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A NEW PROMISING STRATEGY ISLET MACROCELL ENCAPSULATION DEVICE IN THE TREATMENT OF TYPE I DIABETES

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ABSTRACT

Islet transplantation can treat the foremost severe cases of type I diabetes (TID), but it currently requires deceased donor pancreatic as an islet source and chronic immunosuppression to forestall rejection and recurrence of autoimmunity. Stem cell derived insulin-producing cells can overcome the shortage of organ donors, while cell encapsulation can reduce or eliminate the necessity for immunosuppression, reduce the risks related to with the islet transplantation process and potentially prolonged can survive. A range of materials are used to test for microencapsulation in various animal models and a few materials were shown to induce immunosuppression in islet grafts without the necessity for chronic immunosuppression. Despite the initial success of microcapsules within the NHP model, the combined use of islet transplantation and microencapsulation has not yet been successful in clinical trials.

KEYWORDS: Type I diabetes (TID), Immunosuppression, Microencapsulation, Islet transplantation.

INTRODUCTION

Type I Diabetes Mellitus (TIDM) also known as insulin-dependent diabetes mellitus, is an autoimmune disease that causes a progressive destruction of the insulin-producing pancreatic β cells. As a result, patients require exogenous insulin to maintain normal blood glucose levels. In patients with TIDM, long-term hyperglycaemia often causes complications such as nephropathy, neuropathy and retinopathy. According to a report from the American Diabetes Association (ADA), there are nearly three million children and adults living with TIDM in the USA and millions of others affected worldwide. Management of TIDM and other associated complications is burdensome to both individuals and to society as a whole.

About 422 million people worldwide have diabetes until 2020, the majority living in low-and middle-income countries and 1.6 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades. It is estimated that there are around 601 thousand children worldwide who have type I diabetes. Type I diabetes also known as juvenile diabetes or insulin-dependent diabetes, is a condition in which the body cannot produce insulin, requiring people with the condition to take artificial insulin to stay alive. Insulin injection is a common method to directly control blood glucose levels. However, intensive insulin therapy can induce more frequent episodes of hypoglycemic symptoms in certain populations of patients with TIDM.
T1D is an autoimmune disease in which beta cells within the pancreatic islets are destroyed by selecting independent responses against beta cell auto antigens. The pathophysiology of beta cell destruction in T1D has been reviewed previously. Beta cells are responsible for secreting insulin, which regulates glucose metabolism and homeostasis. Currently, patients with T1D are dependent on external insulin injections but insulin injections do not prevent serious and chronic T1D complications, which can be life-threatening4. In addition, severe hypoglycaemia is often diagnosed by patients as a result of external insulin injections. Hypo ignorance about 6 to 10% of all people who die of T1D. In addition to the widespread use of novel analogues of insulin novels, pump therapy, and glucose sensors, uncertainty persists. Restoring normoglycemia without increasing the risk of severe hypo can have a significant impact on the well-being of people with T1D. Pediatric pump therapy with automatic insulin suspension reduced

the combined amount of active and moderate hypo in patients with T1D. Packed pancreas, automatic, bi-hormonal, bionic improved mean glycaemic levels, with very rare episodes, among adults and adolescents with T1D, compared to insulin pump. Mostly, such devices do not represent the T1D solution and are prone to cracking and cracking.

Replacement of β cell function with the reorganization of all cells indicates a possible biological solution. The endocrine portion of the pancreas makes up only ~ 1% of the pancreas. Therefore, in order to reverse euglycemia, replacement of all endocrine cells may require a simple but equally effective procedure and may reduce the severity of the implantation of all pancreases. Since 1st defining an automated method that allows the isolation of human pancreatic islets with high yield, purity and a stored response to glucose rejuvenation, clinical trials on human organ transplants have been initiated. Currently, the adult islets have been separated from the donors by the donors and transplanted into the liver following the depletion of trans hepatic catheterization of the recipient portal vein via T1D. A minimally invasive procedure is usually performed under local anaesthesia with intervention radiology. At present, constant pressure on the recipients is required to prevent allograft rejection and autoimmune recurrence. In addition, the availability of donors is much lower than the number of patients than it would be in the future. The effects of clinical islet replacement have greatly improved over the past two decades. Annual CITR conclude that islet insertion has led to long-term insulin secretion and associated benefits, including normal or near HbA1C levels, a continuous decrease in severe hypoglycemic episodes and a return to awareness with hypoglycaemia.

