Executive Summary of IPITA-TTS Opinion Leaders Report on the Future of β-Cell Replacement

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Summary: The International Pancreas and Islet Transplant Association (IPITA), in conjunction with the Transplantation Society (TTS), convened a workshop to consider the future of pancreas and islet transplantation in the context of potential competing technologies that are under development, including the artificial pancreas, transplantation tolerance, xenotransplantation, encapsulation, stem cell derived beta cells, beta cell proliferation, and endogenous regeneration. Separate workgroups for each topic and then the collective group reviewed the state of the art, hurdles to application, and proposed research agenda for each therapy that would allow widespread application. Herein we present the executive summary of this workshop that focuses on obstacles to application and the research agenda to overcome them; the full length article with detailed background for each topic is published as an online supplement to *Transplantation*.

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This is a critical point in time for the fields of pancreas and islet transplantation. Despite improving short- and long-term outcomes, the numbers of whole organ pancreas transplants performed each year has fallen dramatically over the last decade. Parallel improvements in islet transplant outcomes, along with the imminent release of results of the multicenter United States islet licensing trials, has the potential to establish islet transplantation as the gold standard for care of diabetic patients with severe hypoglycemic unawareness. Countering these positive developments is the limited grant funding available to gain further advances with islets and a variety of competing technologies, including novel biomechanical insulin delivery devices and alternative β-cell replacement strategies (xenogeneic islets, stem cell-derived β cells, and endogenous β-cell regeneration) that all pose threats to transplantation as a definitive therapy for type 1 diabetes.

Against this backdrop, the International Pancreas and Islet Transplant Association (IPITA), in collaboration with the Transplantation Society (TTS), held a scientific workshop in Oxford, England, 2014, to review the current status and needed research agenda of 8 current or nascent β-cell replacement therapies: whole organ pancreas transplantation, isolated islet transplantation, artificial pancreas (AP), immunological tolerance, xenotransplantation, encapsulation technologies, β-cell regeneration, and stem cell-derived β cells. Thirty-two scientists and clinicians representing 4 continents, 7 countries, and 29 institutions, with dedicated expertise in these areas were recruited to participate in 8 topical workgroups along with representatives of the National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Disease, National Institute of Allergy and Infectious Disease), Diabetes Research and Wellness Foundation, the Juvenile Diabetes Research Foundation (JDRF), and industry. In advance of the meeting, the workgroups prepared summaries of their respective topic highlighting the state of their field and the research agenda needed to move the therapy forward to optimal clinical application. Presentation and full group discussion at the meeting generated revised summaries in 8 sections that are presented in detail in *Transplantation*[1] with full background, discussion of the state of the field, obstacles to application, and the needed research agenda. Presented below is an executive summary of that full report with emphasis on current status, obstacles to application, and the needed research agenda.

ALLOGENEIC PANCREAS TRANSPLANTATION

Pancreas transplantation has been available as a cure for diabetes since its first application in 1966 and remains the gold standard. Because of the risks of the procedure and associated immunosuppression, it has been applied mostly in patients already obligated to immunosuppression, such as those receiving or who have received a renal transplant. For those type 1 diabetic patients for whom immunosuppression would otherwise not be needed, solitary pancreas transplants have been largely reserved for patients with brittle diabetes and hypoglycemic unawareness despite optimal medical therapy. Recent registry data indicate improving graft and patient survivals over the last decade, yet, unlike the growth in pancreas transplantation in some European countries, during the same period, the number of pancreas transplant cases in the United States has decreased by 35% since the year 2003. The reasons for the decline in the United States are incompletely understood, but reduced candidate listing and decreased utilization of donor organ pancreases are evident. Declining activity was temporally associated with data suggesting limited survival benefit[2] and better outcomes with islet transplantation.[3] Likely also contributing is an ever-expanding regulatory environment in the United States that penalizes center utilization of marginal organs. In contrast to the recent fall in whole organ pancreas activity in the United States, European countries and Australia have successfully expanded pancreas utilization by adoption of regional policies on pancreas/islet allocation, details of surgical procurement technique, and data-driven selection of preservation solution.

