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Engineering Confined and Prevascularized Sites for Islet Transplantation

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Failure of immunological tolerance to beta cell antigens causes type-1 diabetes (T1D). Autoimmune diabetes is characterized by loss of pancreatic beta cells, leading to patient dependence on exogenous insulin. Insulin replacement therapy does not allow tight glycemic control like beta cells can provide and is associated with blood glucose fluctuations. The inability to sense hypoglycemia and long-term hyperglycemia associated with insulin therapy lead to T1D complications, and in some cases to death. T1D incidence rates alarmingly increased by 1.4% annually while T1D etiology still remains unknown¹. Beta cell replacement through transplantation of islets isolated from cadaveric donors and perfused through the portal vein has shown increasing efficacy in ameliorating poor glycemic control and preventing complications in patients with T1D. However, because of the need for chronic immunosuppression to prevent islet allojection and recurrence of autoimmunity islet transplantation is indicated only in the most severe cases of adult T1D when patients suffer from glycemic instability and life-threatening hyperglycemia or hypoglycemia, despite adherence to optimized medical care. Success of islet transplantation is based on evaluation of the clinical benefits of the procedure, which should outweigh the risk of maintaining immunosuppression. Specifically, successful islet transplantation is determined as a decrease in HbA_{1c} to values below 53 mmol/mol (7%), elimination of severe hypoglycemia, at least 50% reduction in exogenous insulin requirement, and increase in C-peptide as compared to pretransplant levels². Islet graft function, as measured by glucose-stimulated insulin secretion in the clinical setting has been quantified through different approaches, including glucose tolerance test (GTT). It is well known that absence of the first phase of insulin response during an GTT is an early marker of beta cell dysfunction. A recent study showed that both first and second phases of insulin secretion kinetics are altered in insulin-independent islet transplant recipients and that outcomes of islet transplantation can be predicted based on transplanted islet mass³. Therefore, several islet transplant recipients experience marginal mass effects. Increasing islet function, or islet dose per patients could be of assistance to improve efficacy of the islet transplantation

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Dr. Tomei is a co-inventor of intellectual property used in the study and may gain royalties from future commercialization of the technology. Dr. Tomei is also an equity holder in Converge.

procedure. Lack of robust efficacy outcomes following islet transplantation cannot justify clinical approaches that involve high procedural risks or the chronic use of immunosuppression. Approaches that aim at increasing the efficacy while reducing the risks associated with the requirement for chronic recipient immunosuppression will increase the applicability of islet transplantation to children and young adults, who represent the majority of patients with T1D.

One way to increase the efficacy and the safety of islet transplantation is engineering a new transplant site to promote islet engraftment and long-term function, and permit graft retrieval. Current clinical protocols require islet isolation from extracellular matrix and from stromal cells, which are both critical regulators of beta cell function and survival. Further, intraportal islet transplantation exposes isolated islets to instant blood-mediated inflammatory reactions (IBMIR), which can result in early loss of over 50% of the transplanted cells, and to high levels of antirejection drugs, which are deleterious to islet function and survival. Finally, intraportal transplantation does not allow graft monitoring and retrieval in case of adverse events. Several groups have investigated alternative transplantation sites that address issues leading to suboptimal efficacy of current clinical islet transplantation protocols. Among the sites that have been explored are the skin, the pancreas, the submandibular gland, the muscle, the omentum, the bone marrow, the gastric submucosa, the genitourinary tract, the kidney capsule, the anterior eye chamber, the testis, the spleen, the brain, and the thymus^{4–6}. Most alternative sites explored have been disappointing, for reasons that may include poor oxygen tension, slow revascularization and high inflammatory responses to the graft. Approaches for engineering a prevascularized space for islet implantation within a preexisting vascular bed supply^{7,8} may support higher local oxygen tension at the time of islet transplant and minimal inflammatory reactions due to the minimally invasive transplantation procedure.

