

# ISLET TRANSPLANTATION IN RODENTS. Do encapsulated islets really work?

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**ABSTRACT** – *Context* - Diabetes mellitus type I affects around 240 million people in the world and only in the USA 7.8% of the population. It has been estimated that the costs of its complications account for 5% to 10% of the total healthcare spending around the world. According to World Health Organization, 300 million people are expected to develop diabetes mellitus by the year 2025. The pancreatic islet transplantation is expected to be less invasive than a pancreas transplant, which is currently the most commonly used approach. *Objectives* - To compare the encapsulated and free islet transplantation in rodents looking at sites of islet implantation, number of injected islets, viability and immunosuppression. *Methods* - A literature search was conducted using MEDLINE/PUBMED and SCIELO with terms about islet transplantation in the rodent from 2000 to 2010. We found 2,636 articles but only 56 articles from 2000 to 2010 were selected. *Results* - In these 56 articles used, 34% were encapsulated and 66% were nonencapsulated islets. Analyzing both types of islets transplantation, the majority of the encapsulated islets were implanted into the peritoneal cavity and the nonencapsulated islets into the liver, through the portal vein. In addition, the great advantage of the peritoneal cavity as the site of islet transplantation is its blood supply. Both vascular endothelial cells and vascular endothelial growth factor were used to stimulate angiogenesis of the islet grafts, increasing the vascularization rapidly after implantation. It also has been proven that there is influence of the capsules, since the larger the capsule more chances there are of central necrosis. In some articles, the use of immunosuppression demonstrated to increase the life expectancy of the graft. *Conclusion* - While significant progress has been made in the islets transplantation field, many obstacles remain to be overcome. Microencapsulation provides a means to transplant islets without immunosuppressive agents and may enable the performance of xenotransplantation. The use of alternative donor sources, fewer islets per capsule and the appropriate deployment location, such as the peritoneal cavity, may give a future perspective to the application of immunoprotective capsules and viability in clinical practice. A variety of strategies, such as genetic engineering, co-encapsulation, improvement in oxygen supply or the establishment of hypoxia resistance will also improve the islet transplantation performance. It remains to be determined which combination of strategies with encapsulation can fulfill the promise of establishing a simple and safe transplantation as a cure for diabetes.

**HEADINGS** - Diabetes mellitus, type I. Islets of Langerhans transplantation. Rodentia.

## INTRODUCTION

Diabetes mellitus (DM) type I affects around 240 million people in the world<sup>(1)</sup> and only in the USA 7.8% of the population<sup>(5)</sup>. It has been estimated that the costs of its complications account for 5% to 10%<sup>(2)</sup> of the total healthcare spending around the world. According to World Health Organization, 300 million people are expected to develop DM by the year 2025.

Islet transplantation has been considered a safer alternative than whole-organ transplantation and a potentially alternative treatment to conventional exogenous-insulin therapy<sup>(16)</sup>. The main benefit of islet transplantation is the ability to inject it in vascularized organs and it can be considered less invasive. The acute rejection still is a major problem. New alternatives to avoid the rejection have been developed such as, thymic manipulation, co-transplant with other cell types (bone

marrow cells, Sertoli cells etc.), liver transplantation<sup>(27, 37, 41, 42)</sup> and encapsulated islets.

With immunoprotection by encapsulation, islets are enclosed in a matrix surrounded by semipermeable membrane, which allows for the passage of small molecules like insulin and glucose, but not for the entry of the much larger cells and antibodies of the immune system. Such a physical barrier can thus prevent allograft rejection, which depends on recognition of the Major Histocompatibility Complex (MHC) by host lymphocytes. Furthermore it can prevent antibody-mediated cytotoxicity, which plays a role in the autoimmune destruction of beta cells, as well as in allograft and xenograft rejection<sup>(31, 59)</sup>. Immunoprotection by encapsulation can thus enable transplantation of islet tissue in the absence of immunosuppression.

Our aim is to compare the encapsulated and free islet transplantation in rodents looking at site of

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implantation, number of islets, viability and type of immunosuppression.

### METHODS

This research was made through MEDLINE/PUBMED and SCIELO web sites looking for papers on the content “islet transplantation in the rodent”.

We found 2,636 articles but only 56 articles from 2000 to 2010 were selected based on the relevance. Thirty-five (35%) were about encapsulated islet and sixty-five (65%) nonencapsulated islet. There were articles about xenografts, isografts and allografts.