Summary of Research Priorities

(1) *Need for systematic, comprehensive documentation of pancreas transplant outcomes worldwide.* Rigorous study of pancreas transplant outcomes and novel interventions is impeded by lack of standardized outcome measures. A consistent definition of success is required; is it insulin independence, freedom from hypoglycemia with partial function, reduced secondary complications with partial function, improved A1c versus baseline, or merely detectable C-peptide? The answer is essential for progress in the field.

(2) *Develop carefully designed, well-controlled clinical trials that define the impact of pancreas transplantation on mortality and secondary complications, particularly renal function.* The field appeared to have been hurt by data questioning the survival benefit of pancreas after kidney and pancreas transplant alone (PTA). With improved results, better immunosuppression and monitoring, new carefully designed analyses to assess life-saving benefit, and impact on secondary complications might define recipient subjects in which a significant survival benefit is expected.

(3) *The greatest obstacle to growth of pancreas transplantation is low organ utilization rates.* Preservation strategies leading to improved early graft survival and function with greater utilization of poorer quality organs is needed. Fear

of graft failure from marginal organ use impairs organ utilization and limits the number of transplants performed. Exploration of new modalities to improve organ function pretransplant, perhaps through better preservation, oxygenation or oxygenated normothermic, or subnormothermic ex vivo perfusion are vital. Also essential is to promote a change in culture to one that does not penalize programs pushing the frontiers of marginal organ use and rather focuses on patient longevity and quality of life benefit.

(4) *Concern about new onset and recurrent renal dysfunction markedly limits growth of pancreas transplantation.* In the setting of PTA transplantation, a major impediment is risk of further compromising the renal function of a patient with longstanding diabetes. Clinical trials are desperately needed to define non-nephrotoxic immunosuppression regimens that will allow transplantation of brittle type 1 diabetics with a pancreas.

(5) *Detailed clinical studies verifying the risk of recurrent disease are needed to exclude other causes such as β-cell exhaustion and alloimmune injury.* Chronic pancreas graft failure often occurs without definitive pathologic diagnosis. Differentiating recurrent autoimmunity from alloimmunity and other causes of endocrine failure will require improved diagnostic approaches; novel immune and molecular monitoring, autoreactive cell assays, and proximal duodenal-enteric anastomosis to facilitate endoscopic biopsy of the graft duodenal mucosa are all of interest.

(6) *Two parallel randomized trials of whole organ pancreas versus isolated islet transplantation are recommended:* (a) simultaneous kidney pancreas versus simultaneous islet kidney, and (b) PTA and pancreas after kidney vs islet transplant alone and islet after kidney versus best medical therapy. At some point, the question of relative superiority of pancreas versus islet transplantation will be called because a struggle for the best organs is inevitable. In addition, a comparison of best medical therapy versus pancreas and islets will help convince diabetologists of the benefits of transplantation for patients with the most labile disease.

ISLET ALLOTRANSPLANTATION

Over the last 10 years, islet allotransplantation has evolved into an established treatment modality for subjects with type 1 diabetes complicated by hypoglycemia unawareness, and the procedure is currently reimbursed for this indication in several countries. At present, the primary goal of islet transplantation should be optimal glycemic control without severe hypoglycemia rather than insulin independence. This will achieve diabetes-risk reduction while minimizing the cost and procedural and immunological risk incurred with multiple islet infusions from different donors. As in pancreas transplantation, a standardized approach to evaluation of clinical outcomes will be essential for further developments in β-cell replacement. A recently completed multicenter United States prospective phase 3 study[4] demonstrated that: (1) islets can be manufactured reproducibly at multiple sites using a common manufacturing process; (2) independence from exogenous insulin can be achieved in about half of islet recipients at 1 year, with 1 or 2 islet infusions; (3) glycemic control is excellent even when insulin independence is not achieved; (4) hypoglycemia unawareness is treated effectively by islet transplantation, with associated freedom from severe hypoglycemic events. Islet allotransplantation is also an acceptable therapy for patients with end-stage renal failure and T1D, either simultaneous with or after kidney transplantation.[5]

Because of the overall limited availability of human organ donors, islet allotransplantation is unable to provide a cure for all those affected with type 1 diabetes and thus will likely remain indicated primarily for those already obligated to lifelong immunosuppression and those experiencing labile disease with life-threatening hypoglycemia.