Feng Li and colleagues⁹ recently showed that a marginal mass of islets (300 IEQ/mouse) can reverse diabetes long-term after autologous transplantation in a hepatic sinus-tract site in chemically-diabetic C57BL/6 mice. Inspired by previous work in the subcutaneous site in preclinical and clinical settings⁷, Feng Li and colleagues explored a novel tissue-engineered site that combines the advantages of hepatic transplantation with a prevascularized and confined site. Generation of the hepatic sinus-tract site was achieved by implanting a cylindrical nylon rod in the hepatic parenchyma. Four weeks after implantation, the rod was removed and islets were implanted in the prevascularized cylindrical pocket. Graft function in the hepatic sinus-tract site was shown as (i) diabetes reversal, achieved at comparable rate to islets transplanted under the kidney capsules (gold standard site in mice) (Fig. 3D); (ii) maintenance of normoglycemia up to 120 days after transplantation (Fig. 5C); and normal intraperitoneal glucose tolerance (Fig. 4A) 60 days after transplantation, though C-peptide secretion kinetics was not shown. Histological analysis of islet grafts 100 days after transplantation showed that despite formation of a thick fibrotic capsule (Fig. 6A2), islet architecture as relative proportion of alpha and beta cells was not affected and islet cores were not necrotic (Fig. 6A3), suggesting that nutrient transport to the graft was not impaired. CD31+ endothelial cells were found both within the graft and in the fibrotic capsule surrounding the graft (Fig. 6A4) though no perfusion studies were performed to demonstrate functionality.

A main advantage of the hepatic site is the portal insulin drainage which improves glucose control. Advantages of prevascularized sites are higher oxygen tension at the time of islet transplant and bypassed inflammation associated with the implant procedure. Advantages of confined sites are the possibility to monitor the graft after implantation and graft retrieval in case of adverse events. The main limitation of this study is the lack of site evaluation in the context of allotransplantation either in combination with systemic immunosuppression, which may affect graft function, or with encapsulated cell products, which may not fit within the confined site due to the larger volume of the implants¹⁰.

References

1. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002–2012. *N Engl J Med*. 2017; 376(15):1419–1429. [PubMed: 28402773]
2. Piemonti L, de Koning EJP, Berney T, et al. Defining outcomes for beta cell replacement therapy: a work in progress. *Diabetologia*. 2018; 61:1273–1276. [PubMed: 29511779]
3. Villard O, Brun JF, Bories L, et al. The second phase of insulin secretion in non-diabetic islet-grafted recipients is altered and can predict graft outcome. *J Clin Endocrinol Metab*. Published online January 8, 2018.
4. Tomei AA, Villa C, Ricordi C. Development of an encapsulated stem cell-based therapy for diabetes. *Expert Opin Biol Ther*. 2015; 15:1321–1336. [PubMed: 26156291]
5. Baidal DA, Ricordi C, Berman DM, et al. Bioengineering of an Intraabdominal Endocrine Pancreas. *N Engl J Med*. 2017; 376:1887–1889. [PubMed: 28489987]
6. Echeverri GJ, McGrath K, Bottino R, et al. Endoscopic gastric submucosal transplantation of islets (ENDO-STI): technique and initial results in diabetic pigs. *Am J Transplant*. 2009; 9:2485–2496. [PubMed: 19775318]
7. Pepper AR, Gala-Lopez B, Pawlick R, Merani S, Kin T, Shapiro AM. A prevascularized subcutaneous device-less site for islet and cellular transplantation. *Nat Biotechnol*. 2015; 33:518–523. [PubMed: 25893782]
8. Marzorati S, Bocca N, Molano RD, et al. Effects of systemic immunosuppression on islet engraftment and function into a subcutaneous biocompatible device. *Transplant Proc*. 2009; 41:352–353. [PubMed: 19249555]
9. Li F, Jiao A, Li X, Zhang C, Sun N, Zhang J. Survival and Metabolic Function of Syngeneic Mouse Islet Grafts Transplanted into the Hepatic Sinus-tract. *Transplantation*. In press.
10. Manzoli V, Villa C, Bayer AL, et al. Immunoisolation of murine islet allografts in vascularized sites through conformal coating with polyethylene glycol. *Am J Transplant*. 2018; 18:590–603. [PubMed: 29068143]