**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 9976**

**Columns:** **MINIREVIEWS**

**Review of experimental attempts of islet allotransplantation in rodents: Parameters involved and viability of the procedure**

IuamotoLR*et al.* Review of islet allotransplantation in rodents

Leandro Ryuchi Iuamoto, Alberto Meyer, Eleazar Chaib, Luiz Augusto Carneiro D’Albuquerque

**Leandro Ryuchi Iuamoto, Alberto Meyer, Eleazar Chaib, Luiz Augusto Carneiro D’Albuquerque,** Department of Gastroenterology, Liver and Pancreas Transplantation Surgery Unit, University of Sao Paulo, Sao Paulo 05403-090, Brazil

**Author contributions:** Iuamoto LR and Meyer A read all the articles, selected the most relevant of them and edited the manuscript; D’Albuquerque LAC designed the study and was also involved in editing the manuscript; all authors contributed to the manuscript.

**Correspondence to: Dr. Leandro Ryuchi Iuamoto,** Department of Gastroenterology, Liver and Pancreas Transplantation Surgery Unit, University of Sao Paulo, Av. Dr. Eneas de Carvalho Aguiar 255, Sao Paulo 05403-090, Brazil. leandro.iuamoto@gmail.com

**Telephone:** +55-11-30618322 **Fax:** +55-11-30618322

**Received:** March 7, 2014 **Revised:** May 3, 2014

**Accepted:** June 21, 2014

**Published online:**

**Abstract**

The purpose of the present study was to organize the parameters involved in experimental allotransplantation in rodents to elaborate the most suitable model to supply the scarcity of islet donors. We used the PubMed database to systematically search for published articles containing the keywords “rodent islet transplantation” to review. We included studies that involved allotransplantation experiments with rodents’ islets, and we reviewed the reference lists from the eligible publications that were retrieved. We excluded articles related to isotransplantation, autotransplantation and xenotransplantation, *i.e.*, transplantation in other species. A total of 25 studies related to allotransplantation were selected for systematic review based on their relevance and updated data. Allotransplantation in rodents is promising and continues to develop. Survival rates of allografts have increased with the discovery of new immunosuppressive drugs and the use of different graft sites. These successes suggest that islet transplantation is a promising method to overcome the scarcity of islet donors and advance the treatment options for type 1 diabetes.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** Islet transplantation; Allograft; Immunosuppression; Type 1 diabetes; Islet grafts; Diabetes mellitus; Islet; Hyperglycemia

**Core tip:** This is an important systematic review for readers to analyze the different existing methodologies of islet allotransplantation. This article reviews all aspects of donors and recipients, the types and dosages of immunosuppressive therapy, graft survival time and evolution of the recipient’s blood glucose. Therefore, the present article permits reproduction and improvement of the experiments involving islet allotransplantation in rodents to develop alternative therapies for type 1 diabetes.

Iuamoto LR, Meyer A, Chaib E, D’Albuquerque, LAC. Review of experimental attempts of islet allotransplantation in rodents: Parameters involved and viability of the procedure. *World J Gastroenterol* 2014; In press

**INTRODUCTION**

It is estimated that 4% of the world population is affected by diabetes mellitus, of which 10% have type 1 diabetes[1]. Furthermore, the incidence of diabetes cases in Europe has increased, especially in children and teenagers, in whom the incidence of type 1 diabetes increased by 4% last year. One trend is the occurrence of type 1 diabetes mellitus at younger ages, between 10 and 14 years. Today, the disease is already at 0-5 years[2]. According to the IBGE - CENSUS -2010, there are currently 12.054.827 diabetics in Brazil[3]. Thus, approximately 1.2 million diabetics in Brazil may benefit from research aimed at improving treatment of type 1 diabetes.

Currently, insulin is the primary treatment method for diabetes. However, approximately 5%-10% of patients have severe and unexpected fluctuations in their blood glucose levels, resulting in multiple episodes of hypoglycemia, which has serious clinical consequences. In such cases, pancreas transplantation is an alternative treatment option that is already in clinical use. Another alternative option is islet transplantation, which is a less invasive therapeutic method but is still in development[3]. Regarding the effectiveness of treatment, some results showed 80% insulin independence within the first year in postoperative patients treated with islet transplantation[4]; however, the survival rate of islets remains low.