Summary of Research Priorities

(1) *Optimization of pancreas procurement, pancreas transport, and development of targeted methods for islet isolation to improve functional islet yield to permit routine single-donor insulin independence.* Like pancreas transplantation, islet transplantation is limited by the availability of suitable organs. Changes in allocation to allow sharing of the best donors between islets and whole organ pancreas and isolation advances with recombinant enzymes should benefit yield and increase the likelihood of success using single donors.

(2) *Standardization of definition of released islet product to enable accurate comparisons between centers and enable accurate prediction of islet graft outcome. Interventions to improve engrafted islet mass are essential to the goal of gaining single donor success.* To assess these interventions, a standardization of the nature and quality of the transplanted product is needed.

(3) *Development of novel strategies for islet preconditioning to improve islet engraftment and islet graft longevity.* The pretransplant in vitro culture period is an opportunity for islet modification that has not yet been fully exploited. Strategies to reduce immunogenicity and protect islets from ischemia and immediate blood islet inflammatory response (IBMIR) injury are poised for translational assessment.

(4) *Definition of suitable alternative anatomical sites for islet implantation.* Embolization of islets into the liver via the portal system has been the only routinely successful transplant site to date but has a number of deficiencies including damage of islets by IBMIR, suboptimal site for biopsy, low pO_2, and risk of thrombosis. An ideal site should be accessible for safe biopsy and noninvasive imaging, manipulability to promote vascularization, and oxygenation.

(5) *Strategies to minimize or eliminate the need for immunosuppression, enabling the ultimate goal of islet allotransplantation to be reached, that is, islet transplantation in children.* The universal requirement for immunosuppression precludes application of islet transplantation to the average person with diabetes. Recent advances in solid organ transplantation have demonstrated the feasibility of tolerance. These protocols might be readily applied to people with diabetes undergoing simultaneous kidney-islet transplant and once success is proven in adults, application to pediatric patients should be considered.

ISLET XENOTRANSPLANTATION

Islet allotransplantation will never supply sufficient islets for the treatment of the many millions of patients with diabetes. However, the improving human islet allotransplant efficacy and safety outcomes have inspired investigators to seek more widely available cell-based diabetes therapies. Preclinical safety and efficacy data obtained in the last 10 years in the stringent pig-to-nonhuman primate islet transplant setting,[6-17] and preliminary safety data obtained in recent pilot clinical trials,[18] suggest that xenogeneic pig islets can possibly be developed into an islet β-cell replacement therapy with broad applicability.[6-11,14-17] Collectively, the recent results reveal the potential impact of genetic modification of the xenogeneic islet donor and offer promise that an unlimited source of transplantable β cells may be possible.

However, several hurdles remain to be overcome. (1) The IBMIR is more problematic in islet xenotransplantation,

(2) there is a need for a safe and effective antirejection strategy that achieves sustained graft survival, and 3) it will be necessary to demonstrate that porcine-derived islets can be produced in a cost-effective manner. However, the pace of progress is clearly accelerating in this area of study and should only be augmented by recent genome-editing approaches that enable multiple genetic modifications to be made to the pig that will reduce IBMIR and immunogenicity.

The transplantation of adult "naked" islets (ie, not encapsulated) has maintained normoglycemia in immunosuppressed diabetic monkeys for periods well in excess of 1 year,[8,14,15] suggesting that consistent success will soon be achieved, warranting clinical trials. There is evidence that when islets are isolated from genetically engineered pigs, immunosuppressive therapy can be reduced (Park C-G, Cooper DKC, unpublished data). Furthermore, neonatal pig islet transplants may have some advantages over islets from adult pigs, and their transplantation into diabetic monkeys has also been associated with encouraging results.[6,7,10-12]

An alternative approach is the encapsulation of islets in an attempt to protect them from the recipient immune response without the need for exogenous immunosuppressive therapy.[19] Macroencapsulation of adult porcine islets in alginate and their transplantation into abdominal subcutaneous tissue as an islet monolayer on an acellular collagen matrix in a macrodevice maintained fasting blood glucose levels less than 150 mg/dL for 20 to 28 weeks in 5 streptozotocin-induced diabetic, nonimmunosuppressed cynomolgus monkeys.[16] Coencapsulation of islets with mesenchymal stem cells slightly improved oxygenation and neoangiogenesis of subcutaneously placed implants and maintained fasting blood glucose levels in the near-normal range for up to 32 weeks, but did not substantially improve or prolong islet xenograft function.[17]