### RESULTS

The best islet survival rate in encapsulated islet transplantation was achieved in the peritoneal cavity with an average of 4216 islets implanted per capsule, lasting an average of 100 days functionally (Table 1).

TABLE 1. Sites of implantation of encapsulated islets and islets survival rate (days)

Author	Encapsulated	
	No. of islets per capsule	Results days
<b>Peritoneal cavity</b>		
Tatarkiewicz et al. <sup>(53)</sup>	2000	70
Omer et al. <sup>(55)</sup>	3000	21-70
Figliuzzi et al. <sup>(11)</sup>	16000	IS+: 18 ± 8 IS-: 7.5 ± 0.2
Yun Lee et al. <sup>(63)</sup>	1200	>365
Remuzzi A et al. <sup>(39)</sup>	3000	80
O’Sullivan et al. <sup>(36)</sup>	100	14
<b>Subcutaneous tissue</b>		
Sorenby et al. <sup>(48)</sup>	200 to 1000	± 6
Sorenby et al. <sup>(49)</sup>	125 to 375	28
<b>Liver</b>		
Schneider S. et al. <sup>(44)</sup>	1500	95 ± 3

IS+: with immunosuppression;  
IS - : without immunosuppression

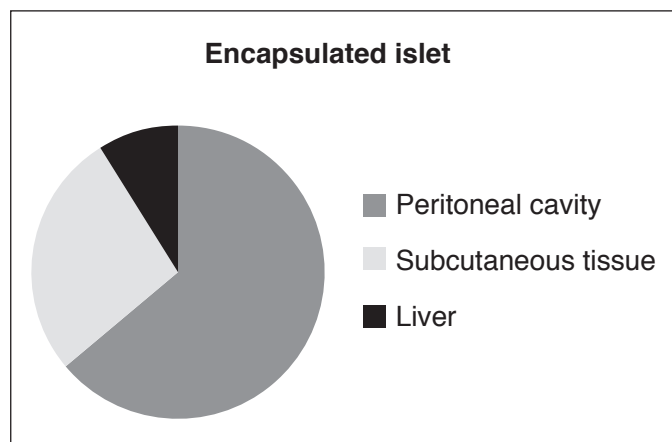


FIGURE 1. Most common sites of implantation of encapsulated islets

The most widely used implantation sites of encapsulated islets (Figure 1).

In contrast, the best islet survival rate in the nonencapsulated islets was achieved by injecting islets into the liver, with an average of 1475 islets implanted per capsule, lasting an average of 164 days with the use of immunosuppression (Table 2).

TABLE 2. Sites of implantation of nonencapsulated islets and islets survival rate (days)

Author	Nonencapsulated	
	No. of islets	Results days
<b>Liver</b>		
Ikebukuro et al. <sup>(19)</sup>	600	> 365
Spadella et al. <sup>(50)</sup>	1500	365
Schneider et al. <sup>(44)</sup>	1500	97 ± 2
Omer et al. <sup>(55)</sup>	4000	70
Taira M. et al. <sup>(52)</sup>	600	30
Ikebukuro et al. <sup>(18)</sup>	600	250
Hara et al. <sup>(16)</sup>	500 to 1500	IS+: 10.5 ± 8.44 IS-: 12.0 ± 2.65
Lee. et al. <sup>(29)</sup>	1500	126
<b>Kidney</b>		
Olsson et al. <sup>(34)</sup>	250	28
Sawada et al. <sup>(42)</sup>	2000	> 100
Lan et al. <sup>(27)</sup>	-	> 60
Hamamoto et al. <sup>(14)</sup>	2500	41
Kover et al. <sup>(24)</sup>	1500	80 –120
Hiramatsu et al. <sup>(17)</sup>	200 or 20	56
Socha-Urbaneck et al. <sup>(47)</sup>	1500 ± 200	150
Laumonier et al. <sup>(28)</sup>	3000 to 3200	19.5 ± 5.8
Omer et al. <sup>(55)</sup>	4000	70
Sharma et al. <sup>(46)</sup>	30	30 – 40
Hara et al. <sup>(16)</sup>	500 to 1500	11.0 ± 2.63
Han et al. <sup>(15)</sup>	-	60

IS+: with immunosuppression;  
IS-: without immunosuppression

Other sites of implantation were: subcutaneous tissue (n = 2500 islets; 58 days of viability), peritoneal cavity (n = 10000 islets; 37 days of viability) and bone marrow (n = 1250 islets; 21 days of viability).