The scarcity of islets is a significant obstacle hindering the widespread use of islet allograft therapy. According to the Network of Organ Procurement and Transplantation, in 2011, only 1562 pancreases were recovered from 8000 donor organs available in the United States. Furthermore, many donated pancreases are not suitable for islet extraction or do not fit the selection criteria. It is also common for islets to be handled incorrectly. For these reasons, only a small number of islet transplantations can be carried out[5].

Some restrictions were found in the technical development of islet transplantation: the number of donor pancreases available for islet transplantation, below that required for healing the millions of people with type 1 diabetes; technical difficulties and the cost of islet isolation; poor durability of insulin independence; and autoimmunity and rejection after transplantation, which must still be overcome. It is therefore essential to develop an unlimited source of cells capable of secreting insulin in response to glucose and that can be transplanted with little or no need for systemic immunosuppression[6-7].

The purpose of the present study was to review experimental allotransplantation procedures that have been attempted in rodents to analyze the parameters involved and the viability of the procedure.

**METHODOLOGY**

***Search process***

The study was performed using the PubMed database to search for published articles containing the keywords "rodent islet transplantation". However, to filter the results, we searched PubMed records for the period January 2000–December 2013 using the following search terms for islet allotransplantation in rodents: “{rodent islet transplantation AND ["2000"(Date-Completion): "3000"(Date-Completion) AND (allotransplantation) NOT porcine] NOT tilapia} NOT nonhuman primate”.

This ensured that articles discussing transplantation in porcine, tilapia and nonhuman primates (more common species used for transplantation) were excluded from the review to focus on those articles related to allotransplantation in rodents. Following the PubMed search, we reviewed the references from the publications retrieved and obtained the entire text of publications that could potentially be included in the systematic review. Unpublished studies and letters were ignored. Studies that did not have a full text available in English were purchased for review.

Eligible studies were selected for analysis based on the following inclusion criteria:- (1) studies must be related to allotransplantation; (2) the species studied must be rodent species; and (3) articles must be relevant and the information up to date.

The review was written in English, and the relevant information, such as donor/recipient, immunosuppression, allotransplantation site, graft survival time, glucose variations and diabetes induction method, was organized into tables.

***Data abstraction***

The authors abstracted the characteristics of the study, such as the source(s) for experimental (*e.g.,* medical records and clinical databases) and relevant data, into the tables-donor/recipient; immunosuppression; allotransplantation site; graft survival time; glucose variations; and diabetes induction method.

**RESULTS**

A total of 2650 articles from 2000 to 2013 were found. Only 25 articles were related to allotransplantation. These articles were selected based on their relevance and updated information (Tables 1-6; Figure 1A and B).

**DISCUSSION**

Islet transplantation has the potential to provide an adequate supply of insulin to the transplanted patient and provide a solution to the problem of islet donor shortage[6].

The first successful islet transplantation for the surgical treatment of diabetes occurred in 1990 by Shapiro *et al*[7] Insulin independence was achieved in a patient with type 1 diabetes at one month post-transplant. However, many technical difficulties were found that needed to be overcome to continue the development of this technique and reproduce this experiment. In the decade between 1991 and 2000, 450 islet transplantation attempts were made in type 1 diabetic patients, with a success rate of only 8%. Fifty percent of successful cases were reported when patients had become diabetic because they were undergoing a pancreatectomy.

Then, in 1999/2000, Shapiro *et al*[7] successfully achieved insulin independence in 7 diabetic patients by performing experiments based on the modified Edmonton protocol[2,7].

Islet transplantation has increasingly been shown to reduce morbidity 20-fold compared to pancreas transplant because it is surgically less invasive[8].

In the present study, we reviewed studies consisting of rodents similar in age and weight undergoing allograft transplantation. Strains of mice aged 6-12 wk and weighing 200 g to 350 g were used. According to these studies (Table 3), C57BL/6 (B6) and Balb/c were the most commonly used strains in allograft experiments as both islet donors (23.8% and 16.67%) and as islet recipients (28.57% and 16.67%). However, no significant difference was observed in the results obtained using other strains.

The efficacy of combined immunosuppressive drug therapy on islet transplantation in rodents has been widely studied. Among these studies, Fotiadis *et al*[9] tested the effects of cyclosporine A (CsA) given in combination with mycophenolate mofetil (MMF) and found that the survival rate increased significantly compared to the isolated use of CsA and MMF; this observation was presumably due to its lower toxicity in the combined regimen.

