Requirements for Success in Clinical Islet Transplantation

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A few groups have endured the challenges of time, anecdotal success stories, logistic and funding impediments, to bring the field of clinical islet transplantation where it stands today. The recent improvement in clinical results has paralleled a renewed interest in islet transplantation and an increasing number of centers have entered the field. Selected institutions have now clearly demonstrated that insulin independence can be a reproducible and achievable goal. Other centers struggle with mixed results, while occasional early failures of islet transplants are still observed. This center effect underlines not just a learning curve, but also the complexity of the approach, which requires multidisciplinary expertise and attention to critical variables that need to be closely monitored to assure adequate clinical outcomes. The future success and large scale applicability of islet transplantation will rely on the synergistic research progress in critical areas that contribute to the sequential and integrated approach required for success in clinical islet transplantation.

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The field of clinical islet transplantation has slowly evolved during the past three decades, largely due to a progressive understanding of the challenges imposed by a cluster of sequential and related variables affecting islet isolation outcome, initial posttransplant islet engraftment and long-term survival in recipients with type 1 diabetes (1, 2). Sufficient numbers of islets can now be routinely obtained from good quality pancreata and diabetes can be generally reversed with islet preparations from one or two donors (3, 4, 5).

In the joint Miami-Houston (Baylor) trials (in Islet Alone and Islet after Kidney Protocols) using Edmonton-like immunosuppressive regimens (including daclizumab induction and sirolimus/tacrolimus maintenance), we have achieved insulin independence, long-term islet graft function, normalization of HbA1c levels and elimination of severe hypoglycemic episodes in 31 out of 31 patients who successfully completed the islet infusion protocol (1, 4, 6). Insulin independence in this combined series as analyzed by Kaplan-Meier (Fig. 1) was 90% at 1 year after transplantation and generally required two islet infusions. Six of the 31 recipients became insulin independent with islets from a single donor infusion, but unfortunately, success with single donors is still limited by the initial quality of donor pancreata, an issue which depends greatly on whether or not the best pancrea are allocated with similar priority to islets and whole organ sources of insulin producing tissue):

pancreas transplantation (i.e., through a local variance in organ allocation).

For most groups this privileged level of allocation is currently not an option. In addition, the current strict criteria for candidate selection in single-donor protocols currently limit their potential applicability to very few highly selected recipients with low insulin requirement and a high level of insulin sensitivity.

Even though reversal of diabetes from a single donor is currently of anecdotal value, it should remain a treatment objective, whenever access to the highest quality pancreata is granted.

Now that several centers have shown that success in islet transplantation can be a reproducible goal, the key question becomes what is needed to make this intervention strategy a reality for a larger number of patients with Type 1 diabetes and eventually for patients with insulin requiring diabetes, including Type 2.

We believe that critical requirements for large-scale success in clinical islet transplantation include careful consideration of all variables that affect outcome in a sequential, integrated approach. Progress is needed in critical areas of multidisciplinary research, where synergy will be key to success. Attention to all details is essential in a procedure that lasts days (from pancreas procurement to pretransplant in vitro culture) before the final product is infused into the recipient. Highly motivated and specialized multidisciplinary teams are also equally important not just for obtaining first quality islet cell products, but also for management of islet transplant recipients. In fact, failure to achieve appropriate therapeutic levels of immunosuppression has been suggested as a possible cause of early failure of islet transplants, even in recent years (7–9).

Figure 2 outlines some of these integrated areas of research which affect clinical islet isolation and transplantation outcome, as well as our ability to expand the indication of islet transplantation to the majority of patients with diabetes (e.g., tolerance, regeneration and expansion, as well as alternative sources of insulin producing tissue):
effect of any individual “improved” strategy on the overall sequential, integrated approach. Any small change in one area could result in the introduction of significant new variables downstream. For example, a novel method for pretransplant culture that could improve islet survival in culture by 20% could also increase initial antigenicity/immunogenicity of the final islet cell product, triggering a much stronger immune response, and leading to an initial loss posttransplant of 50% of the infused islets (1, 10, 11). Similarly, a new immunosuppressive agent that is very effective in blocking the expansion phase of the immune response (Fig. 3, phase #3 of the immune response) could prevent apoptotic mechanisms from occurring in phase #4, therefore preventing the possibility of inducing donor specific tolerance (2, 12). In this regard, it is also important to consider the sequential timing of progress in these selected research fields. In fact, parallel progress in different areas will be needed to capitalize on potential breakthroughs that emerge from any specific research. For example, a successful strategy for tolerance induction would be a key achievement; however, it would open an insurmountable challenge imposed by the sudden increase in the demand for insulin producing cells to be transplanted (among other transplant needs that would exponentially increase) in face of a very scarce supply that is limited by the number of organ donors.

It is therefore critical that at the time a quantum-leap in a single area is achieved, significant progress will also be obtained in areas whose potential for application will immediately be affected by such a step forward, including maximization of islet tissue from available donors, expansion of adult insulin producing cells, and identification of alternative sources of insulin producing tissue (e.g., stem cells and islets from animal sources) (1, 13).

We would predict that the current era of islet transplantation will sequentially evolve into three new eras, possibly within the next decade (Fig. 3). In the current era (Fig. 3, ERA I), we are facing significant challenges that collectively can contribute to a substantial loss in islet mass, both before and after transplantation, including donor factors, pancreas procurement and preservation (6, 14) before islet isolation (A), islet processing (B), pretransplant in vitro culture (1, 15) (C), early islet loss in the posttransplant period for non specific inflammatory events (1, 10, 15–18) (D) and/or long term, chronic decreases in islet mass that are related, for example, to the use of diabeticogenic and/or antiproliferative immunosuppressive agents that could be directly toxic to, or block the degenerative potential of beta cells, or to recurrence of autoimmunity/chronic rejection (E). In ERA I, we are also facing major challenges to control the different phases of the immune response to an islet graft, which could be affected by interventions at different levels, including the initial immunogenicity of the final islet preparation infused into the recipient (19) (Fig. 3; 1), that could differentially trigger the immune response at the time of islet infusion (the activation phase, 2); the expansion phase (3); the contraction and homeostatic control phase (4) and the memory response (5).

The second era (Fig. 3 ERA II) will see advancements in our capabilities to better preserve islet mass, viability and function during the pretransplant manipulations, as well as in the immediate posttransplant period, paralleled by the achievement of immune tolerance in the recipient (2).
allow the use of significantly reduced islet mass to successfully treat diabetes. This will enable the use of islets harvested from living-related donors and allow treatment of multiple recipients with islets from a single cadaveric donor. Additional sources of insulin-producing tissue will be identified.

The fourth era (Fig. 3 ERA IV) will see the twilight of islet transplantation, since restoration of tolerance to autoantigens will be induced in patients with type 1 diabetes, and regeneration of insulin-producing tissue will be obtained from the patient’s own precursor/stem cells. Islet transplant scientists will have accomplished their contributing role, having exploited the procedure to reach this ultimate step in the pathway of reparative medicine.

**REFERENCES**