### DISCUSSION

The concept of islet transplantation is not new. Investigators as early as the English surgeon Charles Pybus (1882–1975) attempted to transplant pancreatic tissue to cure diabetes. Most, however, credit the recent era of islet transplantation research to Paul Lacy’s studies dating back to more than 3 decades. Lacy’s group<sup>(25)</sup> described a novel method to isolate islets using collagenase, paving the way for future of in vitro and in vivo islet experiments. According to Hara et al.<sup>(16)</sup>, Ballinger and Lacy demonstrated that intraportal islet transplantation corrected experimental

diabetes in rodents; since then, many transplantation sites have been tested.

Subsequent studies showed that transplanted islets could reverse diabetes in both rodents and non-human primates<sup>(23, 43)</sup>. Lacy<sup>(26)</sup> observed the feasibility of islet cell transplantation as a therapeutic approach in the probable prevention of the diabetes complications in individuals. Improvements in isolation techniques and immunosuppressive regimens conducted in the first human clinical trials of islet transplantation in the mid of 1980. Tzakiset et al.<sup>(57)</sup> described the first successful trial of human islet allotransplantation resulting in long-term reversal of diabetes. Despite continued procedural improvements, only about 10% of islet recipients in the late of 1990 achieved euglycemia. Shapiro et al.<sup>(45)</sup> described seven consecutive patients who achieved euglycemia after islet transplantation using a steroid-free protocol and large numbers of donor islets.

In the last 10 years numerous studies were made on islet transplantation in the rodent. We reviewed 56 of these studies; 19 articles (34%) concerned encapsulated islet and 37 (66%) non-encapsulated islet.

Nonencapsulated islets may be injected into the liver<sup>(4, 16, 18, 19, 35, 44, 50, 52)</sup>, kidney<sup>(5, 14, 15, 16, 17, 24, 27, 28, 32, 34, 35, 42, 46, 47)</sup>, peritoneal cavity<sup>(11, 35)</sup>, bone marrow<sup>(41)</sup> and subcutaneous tissue<sup>(22, 48)</sup>. Ikebukuro et al.<sup>(19)</sup> showed that islets and bone marrow cells, when injected into the liver using irradiation as immunosuppression, can increase the functionality of the cells for more than 365 days. In addition, Kawakami et al.<sup>(22)</sup> discovered that basic fibroblast growth factor could increase vascularization and thus achieve islets viability for 112 days, when islets were injected in the subcutaneous tissue.

Many factors can influence the islet viability and it is important to review them. While significant progress has been made in the islet transplantation field, many obstacles remain that currently preclude its widespread application. Three of the most important limitations are low tension of O<sub>2</sub> where the islets are implanted, the limited supply of islets for transplantation and also the currently inadequate means for preventing islet rejection.

Encapsulated islets have been used in two ways: micro-encapsulated islets and macro-encapsulated islets. Macro-encapsulated islets have the advantage of being retrievable so that the functions of islets inside can be evaluated at anytime. In contrast, micro-encapsulated islets are one or a few islets enclosed in semi-permeable membranes, which can provide a surface for diffusion, therefore maintaining the functions of islets inside. However, they are irretrievable after transplantation<sup>(38)</sup>.

When islets are transplanted, 50% of the tissue may be lost in the first few days; this is thought to be due to hypoxic death before vascularization develops<sup>(36)</sup>. Revascularization begins in 7-10 days after transplant, when there's already ischemic damage<sup>(21, 33)</sup>. This delayed and insufficient revascularization deprives these islets of oxygen, resulting in cell death and graft failure<sup>(12)</sup>.

The great advantage of the liver as the site of islet transplantation is dual blood supply, which allows the total occlusion of the

portal venules, caused by embolization and the non-infarcted site of transplantation, which is nourished by blood<sup>(4)</sup>.

In the renal subcapsular space, islets are easily retrieved for histological study. However, vascularization is poor and leads to a low tension of oxygen.

When the islets are implanted into the rodent's peritoneal cavity there is plenty of blood supply to use of, which facilitates the wait for a new revascularization, but it is randomly chosen.