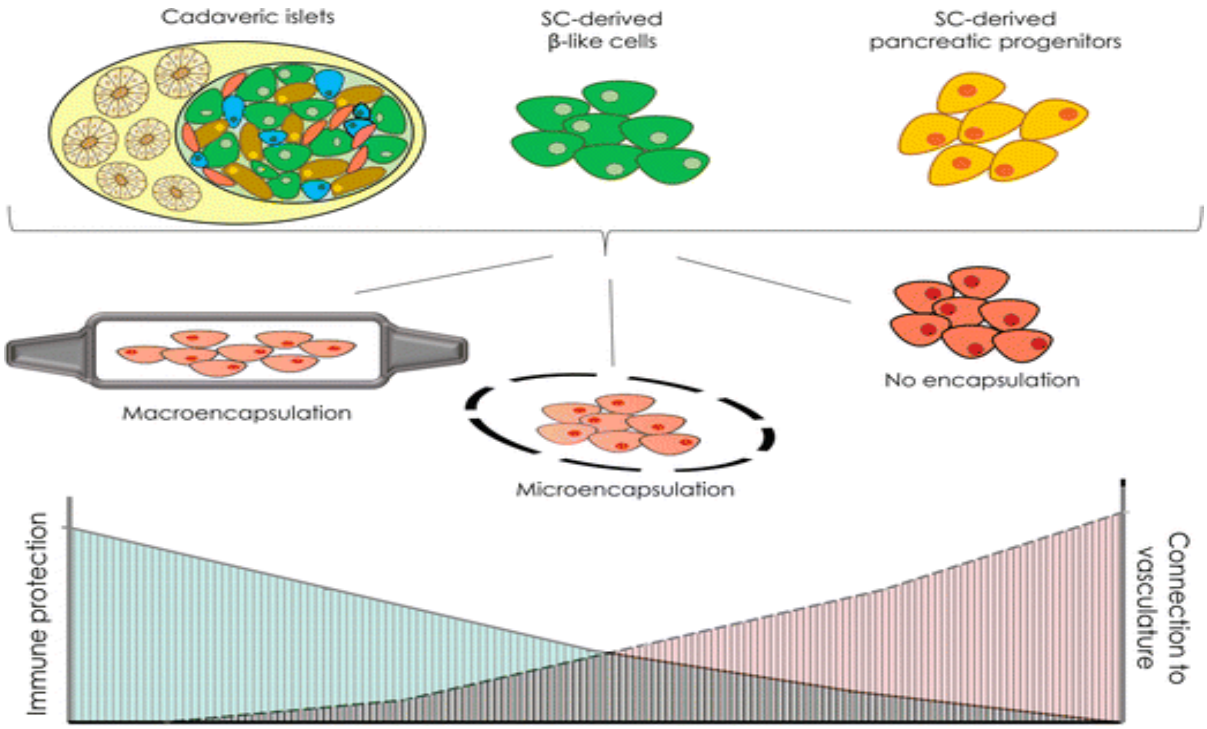
Although progress has been made on the islet's fragmentation, reconstruction and immunosuppression regimes, islet engraftment and long-term performance is not good at all. In addition, side effects associated with chronic immune deficiency include increased risk of infection, kidney failure, hyperlipidaemia, anemias, oral ulcers and increased risk of cancer. Because of the risks associated with the procedure and chronic immunosuppression, islet insertion is currently shown only in a small percentage of T1D patients and in adults only. The major challenges that are still being addressed in making the islet installation available to a large number of T1D subjects are.

- ❖ To avoid chronic physical stress, either by endurance exercise or by self-defence strategies
- ❖ Identification of an unlimited source of insulin-producing cells
- ❖ Identify a suitable replacement site that optimizes islet engraft efficiency and long-term performance

Microencapsulation

In the 1st reports of encapsulation, a large number of islets were immunoisolated between flat-sheet double membranes. This type of single microencapsulation device could be implanted with minimal surgery at different sites, including the peritoneal cavity, subcutaneously or under the renal capsule. Although several types of biomaterial have been used to produce microcapsules, including nitrocellulose, alginate, acrylonitrile and agars, these devices usually had some toxicity and activated nonspecific foreign body reactions, resulting in fibrotic overgrowth with subsequent necrosis of the encapsulated tissue. A subcutaneously transplanted micro device 4 cm in length, shaped like a teabag and made of a bilayer polytetrafluoroethylene membrane, was recently found to be biocompatible. Neonatal pig cells inside the graft and remained viable for up to 8 week after xenotransplantation into non-diabetic cynomolgus monkeys, with no evidence of reaction with adjacent subcutaneous tissue. Moreover, one of 12 non-immuno-suppressed adolescents became insulin independent and 5 children had reduced insulin requirement after transplantation of porcine islets encapsulated in hollow-fibres with porcine Sertoli cells, which likely have Immunomodulating properties.