Summary of Research Priorities

(1) *Prevention of IBMIR*. This will require a multifaceted approach, including the transplantation of islets from pigs specifically genetically engineered to protect the islets from IBMIR, with additional therapy targeting coagulation, complement, inflammatory cytokines/chemokines and granulocytes-monocytes. The IBMIR is a major obstacle to engraftment of intraportal porcine islet xenografts in primates[20]; it is triggered by contact of isolated islets with blood and causes islet destruction by complement and coagulation activation products and other inflammatory mediators released by recruited neutrophils and monocytes.[21-24] Genetic engineering of donor pigs can mitigate IBMIR to intraportally transplanted pig islets.[11,25] The IBMIR was minimal, and intravascular clotting was not observed in baboons after transplantation of neonatal islet-like cell clusters from αGal-deficient porcine donors transgenic for the human complement regulators CD55 and CD59.
(2) *Development of effective and clinically acceptable antirejection regimens*. An important current focus is on targeting CD40-CD154 interactions with anti-CD40 monoclonal antibodies. Also of interest are encapsulation approaches to further blunt the indirect pathway cell-mediated response.

ISLET ENCAPSULATION—AN ONGOING DEVELOPMENT CHALLENGE

Over 40 years of islet encapsulation research has failed to provide an approved clinical product despite many encapsulation approaches and efforts, including several clinical trials. This IPITA effort is critical to focus on future research goals and objectives that have the promise to achieve a successful clinical encapsulated islet product in as short a time as possible. A major review of encapsulated islet studies has recently been published.[26,27] Two major problems have impeded success: loss of membrane exclusivity or permeability over time due to capsule breakdown or a fibrotic reaction to foreign capsule material or the foreign cells they house, respectively. The second obstacle is the indirect immune response in which shed graft antigens pass through the capsule and elicit an immune response in the host; this problem appears to be of much greater magnitude in the setting of xenotransplantation compared with allotransplantation. Another hurdle yet to be confronted is whether normal glycemic control can be achieved given the altered insulin and glucose kinetics imposed by the capsule barrier. Equally important is defining a safe and hospitable site with an adequate pO_2 to harbor a potentially large volume of capsules.

Despite numerous unsuccessful attempts of the past, enthusiasm for this line of investigation remains high and continues to be a focus of industry and foundation support. This fact is highlighted by a recent major initiative by the JDRF, in collaboration with the Helmsley Foundation, to develop a consortium to explore new encapsulation materials and novel device design in basic and translational studies.

Summary of Research Priorities

(1) *Conduct a preliminary trial of alginate encapsulated islet allotransplantation with a short course or low-dose immunosuppressive therapy*. Type 1 diabetics who have already received a renal transplant would be candidates since already obligated to chronic immunosuppressive therapy.
(2) *Development of improved biocompatible encapsulation materials and capsule designs*. Many factors may influence the host response to capsules, including contaminants found in alginates, as well as capsule size and design. Conversely, anti-inflammatory, pre-angiogenic or lymphorepulsive additions (such as CXCL12) may aid in eliminating the host response to the capsule.
(3) *Define new approaches to gain oxygen delivery to encapsulated islets to improve both early engraftment and long-term survival*. Accumulating evidence suggests that encapsulated islet hypoxemia may be a major deterrent to graft survival. Devices incorporating O_2 delivery to the graft have shown promising early results.
(4) *Define optimal transplant sites that have adequate capacity/surface area and that circumvent the difficulties of the intraportal and intraperitoneal sites*. Depending on capsule size and design, the number of islets required, and the number of islets per capsule, the volume of the graft may be quite large (up to a liter for 1 million islets in large capsules). Strategies that minimize graft volume may allow more options for acceptable sites.