Nishimura *et al*[11] conducted studies with tacrolimus and demonstrated a suppression in vascular endothelial growth factors, protein kinase 14 activated by mythogen, tissue factor F, specific cyclin D1 for G1/S cell division and protein kinase 4. Thus, they concluded that the drug inhibits pancreatic islet revascularization. However, hypoxia-inducible factor 1 alpha (HIF1A) was not observed. Thus, there was a minor engraftment of islets and subsequent degeneration. Furthermore, no differences were observed in gene expression between the control group and the group receiving tacrolimus.

Wee *et al*[14] studied the effects of tautomycetin and concluded that it does not affect the viability of the islets and spleen, but it is capable of inhibiting the proliferation of T cells. When tautomycetin was combined with subtherapeutic doses of CsA, it led to increased survival of islets. A dose of CsA of 15 mg/kg prolonged the survival of islets the longest. Thus, the mixture of tautomycetin with CsA or other calcineurin inhibitors increased islet survival.

Merani *et al*[10] demonstrated that inhibition of PKC using the new drug AEB -071 slowed the rejection of islet allografts in rodents. Furthermore, addition of CsA therapy with 5 mg/kg AEB prevented graft rejection in 80% of the rats transplanted by immunosuppressive action of the complement system and had no toxic effects.

Watanabe *et al*[16] conducted studies with DHMEQ, an inhibitor of NF-kß, and concluded that the proinflammatory responses activated by HMGB1 were reduced. Moreover, the immunosuppression allows allograft acceptance even in cases where only a few islets were transplanted.

Xekouki *et al*[19] analyzed the effects of CsA and MMF. Their results suggest a beneficial effect of MMF in maintaining the architecture of the islets without prominent side effects in other organs, such as the kidneys or liver.

Baker *et al*[20] studied CXCR3 gene deletion and αIP-10 antibody therapy and concluded that they modulate post-transplant lymphocytic infiltration into the graft and contribute to prolonging allograft survival.

Fan *et al*[26] concluded that the simultaneous blockade of LIGHT and CD28 prolongs graft survival because of a synergistic effect; the presence of T-regulatory cell activity develops donor-specific immunological tolerance. Moreover, prevention of allograft rejection and induction of donor-specific tolerance in lymphocyte-sufficient recipients can be achieved by local cotransplantation of the allografts with regulatory T cells.

Jung *et al*[27] concluded that the combination of Ros A and MR1 in a murine allogeneic islet transplantation model prolonged graft survival compared to the MR1-alone treatment group.

Påhlman *et al*[28] evaluated the immunosuppressive limitations of AR-C117977, an immunosuppressant drug that maintains long-term graft survival and induces operational tolerance, and concluded that AR-C117977 combined with CsA resulted in significant prolongation of graft survival compared with AR-C117977 or CsA therapy alone. Furthermore, CsA therapy alone did not prevent acute rejection.

Wang *et al*[29] studied local expression of B7-H4 and concluded that it prolongs islet allograft survival in vivo.

Studies investigating immunosuppressant drugs and their toxic effects on islets in vivo are still in development. The most utilized immunosuppressants were CsA, MMF and CTLA4 Ig, as shown in Table 4. The concomitant use of glucocorticoids was associated with high rejection rates and is not recommended. Their immunosuppressive and toxic effects have not been rigorously tested, and studies are still underway.

In relation to the different locations for transplantation studied according to the table, the kidney capsule was the most frequently used site for transplantation. Second was the portal vein in the liver[14]. The spleen[9,19],intraperitoneal site[32], bone marrow (tibia)[13], dorsal skin fold-intra-abdominal[30] nonmetallic chamber[11] or subcutaneous[22] was used in a small percentage of studies.

In our review of the studies, it was found that the highest survival rate was obtained by Wee *et al*[14], who used the portal vein (liver) as the site of allograft transplantation and sacrificed the mice at 100 days postoperative. Melzi *et al*[24], Watanabe *et al*[16] and Merani *et al*[10] obtained a survival rate of 100 d, where the site of engraftment was the kidney capsule.

It is important to note that there was no standard level of hyperglycemia that the mice must present to be recipients of islet transplantation. A range of blood glucose levels from 180 mg/dL to 500 mg/dL was observed, as shown in Table 7.

 The articles have many independent variables that influence the study results, such as species of rodent, immunosuppressant drugs and dosages, criteria for diabetes and allograft site. Thus, more research is needed to develop the ideal allograft model of islet transplantation.