Trying to increase the blood supply of the graft soon after implantation, Cheng et al.<sup>(5)</sup> have injected vascular endothelial cells L and vascular endothelial growth factor (VEGF) to stimulate angiogenesis. The use of growth factors was made of in other works too<sup>(5, 33, 62)</sup>. They saw that in chronically ischemic tissues these factors were decreased and that premature islet revascularization could improve the outcome of islet transplantation and enhance the graft survival. Yu et al.<sup>(62)</sup> combined SDF-1 $\alpha$  and VEGF achieving not only new vessels but mature and stable ones.

In a different way, joining bone marrow - derived mesenchymal stem cells function as VEGF secretor to pancreatic islets, Figliuzzi et al.<sup>(12)</sup> also promoted vascularization. Johansson et al.<sup>(21)</sup> questioned the early capability of forming new blood vessels, lost days later. They saw that the islets attract blood vessels but fail to grow and connect to recipient blood vessels. He then inhibited the angiostatic factors and restored that capability without any growth factors.

All of these different approaches towards a better vascularization are new and of these, need yet to be sorted the best one.

The difficulty in isolating an adequate number of islets lies on the fact that multiple donors are needed to get patients off exogenous insulin after islet transplantation. Therefore, it is crucial to prepare large numbers of viable and functional islets from a single donor pancreas for clinical transplantation.

It has been proven that the volume of the capsules influences, since the larger the capsule more chances are there of central necrosis<sup>(36)</sup>. Besides necrosis, a major concern is that the low tension of O<sub>2</sub> can lead the release of pro-inflammatory factors. These pro-inflammatory factors elicit a host immune response even in the encapsulated islets. An alternative to prevent these factors is the use of capsules. These can reduce immunogenicity by preventing cellular immune reactions while simultaneously transfers nutrients, oxygen and therapeutic factors. This permits the imitation of moment-to-moment fine regulation of the missing therapeutic factors, avoids a lifetime of immunosuppressive therapy and allows the use of non-human cells, thus overcoming the limited supply of human donor cells<sup>(65)</sup>.

Zhao et al.<sup>(64)</sup> have demonstrated that encapsulated islets cultured in 3D peptide nanofiber provides a superior simulated microenvironment for improving the viability and the secretion function of the islets.

Graft failure of encapsulated islets is usually interpreted as a consequence of a nonspecific body reaction against the capsules that results in fibrotic overgrowth of the capsules,

with ischemia and subsequent necrosis of the islets<sup>(9)</sup>. Pericapsular overgrowth should not impose a problem as long as the majority of the islet-containing microcapsules is not affected by overgrowth, and remains efficient<sup>(6)</sup>. However, macrophage-derived factors from the overgrown part of the graft may affect the non-overgrown part.

An alternative to these are capsules with new components. Zimmermann et al.<sup>(65)</sup> have demonstrated that alginate based matrix with BaCl<sub>2</sub> crystals enhances the immunoprotecting encapsulation and therefore stabilizes the membrane when in contact with the external Ba<sup>2+</sup>. Yun et al.<sup>(63)</sup> have reported that PEG-based chemical immunomodulation can provide a semi-permanent effective therapy that protects transplanted islets at least for 1 year when accompanied by cyclosporine. Furthermore, Vériter et al.<sup>(58)</sup> have tested original alginates with respect to sterile lyophilized high mannuronated and they have had an optimum result with high mannuronated with high viscosity alginate.

Another option is the use of TheraCyte™ which is suited for the maintenance of islets *in vivo* by allowing cells to be loaded into the chamber at controlled densities and spatial configurations and the promotion of vascularization by the outer membrane of the device<sup>(51)</sup>. In addition, Teramura et al.<sup>(54)</sup> have proposed as up-to-the-minute method for islet microencapsulation with amphiphilic poly (ethylene glycol)-conjugated phospholipid derivative (PEG-lipid) and DNA hybridization. This enables an individually islet encapsulation and no central necrosis have been observed.

Qi et al.<sup>(38)</sup> have suggested the use of polyvinyl alcohol macro-encapsulated islets for long-term preservation (7 days) is better, because they allow overcoming the obstacles of insufficient donors and the side effects of immunosuppressive drugs.

In the past decades, allograft survival improved because the development of new and more specific immunosuppressive agents.