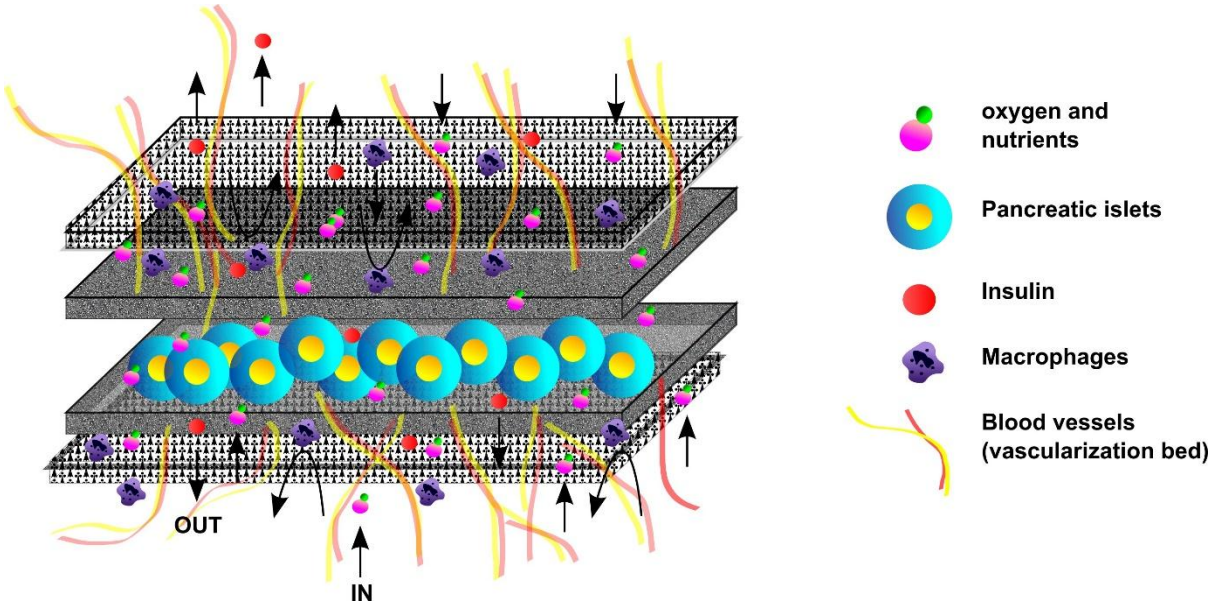
A "monolayer" configuration of microencapsulated pig islets (monolayer cellular device) implanted subcutaneously has been found to significantly improve diabetes control in primates for 6 months without any immunosuppression. In this encapsulation system, islets were seeded as a monolayer on an acellular collagen matrix, enhancing their interactions with a biologic membrane and increasing islet concentration per unit surface area. In addition, diabetes was controlled for up to 1 year in 2 diabetic primates after re-transplantation with new monolayer cellular devices. Unfortunately, the lifespan of adult pig islets limited long-term graft function. Diabetic control was completely maintained for > 32 week after the co-transplantation of adult pig islets and adipose mesenchymal stem cells. A phase 1 clinical study is currently on going to assess the safety and efficacy of this device for allotransplantation of encapsulated islets into humans.



Material Types: The choice of the material you can use for cellular implantation is an important factor because the failure of microencapsulated islet graphic is often considered to be the result of biocompatibility imbalances, resulting in abnormal immune response against microcapsules and leading to continued fibrotic growth of tablets. This overgrowth disrupts the nutrition of the islets and consequently causes the death of the islet cell. There are significant differences between water-soluble polymers, such as alginate and water-soluble polymers, such as poly (Hydroxyethyl methacrylate-methyl methacrylate). However, a major obstacle in the use of water-soluble polymers is the threat to cells by the need for organic solvent, which often disrupts cellular function. In addition to soluble aqueous solutions, alginate-based tablets have been shown to remain stable for several years in small and large animals and humans. The structure of the alginate capsule is based on the adhesion of the alginate droplets, which are converted into solid beads by the incorporation of a divalent cations solution, especially Ca2 +. In many studies to date, alginate beads have been placed in a second layer to reduce the porosity of the capsule membrane. In the pig-to-primate model, flexible layers of poly-lysine and polyornithine are used around the alginate content. The latter type, however, has been associated with polyamino acid cytotoxicity and mechanical instability of microcapsules, reducing their effectiveness. Although the chemical composition of several alginate is elevated to islet immuno-isolation, we found that high-mannuronic alginate is best suited for detecting incomplete selections of more than 150 kDa molecules before and after transplantation, as well as inconsistent anti-inflammatory response associated with surrounding angiogenesis, resulting in insufficient oxygen uptake (approximately 40 mmHg) for survival and function of closed islets. This type of alginate was not only understood in the model of small animals but also in the pig-to-primate model of xenotransplantation under the kidney and skin capsule up to 6 months.