AP AND INSULIN DELIVERY SYSTEMS

Current technology has shown that an AP is able improve average glycemic control and simultaneously reduce moderate hypoglycemia; thus it is likely but untested that an AP would be able to prevent severe hypoglycemia known to cause seizures or loss of consciousness. Ongoing AP trials aim to reduce mild hypoglycemia sufficiently to allow consistent restoration of hypoglycemia awareness with similar efficacy to the results of current studies of islet transplantation. There are still technological problems, such as accuracy of

the glucose sensor, network connectivity between the devices comprising the AP system, and reliability of the insulin pump. Most of these problems are currently being mitigated by algorithm development and technology improvements, such as the vast new processor power of mobile smartphone devices. These technological developments are likely to bring the AP to mainstream use in the not too distant future.[28-30]

Summary of Research Priorities

(1) *Assessment of state of the art AP technology with standardized measures of glycemic lability and hypoglycemic severity.* Rigorous assessment of the technology is required in long-term studies to determine the comparability of glycemic control to biologic β-cell replacement; outcome measures standardized for recent islet transplant trials are potentially applicable for this purpose.
(2) *Full incorporation of consumer electronics (smart phone technology) to allow remote monitoring/supervision, opportunity for frequent hardware and software updates and to negate the psychological stigma of in public pump use.* This feature is particularly valuable to the pediatric/adolescent population in which cell phone use is already commonplace and where the potential for social embarrassment is great.
(3) *Consider assessment of combined AP-islet transplant therapy to address the limited islet supply and need for multiple islet transplants and perhaps limit β-cell stress, thereby improving islet performance and longevity.* There is potential for natural synergy between AP and allogeneic islets where the islet mass from a single donor is often inadequate for a curative result. Combining AP and islets may allow the former to deliver a large fraction of needed insulin and the latter to provide exquisite fine tuning of glucose levels deliverable only by biologic means.

IMMUNE TOLERANCE FOR ISLET AUTOIMMUNITY AND ALLOIMMUNITY

There are no currently widely available, safe, and extensively validated approaches for establishing tolerance for islet transplantation in humans. Although a large number of approaches seem to be efficacious in rodent models, most have failed to translate into success in primate or porcine large animal models. Some success has been achieved in humans with renal transplant protocols that require low-risk donors and recipients, extensive immunosuppression, and components of hematopoietic chimerism. Moving forward, there are several principles to be taken into account. First, when assessing tolerance for islets and because of the unique characteristics of different immune responses (eg, memory, cross-reactivity, number of reactive clones, and cells), it is very important to separately measure and assess responses to autoantigens and to alloantigens. Depending on future development, responses to xenoantigens will also have to be separately addressed. Second, to prospectively monitor recipients, it is important to have measures not only of islet function and injury, but also measures of immune reactivity and immune regulation. Third, it is clear from murine studies that there are many components to immunity, and that tolerance is achieved only by targeting the distinct arms of the immune response. Broadly speaking, innate, and B-cell and T cell responses must be controlled to induce and maintain tolerance. It is also clear that tolerance is achieved not only by preventing these distinct responses but also by generating regulatory phenomena. Fourth, it is clear from murine studies that the most robust tolerance for both autoimmunity and alloimmunity is achieved in protocols that incorporate some form of hematopoietic stem cell chimerism along with immune regulation.[31,32] Chimerism successfully prevents the B-cell and T cell components of adaptive immunity while simultaneously generating a variety of suppressor and regulatory mechanisms (eg, anergy, deletion, suppressor cells).[33]

Summary of Research Priorities

(1) *The recent success of chimeric tolerance in renal transplantation potentially sets the stage for application to islets.* The use of protocols with high-level donor chimerism may simultaneously achieve allotolerance and rid the host of their native autoimmune-prone T cell repertoire. Currently, however, the conditioning regimens in these first-generation trials are too intensive and carry an unacceptable risk profile to justify application to nonuremic type 1 diabetics. An interesting first step would be trial of tolerance induction in combined kidney-islet transplants in uremic diabetics.
(2) *Costimulation blockade with simultaneous targeting of CD28-B7 and CD40-CD154 remains a scientifically attractive approach.* A less toxic nonablative approach would represent a major advance. New CD40 targeting agents in conjunction with the recently approved anti-B7 agent, belatacept, may permit such testing in the near future.
(3) *Trial of innovative regulatory cell-based approaches is also attractive in that it may be possible to interrupt in parallel autoimmunity and alloimmunity with precise antigen specificity.* Separate Treg trials are in progress in allotransplantation and in autoimmunity, including for type 1 diabetes. The results of these trials could set the stage for an islet trial in type 1 diabetes targeting both allo and autoimmunity.