Recently it was stated that porcine islet xenotransplantation is possible using cyclosporine A (CsA) as an immunosuppressive agent. They isolated islets from adult pigs, cultured for 1.5-3 weeks and transplanted in rodents using CsA. The treatment with CsA achieved graft survival to over 134 days<sup>(40)</sup>.

A further immunosuppressive agent used is AEB-071 (AEB). AEB-071 is a specific inhibitor of protein kinase C, which prevents T-lymphocyte activation. Merani et al.<sup>(32)</sup> investigated the effect of AEB on rat islet allotransplantation alone or in combination with CTLA4-Ig, mycophenolate mofetil or CsA in rodent allogeneic islets transplant model. They demonstrated that AEB is an appropriate immunosuppressive agent for islet transplantation, because it can prolong islet graft survival alone or with CsA, without toxicity on glucose metabolism.

In another study, researchers combined CsA with FTY720 in islet xenotransplantation. They found that this combination inhibited almost all morphological signs of pig-to-rat islet xenograft rejection for up to 24 days after transplantation<sup>(30)</sup>.

Fotiadis et al.<sup>(13)</sup> used mycophenolatemofetil (MMF) and CsA to check the positive or adverse effects of MMF as a

single agent. They proved that the administration of MMF as immunosuppression agent was safe in an experimental model of islet allotransplantation and was equally effective with cyclosporine, with less toxicity.

Balamurugan et al.<sup>(2)</sup> described the effect of CsA, FK506 or prednisolone monotherapy on preventing monkey islet graft rejection after xenotransplantation in a rodent model. Histological examination indicated that monkey islets survived in the presence of continuous high-dose of immunosuppressive monotherapy in rodents.

Most immunosuppressive drugs, that support successful allograft survival act by inhibiting or depleting T lymphocytes. Tautomycin (TMC) is a specific inhibitor of protein phosphatase 1, which has a role in cell-cycle control and T-cell activation and promotes T-cell-specific apoptosis. Wee et al.<sup>(60)</sup> investigated the effect of TMC alone and in combination with CsA on rodent islet transplantation. They suggested that CsA and TMC act synergistically to reduce the function of T-effector cells and enhance regulatory cell function in a rodent islet allotransplantation model.

Tacrolimus (FK506) is a different immunosuppressive agent used in the islet transplantation. Balibreadel et al.<sup>(3)</sup> evaluated *in vitro* islet low-dose tacrolimus response after pro-inflammatory stimulation. They found that *in vitro* cytoprotective effect of low-dose tacrolimus on isolated rodent islets decreases both oxidative stress and apoptosis markers after stimulation of pro-inflammatory mediators.

Activation of both the coagulation and the complement cascades is one of the serious obstacles to successful island engraftment. Tokodai et al.<sup>(56)</sup> suggested that C5a- inhibitory peptide combined with gabexatemesilate may be a useful approach to control the instant blood-mediated inflammatory reaction induced in clinical islet transplantation and one that is free of side effects.

It was demonstrated that graft survival of allograft islets transfected with indoleamine 2, 3-dioxygenase (IDO) transplanted without any immunosuppression was superior to the control group. It is known that IDO exerts immunoregulatory functions suppressing T-cell responses. These data demonstrated that IDO expression induced in islets by lipofection improved metabolic control of streptozotocin-diabetic rodents and prolonged allograft survival<sup>(10)</sup>.

The cytoprotection of chitosan hydrogels in xenogeneic islet transplantation was demonstrated by Yang et al.<sup>(61)</sup>. It has showed that islets encapsulated in chitosan hydrogels secreted insulin in response to the glucose stimulation as naked islets with higher cell survival. This study indicates that the chitosan hydrogels deliver and protect encapsulated islets successfully in xenotransplantation.

Finally, a better insight into the causes of microencapsulated islet graft failure may help in finding a way to improve graft survival. One important observation is that microencapsulated autograft and allograft survival rates are similar, which implies that graft failure is not caused by rejection due to allograft recognition<sup>(7)</sup>. If graft failure cannot be explained by allograft rejection, others factors must be involved. De Vos et al.<sup>(8)</sup> have showed that there



is a gradual decrease in islet function, a gradual increase in central necrosis, a continuous increased replication of islet cells, and a nonprogressive overgrowth of a portion of microencapsulated islet graft. Three important aspects of the microencapsulated islet graft technique may be associated with these phenomena. The first is related to the biocompatibility, which explains the occurrence of overgrowth. The second is related to the immunoprotective properties of the microcapsules. Immunoprotection is incomplete because capsules may allow the passage of small pro-inflammatory factors, which lead to cell death and dysfunction. The third factor is related to the great distance between the encapsulated islets and the blood supply. An important consequence of the great diffusion distance is the limited supply of oxygen, which leads to hypoxia, causes islet dysfunction and necrosis, and may be responsible for the increase in islet replication.