**CONCLUSION**

Based on the analyzed studies, we can infer that islet allotransplantation in rodents is promising and continues to develop. The survival rates of allografts have increased with the discovery of new immunosuppressive drugs and the use of different graft sites. These advancements have the potential to overcome the scarcity of islet donors and improve the treatment of type 1 diabetes.

**REFERENCES**

1 **Delfino VDA,** Mocelin AJ. Transplante de Pâncreas e de Ilhotas Pancreáticas: Visão de Nefrologista. *Arq Bras Endocrinol Metab* 2002; **46**: 177-185 [DOI: 10.1590/S0004-27302002000200011]

2 **Chaves G.** Incidência de diabetes tipo 1 aumenta 3% ao ano. Minas Gerais: Saúde Plena; 2013 [updated 2013 July 21; cited 2013 July 22]. Available from: URL: http: //sites.uai.com.br/app/noticia/saudeplena/noticias/2013/07/22/noticia\_saudeplena,144088/incidencia-de-diabetes-tipo-1-aumenta-3-ao-ano.shtml

3 Sociedade Brasileira de Diabetes [Internet]. São Paulo: Sociedade Brasileira de Diabetes; 2012 [cited 2012 April 18]. Available from: URL: http: //www.diabetes.org.br/sala-de-noticias/2116-sao-12-milhoes-de-diabeticos-no-brasil

4 **Merani S**, Shapiro AM. Current status of pancreatic islet transplantation. *Clin Sci* (Lond) 2006; **110**: 611-625 [PMID: 16689680 DOI: 10.1042/CS20050342]

5 **United States of America.** National Institute of Diabetes and Digestive and Kidney Diseases. Pancreatic Islet Transplantation. NIH Publication 07–4693; 2007.

6 **Eliaschewitz DG,** Franco DR, Mares-Guia TR, Noronha IL, Labriola L, Sogayar MC. Transplante de ilhotas na prática clínica: estado atual e perspectivas. *Arq Bras Endocrinol Metab* 2009; **53**: 15-23 [PMID: 19347181 DOI: 10.1590/S0004-27302009000100004]

 7 **Shapiro AM**, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000; **343**: 230-238 [PMID: 10911004 DOI: 10.1056/NEJM200007273430401]

8 **Ryan EA**, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, Lakey JR, Shapiro AM. Five-year follow-up after clinical islet transplantation. *Diabetes* 2005; **54**: 2060-2069 [PMID: 15983207 DOI: 10.2337/diabetes.54.7.2060]

9 **Fotiadis C**, Xekouki P, Papalois AE, Antonakis PT, Sfiniadakis I, Flogeras D, Karampela E, Zografos G. Effects of mycophenolate mofetil vs cyclosporine administration on graft survival and function after islet allotransplantation in diabetic rats. *World J Gastroenterol* 2005; **11**: 2733-2738 [PMID: 15884112]

10 **Merani S**, Pawlick RL, Edgar RL, Toso C, Emamaullee J, Anderson CC, Shapiro AM. Protein kinase C inhibitor, AEB-071, acts complementarily with cyclosporine to prevent islet rejection in rats. *Transplantation* 2009; **87**: 59-65 [PMID: 19136892 DOI: 10.1097/TP.0b013e31819198b4]

11 **Nishimura R**, Nishioka S, Fujisawa I, Shiku H, Shimada M, Sekiguchi S, Fujimori K, Ushiyama A, Matsue T, Ohuchi N, Satomi S, Goto M. Tacrolimus inhibits the revascularization of isolated pancreatic islets. *PLoS One* 2013; **8**: e56799 [PMID: 23613708 DOI: 10.1371/journal.pone.0056799]

12 **Makhlouf L**, Duvivier-Kali VF, Bonner-Weir S, Dieperink H, Weir GC, Sayegh MH. Importance of hyperglycemia on the primary function of allogeneic islet transplants. *Transplantation* 2003; **76**: 657-664 [PMID: 12973104 DOI: 10.1097/01.TP.0000080881.75767.0E]

13 **Salazar-Bañuelos A**, Wright JR, Sigalet D, Benítez-Bribiesca L. Pancreatic islet transplantation into the bone marrow of the rat. *Am J Surg* 2008; **195**: 674-68; discussion 678 [PMID: 18424287 DOI: 10.1016/j.amjsurg.2007.12.040]