STEM CELLS AS A SOURCE FOR β CELLS

To overcome the supply limitations of currently available therapies from deceased organ donors, research efforts have focused intensively on generating functional β cells or endocrine cell clusters from stem cells. A variety of stem cell types have been considered as potential future sources of transplantable β cells, which include human pluripotent stem cells (hPSCs), such as human embryonic stem cells and human-induced pluripotent stem cells, mesenchymal stem cells generally isolated from bone marrow or cord blood, stem cells isolated from adult tissues, or directly reprogrammed somatic cells. Focus has been on PSC and reprogrammed somatic cell sources. Although the concept of reprogramming somatic cells directly into β-like cells is in its infancy, recent exciting progress in the PSC field has led to refined protocols yielding highly enriched populations of monohormonal insulin-secreting cells and the initiation of pilot clinical trials.

The majority of research remains in the preclinical realm, optimizing methods for the in vitro conversion of stem cells or somatic cells to high-yield, functional cells that resemble adult human islets/β cells. Given the complexity of the developmental processes scientists are trying to mimic, it is not surprising that this has proven a difficult task. Nonetheless, progress is occurring, and there is anticipation that physiologically normal adult β-like cells will be generated in the near future. Even without achieving this in vitro milestone, companies are moving ahead with pilot clinical trials. For example, ViaCyte, Inc. (http://viacyte.com) has proposed a phase I safety and dosage trial combining a human embryonic stem cell-derived pancreatic progenitor cell product

delivered in a macroencapsulation device and transplanted into type 1 diabetic recipients. Still, many unanswered questions need to be addressed and new technologies were devised to support the responsible development of the field.

Summary of Research Priorities

(1) *Recent reports highlight progress in achieving refined differentiation protocols for driving hPSCs to β-like cells with improved physiological function and greater capacity for more rapid correction of diabetes in mice.* However, further work is needed to understand the reasons why these cells still do not exhibit normal stimulus-secretion coupling or dynamic insulin release in perfusion assays.
(2) *Additional studies evaluating host allo- and autoimmune responses to encapsulated and unencapsulated hPSC-derived β cells, in both the syngeneic and allogeneic settings, are needed.* Because the initial stem cell-derived islets will be allogeneic, the field would benefit by testing strategies incorporating new encapsulation technologies, novel cellular delivery methods and sites, and innovative tissue engineering approaches.
(3) *Further experimental work is needed to study the ability to directly reprogram somatic cells into β-like cells and assess their function in vitro and in animal models.* Progress in this area has also been thwarted by the fact that each individualized cell line may have to go through a full regulatory process; this has naturally discouraged industry and funding agency interest if the work will not lead to a viable product.
(4) *Teratoma formation is a key safety issue with regard to the potential therapeutic application of hPSC-derived β cells.* Studies that define this risk and assays that better predict this risk will advance the field. Preliminary testing will likely require monitoring and containment to mitigate risk; this may render intraperitoneal delivery unacceptable.

β-CELL REGENERATION FROM PROLIFERATION AND NEOGENESIS

There is a compelling need to identify sources of β cells that can be used to replenish those that have been lost in diabetes. We consider the potential of the pancreas to regenerate β cells that can reverse the diabetic state for type 1 and type 2 diabetic patients. There are reasons to be optimistic that new β cells can be generated by proliferation of existing β cells and by neogenesis, the production of new islet cells from non-islet cells in the pancreas or other organs. The major questions being addressed are whether β-cell replication can be significantly enhanced and whether there are cells in the endocrine pancreas or other organs that can serve as precursors for the formation of new β cells.

Summary of Research Priorities

(1) *Evidence has been presented that there is a slow rate of β-cell turnover in the human adult pancreas, occurring from replication of existing β cells and the birth of new β cells through neogenesis.* Basic research to understand how these processes are regulated is essential for progress.
(2) *There is also a slow rate of β-cell death in the adult human pancreas occurring through apoptosis and necrosis.* Understanding these, processes may give rise to new strategies to increase the native β-cell mass.
(3) *There is evidence that the rate of β-cell death is increased in type 2 diabetes, and the contributing mechanisms are thought to include endoplasmic reticulum stress, toxic amyloid oligomers, oxidative injury and the ill-defined processes of overwork and glucose toxicity.* Identification of agents that mollify these processes could forestall disease progression.

