applicable for large-scale islet manufacturing, and it is still the most applied in most laboratories, even though several modifications and improvements have been introduced over the years. Over the years, the automation of islet purification (8), new enzymes for organ digestion, a new system for organ perfusion, improved islet viability assessment (9), and a quality assurance system for guaranteeing the quality and the safety of the procedures (10) have been progressively introduced. During the Edmonton multicenter trial (11), there was an attempt to define a common method for islet production but islet retrieval and islet transplantation outcome remained significantly different between the participating islet transplant centers.

The article by Ricordi et al. (12) in the current issue of *Diabetes* proposes a new standardized method for islet isolation and purification. This represents the culmination and coordination of multicenter efforts in North America and Europe for the past 8 years, and it is clearly a landmark and a new standard for future reference. The current procedures (Fig. 1) should be therefore considered the completion of a long journey, from the first pioneer activities (13) to the current sophisticated Good Manufacturing Practices and Good Tissue Practices, which allowed for successful completion of the first phase 3 trial in the U.S., opening the way to a Biologics License Application

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COMMENTARY

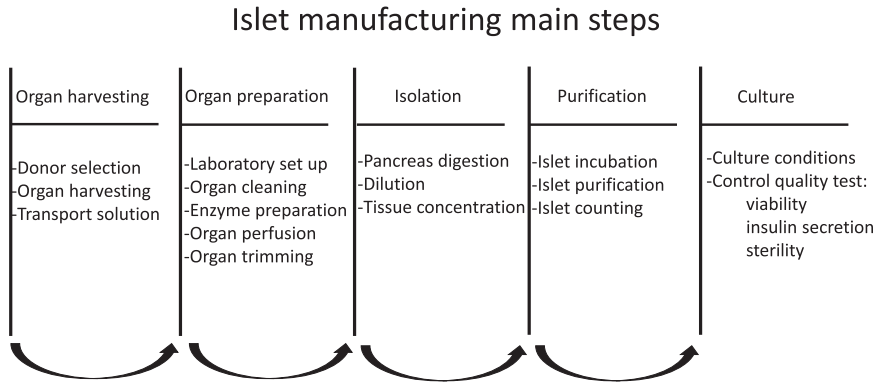

Figure 1—Flowchart of the different steps and relative main procedures of the human islet manufacturing.

and eventual approval by the U.S. Food and Drug Administration of islet transplantation in the U.S. These current Good Manufacturing Practices standardized procedures represent the basis for further improvement of the clinical success rate of islet transplantation for treatment of type 1 diabetes. The availability of standardized procedures will allow other islet centers to compare and hopefully to update their manufacturing protocols or, in the case of a new islet transplant program, to reduce the learning curve. Standardization will favor the activation of multicenter trials and will improve the collaboration activities and the share of research between different islet centers.

The authors recognized that there is still some work to be done and some aspects need to be further modified for the development of a fully standardized islet manufacturing process. The main factor still variable is the enzyme quality. The enzymes are the main determinant the outcome of pancreas digestion, and their activity is still variable and sometimes unpredictable (14). Therefore, the organ digestion sometimes fails, and the isolation does not yield sufficient numbers of high-quality islets that could meet the product release criteria for clinical use. Perhaps recombinant enzymes can be of assistance to resolve some of these challenges (15). Organ donor clinical conditions are variable, too: the procedures have to be often adapted to the different pancreas donor characteristics, but this is not easily realized (16). These aspects need to be further studied and additional solutions identified.

In conclusion, human pancreatic islet manufacturing does not represent a technical curiosity but is a key determinant for the success of islet transplantation and the advancement of this field. Thanks to the work done by the Clinical Islet Transplantation Consortium (12), the standardization of islet cell product manufacturing across multiple centers is now more efficient and could be of assistance representing the new reference standard. Islet production moves from an experimental activity to a standardized protocol that will be of assistance to move novel islet transplantation strategies from bench to bedside. Several challenges still need to be resolved to define the next quantum leap forward in clinical islet transplantation, such as improved engraftment and transplant site, the elimination of the need for continuous recipient immunosuppression, long-term exhaustion of the transplanted insulin-producing cells, and recurrence of autoimmunity or immune rejection of the transplanted islets. Nevertheless, it should be easier now to conduct proper clinical trials and work toward resolution of the remaining challenges in the field.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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