Types of Implantation sites: The lack of rehabilitation of closed islets hinders the efficient operation and longevity of the equipment. Clearly, the area where closed islets are closest to blood flow is the responsibility of applying for a clinic. Unfortunately, it is difficult to find such a site because it has to be large enough to carry a large amount of connectivity and close to the blood vessels. Sites that have been reported to allow effective water-free islet implants, such as liver and spleen, do not meet these requirements because these sites cannot tolerate the large volumes (> 16 mL) of tablets required to be installed on primates. Therefore, most implants of the combined pig islets in the bugs were intraperitoneal. Although this method seemed simple, the peritoneal site was incorrect. Indeed, recent studies in mice have found that macrophages and lymphocytes are involved in the rapid deterioration of closed pig islets after their insertion into the peritoneum. The peritoneum, in fact, is the preferred site for inflammation and the immunologic response and peritoneal mesothelium cells perform the action of powerful immune mechanisms. Studies in mice have shown that the immune system has beneficial effects, improving the cohesiveness of the material and prolonging the survival time of implanted pig islets implanted in the peritoneum. This method of combining encapsulation and immunosuppression, however, remains incompatible with clinical applications. The biocompatibility availability of piglets incorporated into the alginate depends on the planting area. The implanted piglets placed under the kidney pill and under the skin showed better compatibility than implanted implants in

the peritoneum. Indeed, cellular response to macrophages was observed 7 days after implantation in the peritoneum. These findings are consistent with the results showing that macrophages were reconstituted 7 days after transplantation of pig islets implanted in the peritoneum of rats and mice. In addition, strong fibrosis surrounding the internally encapsulated capsules was observed 30 days after implantation and was associated with the loss of porcine C-peptide 7 days after implantation. In contrast, transplantation of the skin or kidneys has been implicated in the weakening of the immune system against closed pig islets, as well as improved porcine islet function; Porcine C-peptide was obtained from mouse of 30 days after reintroduction of enclosed pig islets on both sites. These findings suggest that implantation of the lower extremities of the kidneys and subcutaneous areas improves biological integration and in vivo survival of closed pig islets, as well as improving the performance of the pig islet during the 1st 7 days post-transplantation. Loss of in vivo activity of the piglets implanted in the peritoneum associated with significant changes in islet function, loss of insulin content and significant decrease in insulin secretion after glucose stimulation. These findings may be related to the proliferation of macrophages in the area around the capsules, creating a small dense, oxygen-rich environment, of pig islets. Indeed, macrophage activation, as indicated by NO production and release of cytokines L-1β and tumour necrosis factor-alpha, had a negative impact on islet function and function. We have found that implants in the sub capsular and subcutaneous kidney segments improve the incompatibility of the piglet-derived organisms and significantly reduce macrophage recruitment. This reduction in swine islet pressure and improved islet performance maintain insulin level in each islet and insulin protection after glucose stimulation. The tissues under the skin have recently been shown to provide oxygen-related stress associated with the function and survival of closed islets. Among the sites tested for islet insertion, with or without encapsulation, to improve survival, insertion and function of the arteries, are brachioradialis muscles, ligaments, a large omentum and an inner chamber.



CONCLUSION

Immunosuppression remains the major limitation of allotransplantation or xenotransplantation of islets for type I diabetes. Extended survival of transplanted pig islets has recently been observed in primate models, but several questions and problems associated with immunosuppression remain to be resolved in terms of adjustment before clinical trials. A bio artificial pancreas made of encapsulated pig islets may overcome the 2 major hurdles to islet transplantation, the shortage of human organ donors and the requirement for immunosuppressive regimens. The development of a bio artificial pancreas for preclinical/clinical studies requires the conjunction of integrated parameters such as the choice of a biocompatible material for encapsulation to maintain selective permeability. The encapsulation device should be designed to maintain mechanical properties and stability at an implantation site compatible with the viability and physiology of the encapsulated islets to control glycaemic homeostasis. Of the 3 major types of bio artificial pancreases, the macro encapsulation system is the only method that has demonstrated the capacity to control diabetes in large animals and in preliminary clinical studies. Several improvements must be made to reduce the size of the implant, to improve oxygenation of islets and to develop a simple clinical procedure for bio artificial transplantation and easy access to a device allowing re-alimentation of the islets.