SUMMARY

The research agenda we have detailed is designed to facilitate full exploration of the potential of each proposed β-cell replacement solution so the optimal therapy is advanced as quickly as possible. Success in this endeavor will require broad and deep financial support from philanthropic (JDRF, Diabetes Research and Wellness Foundation, American Diabetes Association, and so on) and public funding agencies worldwide; the investment needed is large but the potential reward will be monumental. It is imperative that high impact, scientifically sound approaches are not overwhelmed by industry, private, or venture capital-supported priorities just because they hold a more lucrative near-term business model; scientific merit should dictate the course. Reliance on funding agencies that use traditional peer-reviewed methodology will be the incubator of novel approaches.

Our assessment of the data presented creates the opportunity for IPITA/TTS to endorse the following broad agenda for specific support by the peer-reviewed agencies.

(1) Allogeneic islet engraftment, enhance graft longevity, and ultimately gain immunosuppression-free survival in adult and pediatric patients.
(2) Xenogeneic islet-based approaches with and without encapsulation.
(3) Stem cell-based therapy.
(4) Regeneration-based therapy.
(5) Mobile device-based control of glucose sensing-insulin delivery: AP.

This is a rapidly evolving landscape and new data and novel ideas may radically redirect the path forward. However, the diverse recent progress is tangible and undeniable, and the next decade is bound to witness a fascinating unfolding of competing solutions to cure insulin-dependent diabetes.

REFERENCES

1. Bartlett ST, Markmann JF, Johnson P, et al. Report from IPITA-TTS Opinion Leaders Meeting on the future of β-cell replacement. *Transplantation*. 2016;100(Suppl 2S):S1–S44.
2. Venstrom JM, McBride MA, Rother KI, et al. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. *JAMA*. 2015;313:2017–2023.
3. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med*. 2000;343:230–238.
4. Hering BJ, Clarke WR, Bridges ND, et al. Phase 3 trial of human islets in type 1 diabetes. 2015; submitted.
5. CIT 07 islet transplantation. http://citregistry.org/.
6. Hering BJ, Wijkstrom M, Graham ML, et al. Prolonged diabetes reversal after intraportal xenotransplantation of wild-type porcine islets in immunosuppressed nonhuman primates. *Nat Med*. 2006;12:301–303.
7. Cardona K, Korbutt GS, Milas Z, et al. Long-term survival of neonatal porcine islets in nonhuman primates by targeting costimulation pathways. *Nat Med*. 2006;12:304–306.
8. van der Windt DJ, Bottino R, Casu A, et al. Long-term controlled normoglycemia in diabetic non-human primates after transplantation with hCD46 transgenic porcine islets. *Am J Transplant*. 2009;9:2716–2726.
9. Hecht G, Eventov-Friedman S, Rosen C, et al. Embryonic pig pancreatic tissue for the treatment of diabetes in a nonhuman primate model. *Proc Natl Acad Sci U S A*. 2009;106:8659–8664.
10. Thompson P, Cardona K, Russell M, et al. CD40-specific costimulation blockade enhances neonatal porcine islet survival in nonhuman primates. *Am J Transplant*. 2011;11:947–957.