14 **Wee YM**, Choi MY, Kang CH, Kim YH, Kim JH, Lee SK, Yu SY, Kim SC, Han DJ. The synergistic effect of Tautomycetin on Cyclosporine A-mediated immunosuppression in a rodent islet allograft model. *Mol Med* 2005; **16**: 298-306 [PMID: 20440443 DOI: 10.2119/molmed.2009.00099]

15 **Plesner A,** Liston P, Tan R, Korneluk RG, Verchere CB. Diabetes.The X-linked inhibitor of apoptosis protein enhances survival of murine islet allografts. *Diabetes* 2005; **54**: 2533-2540 [PMID: 16123340]

16 **Watanabe M**, Yamashita K, Kamachi H, Kuraya D, Koshizuka Y, Shibasaki S, Asahi Y, Ono H, Emoto S, Ogura M, Yoshida T, Ozaki M, Umezawa K, Matsushita M, Todo S. Efficacy of DHMEQ, a NF-κB inhibitor, in islet transplantation: II. Induction DHMEQ treatment ameliorates subsequent alloimmune responses and permits long-term islet allograft acceptance. *Transplantation* 2013; **96**: 454-462 [PMID: 23860082 DOI: 10.1097/TP.0b013e31829b077f]

17 **Gysemans CA**, Waer M, Valckx D, Laureys JM, Mihkalsky D, Bouillon R, Mathieu C. Early graft failure of xenogeneic islets in NOD mice is accompanied by high levels of interleukin-1 and low levels of transforming growth factor-beta mRNA in the grafts. *Diabetes* 2000; **49**: 1992-1997 [PMID: 11117999 DOI: 10.2337/diabetes.49.12.1992]

18 **Xekouki P,** Papalois A, Fotiadis C, Sfiniadakis J, Karampela E, Papadopoulou A et al. In vivo test of two low doses of mycophenolate mofetil in an experimental model of islet allotransplantation. *Transplant Proc* 2002; **34**: 1446-1448 [DOI: 10.1016/S0041-1345(02)02922-6]

19 **Baker MS**, Chen X, Rotramel AR, Nelson JJ, Lu B, Gerard C, Kanwar Y, Kaufman DB. Genetic deletion of chemokine receptor CXCR3 or antibody blockade of its ligand IP-10 modulates posttransplantation graft-site lymphocytic infiltrates and prolongs functional graft survival in pancreatic islet allograft recipients. *Surgery* 2003; **134**: 126-133 [PMID: 12947308 DOI: 10.1067/msy.2003.213]

20 **Li X**, Chen H, Epstein PN. Metallothionein protects islets from hypoxia and extends islet graft survival by scavenging most kinds of reactive oxygen species. *J Biol Chem* 2004; **279**: 765-771 [PMID: 14576162 DOI: 10.1074/jbc.M307907200]

21 **Vieiro M**, Ceballos C, Barrionuevo P, Hyon SH, Isturiz M, Argibay P. Inhibition of allospecific response in pancreatic islet transplantation: the glycan approach. *Transplant Proc* ; **37**: 243-244 [PMID: 15808608 DOI: 10.1016/j.transproceed.2004.12.298]

22 **Neuzillet Y**, Giraud S, Lagorce L, Eugene M, Debre P, Richard F, Barrou B. Effects of the molecular weight of peg molecules (8, 20 and 35 KDA) on cell function and allograft survival prolongation in pancreatic islets transplantation. *Transplant Proc* 2006; **38**: 2354-2355 [PMID: 16980088 DOI: 10.1016/j.transproceed.2006.06.117]

23 **Melzi R**, Battaglia M, Draghici E, Bonifacio E, Piemonti L. Relevance of hyperglycemia on the timing of functional loss of allogeneic islet transplants: implication for mouse model. *Transplantation* 2007; **83**: 167-173 [PMID: 17264813 DOI: 10.1097/01.tp.0000250659.24286.43]

24 **Fiorina P**, Jurewicz M, Tanaka K, Behazin N, Augello A, Vergani A, von Andrian UH, Smith NR, Sayegh MH, Abdi R. Characterization of donor dendritic cells and enhancement of dendritic cell efflux with CC-chemokine ligand 21: a novel strategy to prolong islet allograft survival. *Diabetes* 2007; **56**: 912-920 [PMID: 17287465 DOI: 10.2337/db06-1445]

25 **Fan K**, Wang H, Wei H, Zhou Q, Kou G, Hou S, Qian W, Dai J, Li B, Zhang Y, Zhu T, Guo Y. Blockade of LIGHT/HVEM and B7/CD28 signaling facilitates long-term islet graft survival with development of allospecific tolerance. *Transplantation* 2007; **84**: 746-754 [PMID: 17893608 DOI: 10.1097/01.tp.0000280545.14489.df]