## CONCLUSION

While significant progress has been made in the islets transplantation field, many obstacles remain to be overcome. Microencapsulation provides a means to transplant islets without immunosuppressive agents and may enable the performance of xenotransplantation. The use of alternative donor sources, fewer islets per capsule and the appropriate deployment location, such as the peritoneal cavity, may give a future perspective to the application of immunoprotective capsules and viability in clinical practice. A variety of strategies, such as genetic engineering, co-encapsulation, improvement in oxygen supply or the establishment of hypoxia resistance will also improve the islet transplantation performance. It remains to be determined which combination of strategies with encapsulation can fulfill the promise of establishing a simple and safe transplantation as a cure for diabetes.

Souza YEDM, Chaib E, Lacerda PG, Crescenzi A, Bernal-Filho A, D'Albuquerque LAC. Transplante de ilhotas de Langerhans em modelos experimentais em roedores. Ilhotas encapsuladas realmente funcionam? *Arq Gastroenterol.* 2011;48(2):146-52.

**RESUMO** – *Contexto* - Diabetes mellitus tipo I afeta cerca de 240 milhões de pessoas no mundo e 7,8% só nos EUA. Foi estimado que o custo de suas complicações fosse de 5%-10% dos custos mundiais em saúde. De acordo com a OMS (Organização Mundial de Saúde), espera-se que cerca de 300 milhões de pessoas desenvolvam o diabetes mellitus até o ano de 2025. É esperado que o transplante de ilhotas pancreáticas seja menos invasivo que o transplante pancreático, opção atual de maior uso. *Objetivos* - Comparar as ilhotas encapsuladas e as ilhotas livres em roedores nos seguintes aspectos: local de implantação das ilhotas, número de ilhotas, viabilidade e imunossupressão. *Métodos* - A pesquisa bibliográfica foi conduzida com o uso de citações do MEDLINE/PUBMED e SCIELO que apresentassem termos sobre transplante de ilhotas em roedores no período de 2000 a 2010. Foram achados 2.636 artigos, mas somente 56 desse período foram selecionados. *Resultados* - Nos 56 artigos utilizados, 34% eram encapsulados e 66% eram não-encapsulados. Analisando ambos os tipos de transplante de ilhotas, a maioria delas encapsuladas, foi implantada na cavidade peritoneal e as não-encapsuladas, através da veia porta, no fígado. A grande vantagem da cavidade peritoneal como local de transplante era a oferta sanguínea. As células endoteliais e o fator de crescimento endotelial foram usados para estimular a angiogênese nas ilhotas, aumentando a vascularização rapidamente após a implantação. Foi também provada a influência das cápsulas, dado que quanto maior a cápsula maior era a chance de necrose central. Em alguns artigos, o uso de imunossupressão demonstrou aumento da expectativa de vida do enxerto. *Conclusão* - Enquanto algum progresso significativo não tenha sido obtido no campo de transplante de ilhotas, restam ainda muitos obstáculos a serem vencidos. A microencapsulação viabiliza o transplante de ilhotas sem o uso de imunossuppressores, o que pode permitir o xenotransplante. O uso de fontes doadoras alternativas, menor quantidade de ilhotas por cápsula e local de implantação adequado, como a cavidade peritoneal, podem dar melhor perspectiva na aplicação de cápsulas imunoprotetidas, aumentando viabilidade na prática clínica. Uma série de estratégias, como engenharia genética, coencapsulamento, melhora da oferta de oxigênio ou o estabelecimento de resistência à hipóxia também podem aprimorar os resultados do transplante de ilhotas. Deve-se determinar ainda qual a combinação de estratégias com relação ao uso de ilhotas encapsuladas que possam cumprir com as promessas de um transplante simples e seguro para a cura do diabetes.

**DESCRITORES** - Diabetes mellitus tipo I. Transplante das ilhotas pancreáticas. Roedores.

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