11. Thompson P, Badell IR, Lowe M, et al. Islet xenotransplantation using gal-deficient neonatal donors improves engraftment and function. *Am J Transplant*. 2011;11:2593–2602.
12. Thompson P, Badell IR, Lowe M, et al. Alternative immunomodulatory strategies for xenotransplantation: CD40/154 pathway-sparing regimens promote xenograft survival. *Am J Transplant*. 2012;12:1765–1775.
13. Jung KC, Park CG, Jeon YK, et al. In situ induction of dendritic cell-based T cell tolerance in humanized mice and nonhuman primates. *J Exp Med*. 2011;208:2477–2488.
14. Kang HJ, Lee H, Ha JM, et al. The role of the alternative complement pathway in early graft loss after intraportal porcine islet xenotransplantation. *Transplantation*. 2014;97:999–1008.
15. Bottino R, Wijkstrom M, van der Windt DJ, et al. Pig-to-monkey islet xenotransplantation using multi-transgenic pigs. *Am J Transplant*. 2014; 14:2275–2287.
16. Dufrane D, Goebbels RM, Gianello P. Alginate macroencapsulation of pig islets allows correction of streptozotocin-induced diabetes in primates up to 6 months without immunosuppression. *Transplantation*. 2010;90: 1054–1062.
17. Veriter S, Gianello P, Igarashi Y, et al. Improvement of subcutaneous bioartificial pancreas vascularization and function by coencapsulation of pig islets and mesenchymal stem cells in primates. *Cell Transplant*. 2014;23:1349–1364.
18. Matsumoto S, Tan P, Baker J, et al. Clinical porcine islet xenotransplantation under comprehensive regulation. *Transplant Proc*. 2014;46: 1992–1995.
19. Sun Y, Ma X, Zhou D, et al. Normalization of diabetes in spontaneously diabetic cynomologus monkeys by xenografts of microencapsulated porcine islets without immunosuppression. *J Clin Invest*. 1996; 98:1417–1422.
20. Bennet W, Sundberg B, Lundgren T, et al. Damage to porcine islets of Langerhans after exposure to human blood in vitro, or after intraportal transplantation to cynomologus monkeys: protective effects of sCR1 and heparin. *Transplantation*. 2000;69:711–719.
21. Kirchhof N, Shibata S, Wijkstrom M, et al. Reversal of diabetes in non-immunosuppressed rhesus macaques by intraportal porcine islet xenografts precedes acute cellular rejection. *Xenotransplantation*. 2004; 11:396–407.
22. Goto M, Johansson H, Maeda A, et al. Low molecular weight dextran sulfate prevents the instant blood-mediated inflammatory reaction induced by adult porcine islets. *Transplantation*. 2004;77:741–747.
23. Van der Windt DJ, Bottino R, Casu A, et al. Rapid loss of intraportally transplanted islets: an overview of pathophysiology and preventive strategies. *Xenotransplantation*. 2007;14:288–297.
24. Goto M, Tjernberg J, Dufrane D, et al. Dissecting the instant blood-mediated inflammatory reaction in islet xenotransplantation. *Xenotransplantation*. 2008;15:225–234.
25. Hawthorne WJ, Salvaris EJ, Phillips P, et al. Control of IBMIR in neonatal porcine islet xenotransplantation in baboons. *Am J Transplant*. 2014;14: 1300–1309.
26. De Voss P, editor. *Cell Encapsulation and Drug Delivery. In Advanced Drug Reviews.)*. Elsevier Press; 2014:67 & 68:1-154.
27. Scharp DW, Marchetti P. Encapsulated islets for diabetes therapy: history, current progress, and critical issues requiring solution. *Adv Drug Deliv Rev*. 2014;67–68:35–73 In "Cell Encapsulation and Drug Delivery", De Voss P (Ed) 2014; 67-68:1-154.
28. Renard E, Cobelli C, Zisser HC, et al. Artificial pancreas outpatient: a new diabetes ecosystem. *J Diabetes Sci Technol*. 2013;7:1411–1415.
29. Peyser T, Dassau E, Breton M, et al. The artificial pancreas: current status and future prospects in the management of diabetes. *Ann N Y Acad Sci*. 2014;1311:102–103.
30. Thabit H, Tauschmann M, Allen JM, et al.; APCam Consortium; AP@home Consortium. Home Use of an Artificial Beta Cell in Type 1 Diabetes. *N Engl J Med*. 2015;373:2129–2140.
31. Nikolic B, Takeuchi Y, Leykin I, et al. Mixed hematopoietic chimerism allows cure of autoimmune diabetes through allogeneic tolerance and reversal of autoimmunity. *Diabetes*. 2004;53:376–383.
32. Nikolic B, Onoe T, Takeuchi Y, et al. Distinct requirements for achievement of allotolerance versus reversal of autoimmunity via nonmyeloablative mixed chimerism induction in NOD mice. *Transplantation*. 2010;89:23–32.
33. Li HW, Sykes M. Emerging concepts in haematopoietic cell transplantation. *Nat Rev Immunol*. 2012;1:403–416.