26 **Jung da Y**, Kim EY, Joo SY, Park JB, Moon C, Kim SH, Sim EY, Joh JW, Kwon CH, Kwon GY, Kim SJ. Prolonged survival of islet allografts in mice treated with rosmarinic acid and anti-CD154 antibody. *Exp Mol Med* 2008; **40**: 1-10 [PMID: 18305392 DOI: 10.3858/emm.2008.40.1.1]

27 **Påhlman C**, Malm H, Qi Z, Veress B, Ferguson D, Bundick R, Murray C, Donald D, Ekberg H. Operational tolerance in nonvascularized transplant models induced by AR-C117977, a monocarboxylate transporter inhibitor. *Transplantation* 2008; **86**: 1135-1138 [PMID: 18946353 DOI: 10.1097/TP.0b013e318186b978]

28 **Wang X**, Hao J, Metzger DL, Mui A, Ao Z, Verchere CB, Chen L, Ou D, Warnock GL. Local expression of B7-H4 by recombinant adenovirus transduction in mouse islets prolongs allograft survival. *Transplantation* 2009; **87**: 482-490 [PMID: 19307783 DOI: 10.1097/TP.0b013e318195e5fa]

29 **Chen X**, Shao W, Chen JB, Zhang L, Matthias C, Shan SG, Qi ZQ. Allotransplantation of sulphate glucomannan-alginate barium (SGA)-microencapsulated rat islets for the treatment of diabetes mellitus. *Immunol Invest* 2009; **38**: 561-571 [PMID: 19811421 DOI: 10.1080/08820130902984828]

30 **Giraud S**, Bon D, Neuzillet Y, Thuillier R, Eugene M, Hauet T, Barrou B. Concentration and chain length of polyethylene glycol in islet isolation solution: evaluation in a pancreatic islet transplantation model. *Cell Transplant* 2012; **21**: 2079-2088 [PMID: 22507302 DOI: 10.3727/096368912X638928]

31 **Qi Z**, Yamamoto C, Imori N, Kinukawa A, Yang KC, Yanai G, Ikenoue E, Shen Y, Shirouzu Y, Hiura A, Inoue K, Sumi S. Immunoisolation effect of polyvinyl alcohol (PVA) macroencapsulated islets in type 1 diabetes therapy. *Cell Transplant* 2012; **21**: 525-534 [PMID: 22793061 DOI: 10.3727/096368911X605448]

32 **Potiron N**, Chagneau C, Boeffard F, Soulillou JP, Anegon I, Le Mauff B. Adenovirus-mediated CTLA4Ig or CD40Ig gene transfer delays pancreatic islet rejection in a rat-to-mouse xenotransplantation model after systemic but not local expression. *Cell Transplant* 2005; **14**: 263-275 [PMID: 16052908 DOI: 10.3727/000000005783983052]

33 **Jahr H**, Hussmann B, Eckhardt T, Bretzel RG. Successful single donor islet allotransplantation in the streptozotocin diabetes rat model. *Cell Transplant* 2002; **11**: 513-518 [PMID: 12428740]