REFERENCES

1. Shapiro A M, Lakey J R, Ryan E A, Korbutt G S, Toth E, Warnock G L, Kneteman N M, Rajotte R V, Islet transplantation in seven patients with type I

DM using a glucocorticoid-free immunosuppressive regimen, New England Journal of Medicine, 2000; 343: 230–238.
2. Frank A M, Barker C F, Markmann J F, Comparison of whole organ pancreas and isolated islet transplantation for type I diabetes, Advanced Surgery, 2005; 39: 137–163.
3. Ryan E A, Paty B W, Senior P A, Bigam D, Alfadhli E, Kneteman N M, Lakey J R, Shapiro A M, 5 year follow-up after clinical islet transplantation, Diabetes, 2005; 54: 2060–2069.
4. Cooper D K, Gollackner B, Sachs D H, Will the pig solve the transplantation backlog? Annual Review medicine, 2002, 53: 133–147.
5. First M R, Xenotransplantation: social, ethical, religious and political issues, Kidney International Supply, 1997; 58: S46–S47.
6. Sachs D H, The pig as a potential xenograft donor, Vet Immunology Immunopathology, 1994; 43: 185–191.
7. Kurz H, Physiology of angiogenesis, Journal of Neurooncology, 2000; 50: 17–35.
8. Mendola J F, Conget I, Manzanares J M, Corominola H, Vinas O, Barcelo J, Gomis R, Follow-up study of the revascularization process of purified rat islet beta-cell grafts, Cell Transplant, 1997; 6: 603–612.
9. Menger M D, Jaeger S, Walter P, Feifel G, Hammersen F, Messmer K, Angiogenesis and haemodynamics of microvasculature of transplanted islets of Langerhans, Diabetes, 1989; 38(1): 199–201.
10. Patan S, Vasculogenesis and angiogenesis as mechanisms of vascular network formation, growth and remodelling, Journal of Neurooncology, 2000; 50: 1–15.
11. Vajkoczy P, Menger M D, Simpson E, Messmer K, Angiogenesis and vascularization of murine pancreatic islet isografts, Transplantation, 1995; 60: 123–127.
12. Vajkoczy P, Olofsson A M, Lehr H A, Leiderer R, Hammersen F, Arfors K E, Menger M D, Histogenesis and ultrastructure of pancreatic islet graft microvasculature, Evidence for graft revascularization by endothelial cells of host origin, American Journal Pathology, 1995; 146: 1397–1405.
13. Korsgren O, Jansson L. Discordant cellular xenografts revascularized in intermediate athymic hosts fail to induce a hyperacute rejection when transplanted to immunocompetent rats, Transplantation, 1994, 57: 1408–1411.
14. Soderlund J, Wennberg L, Castanos - Velez E, Biberfeld P, Zhu S, Tibell A, Groth C G, Korsgren O, Fetal porcine islet-like cell clusters transplanted to cynomolgus monkeys: an immunohistochemical study, Transplantation, 1999; 67: 784–791.
15. Kirchhof N, Shibata S, Wijkstrom M, Kulick D M, Salerno C T, Clemmings S M, Heremans Y, Galili U, Sutherland D E, Dalmasso A P, et al., Reversal of diabetes in non-immunosuppressed rhesus macaques by intraportal porcine islet xenografts precedes acute cellular rejection, Xenotransplantation, 2004; 11: 396–407.
16. Cantarovich D, Blancho G, Potiron N, Jugeau N, Fiche M, Chagneau C, Letessier E, Boeffard F, Loth P, Karam G et al., Rapid failure of pig islet transplantation in non-human primates, Xenotransplantation, 2002; 9: 25–35.
17. Bühler L, Deng S, O'Neil J, Kitamura H, Koulmanda M, Baldi A, Rahier J, Alwayn I P, Appel J Z, Awwad M, et al., Adult porcine islet transplantation in baboons treated with conventional immunosuppression or a non-myeloablative regimen and CD154 blockade, Xenotransplantation, 2002; 9: 3–13.
18. Nishimaki T, Kano K, Milgrom F, Hanganutziu - Deicher antigen and antibody in pathologic sera and tissues, Journal Immunology, 1979; 122: 2314–2318.
19. Komoda H, Miyagawa S, Kubo T, Kitano E, Kitamura H, Omori T, Ito T, Matsuda H, Shirakura R, A study of the xenoantigenicity of adult pig islets cells, Xenotransplantation, 2004; 11: 237–246.
20. Auchincloss H, Sachs D H, Xenogeneic transplantation, Annuals of Review of Immunology, 1998; 16: 433–470.