**P-Reviewers:** Oh SH **S-Editor:** Qi Y **L-Editor: E-Editor:**

**Figure 1Quantitative and comparative analysis of the different donor strains (A) and recipient strains (B).**

**A**



B



**Table 1 Description of the experimental studies on allografts in rodents**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Donor/Recipient** | **Immunosuppression** | **Allotransplantation Site** | **Graft Survival Time** |
| Fotiadis *et al*[9] | Lewis→ Wistar | Mycophenolate mofetil (MMF) and Cyclosporine A (CsA) | Spleen | N/A |
| Merani *et al*[10] | Lewis→ Wistar | AEB-071 (Protein kinase C inhibitor) + CsA, CTLA4-Ig, MMF | Kidney capsule | 100 d |
| Nishimura *et al*[11] | C57BL/6 → Balb/c  | Tacrolimus | Nonmetallic dorsal skinfold chamber | N/A |
| Makhlouf *et al*[12] | C57BL/6/Balb/c | Blockade of CD28:B7 and anti-CD40L; CTLA-4 | Kidney capsule | 1 wk  |
| Salazar-Bañuelos *et al*[13] | Wistar→ Sprague Dawley | No immunosuppression | Medullary channel | 21 d |
| Wee *et al*[14] | Lewis→ Fisher | CsA + Tautomycetin (synergist) | Liver (portal vein) | Control group - 5.2 d ± 0.5TMC – 5.1 d ± 0.9 TMC (0.03 mg/kg) + CsA (5 mg/kg) - > 41 days TMC (0.1 mg/kg) + CsA (5 mg/kg) - 103.8 d ± 56.8 |
| Plesner *et al*[15] | Balb/c→ EBA | No immunosuppression | Kidney capsule | 60 d |
| Watanabe *et al*[16] | Balb/c→ C57BL/6 | Tacrolimus and DHMEQ (NF-kB inhibitor) | Kidney capsule | 100 d |
| Gysemans *et al*[17] | Balb/c→ C57BL/6 | No immunosuppression | Kidney capsule | 9.2 ± 4.9 d (Autoimmune diabetes)15 ± 3 d (Not chemically diabetic autoimmune) |
| Xekouki *et al*[18] | Wistar→Lewis | CsA and MMF | Spleen (parenchyma) | 8 d (CsA)10.92 days (MMF × 1)11 d (MMF × 2) |
| Baker *et al*[19] | A/J→ C57Bl/6J | Monoclonal antibody antiBIP-10  | Kidney capsule | 19.7 ± 2.3 d (C57Bl/6J)20.2 ± 2.7 d (CXCR3-/-C57Bl/6J |
| Li *et al*[20] | FVB→ Balb/c | No immunosuppression | Kidney capsule | N/A |
| Vieiro *et al*[21] | C57Bl/6→ C3H | Tritiated thymidine (preoperative) and CsA | Subcutaneous | N/A |
| Neuzillet *et al*[22] | C3H → Balb/c | No immunosuppression | Kidney capsule | 13.8-27.5 d |
| Melzi *et al*[23] | C57Bl/6 → Balb/c | Rapamycin+ FK506+ anti–IL-2Ra chain mAbs and rapamycin+IL-10 | Kidney capsule | > 100 d |
| Fiorina *et al*[24] | Balb/c→ C57Bl/6 | No immunosuppression | Kidney capsule | 14 d |
| Fan *et al*[25] | C57Bl/6 → Balb/c | LTß R-Ig, CTLA4-Ig or LTR mAb anti mouse | Kidney capsule | LTß R-Ig-27 daysCTLA4-Ig-55 dLTß R-Ig+CTLA4-Ig - > 100 dLTR mAb anti mouse - 11 d |
| Jung *et al*[26] | Balb/c → C57Bl/6 | CD154 mAb (MR1) anti mouse and ROS-A (Reactive Oxygen Specie - A) | Kidney capsule | ROS-A - 53 dMR1 - 82 dROS-A+MR1 - > 160 d |
| Påhlman *et al*[27] | Balb/c → C57Bl/6J | AR-C117977 (10 or 30 mg/kg) or CsA 20 mg/kg | Kidney capsule | CsA - 16 dAR-C117977, 10 mg/kg - >100 dAR-C117977, 30 mg/kg -29,33 d |
| Wang *et al*[28] | Balb/c → C57Bl/6 | B7-H4 and Ad-LacZ | Kidney capsule | B7-H4 - approximately 60 dAd-LacZ - approximately > 20 d |
| Chen *et al*[29] | Sprague Dawley → Lewis | No immunosuppression | Intra-abdominal | 8 wk |
| Giraud *et al*[30] | C3H → Balb/c | No immunosuppression | Kidney capsule | SCOT + PEG20 kDa ³10 g/L - 20 d,CMRL-1066 + 1% BSA - 17.5 ± 1 d,Solution UW - 17.2 ± 0.4 d, SCOTwithout PEG -14 ± 0.9 dSolution HBSS + 0.5% BSA - 14 ± 0.7 d |
| Qi *et al*[31] | Wistar/Lewis → Lewis | No immunosuppression | Intraperitoneal (Macroencapsulated)Kidney capsule (not macroencapsulated) | 24 wk (Macroencapsulated)48 h (not macroencapsulated) |
| Potiron *et al*[32] | Wistar → C57Bl/6 | CTLA4 Ig or CD40 Ig | Kidney capsule | 24.3 (± 9.7) d |
| Jahr *et al*[33] | Lewis → Wistar | Anti-rat antilymphocyte serum | Liver (portal vein) |  |

N/A: Not Available.

**Table 2 Sites of islet infusion based on the literature from the PubMed database**

|  |  |
| --- | --- |
| **Sites of islet infusion** | **Literature from the PubMed database** |
| Kidney capsule | 70% |
| Liver | 23% |
| Other sites1 | 7% |

1Subcutaneous, bone marrow, sub-retinal space, sub-conjunctival space, spleen, intraperitoneal cavity and sub-mucosal space of the duodenum.

**Table 3 Comparative analysis of the different types of rodents used and their basic characteristics-Age and Weight**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Donor/recipient** | **Age** | **Weight** |
| Fotiadis *et al*[9] | Lewis→ Wistar | N/A | 220 g-300 g |
| Merani *et al*[10] | Lewis→ Wistar | N/A | 200 g (male)/150 g (female) |
| Nishimura *et al*[11] | C57BL/6 → Balb/c  | 9-12 wk /8-12 wk | N/A |
| Makhlouf *et al*[12] | C57BL/6→ Balb/c | 6-8 wk (male)/ N/A | N/A |
| Salazar-Bañuelos *et al*[13] | Wistar→ Sprague Dawley | N/A | 260 -326 g |
| Wee *et al*[14] | Lewis→ Fisher | 10-12 wk | N/A |
| Plesner *et al*[15] | Balb/c→ EBA | 8-10 wk /N/A | N/A |
| Watanabe *et al*[16] | Balb/c→ C57BL/6 | 10-14 wk /male | N/A |
| Gysemans *et al*[17] | Balb/c→ C57BL/6 | (8-21 d) → (> 180 d) | N/A |
| Xekouki *et al*[18] | Wistar→Lewis | N/A/male | 220 -300 g |
| Baker *et al*[19] | A/J→ C57Bl/6J | 8-12 d/male | N/A |
| Li *et al*[20] | FVB→ Balb/c | 8-12 wk | N/A |
| Vieiro *et al*[21] | C57Bl/6→ C3H | N/A | N/A |
| Neuzillet *et al*[22] | C3H → Balb/c | N/A | N/A |
| Melzi *et al*[23] | C57Bl/6 → Balb/c | 9 wk (female) → 9 wk (female) | 20 -22 g |
| Fiorina *et al*[24] | Balb/c→ C57Bl/6 | N/A | N/A |
| Fan *et al*[25] | C57Bl/6 → Balb/c | N/A - adults (female) | N/A |
| Jung *et al*[26] | Balb/c → C57Bl/6 | 12 wk (male) → 12 wk (male)  | 25 -30 g |
| Påhlman *et al*[27] | Balb/c → C57Bl/6J | N/A - (female) | N/A |
| Wang *et al*[28] | Balb/c → C57Bl/6 | 8-10 wk (female) → 8-10 wk | N/A |
| Chen *et al*[29] | Sprague Dawley → Lewis | N/A (male) | 250 -350 g → 196 (± 15 g) |
| Giraud *et al*[30] | C3H → Balb/c | 6 wk | N/A |
| Qi. *et al*[31] | Wistar/Lewis → Lewis | 9-10 wk (male) | 250 -300 g |
| Potiron *et al*[32] | Wistar → C57Bl/6 | N/A (male) | 200 -300 g |
| Jahr *et al*[33] | Lewis → Wistar | N/A (male)--> N/A (male) | 310 -330 g→ 215 -245 g |

N/A: Not available.

**Table 4 Analysis of the immunosuppressant drugs used at international islet transplantation research centers**

|  |  |
| --- | --- |
| **Immunosuppressant** | **Number of centers using the immunosuppressant (based on data from the literature)** |
| CsA | 6 |
| MMF | 3 |
| CTLA4 Ig | 4 |
| CD40 Ig | 2 |
|  NF-kB Inhibitor (DHMEQ) | 1 |
| Anti-CD154 mAb (MR1)  | 2 |
| Tritiated thymidine | 1 |
| Tacrolimus | 1 |
| Blockade of CD28:B7  | 1 |
| Tautomycetin | 1 |
| Protein Kinase C Inhibitor (AEB-071) | 1 |
| Monoclonal antibody anti-BIP-10  | 1 |
| Rapamycin+FK506+anti–IL-2Ra chain mAbs, n31 and rapamycin+IL-10; n29 | 1 |
| LTß R-Ig | 1 |
| LTR mAb  | 1 |
| ROS-A  | 1 |
| AR-C117977 | 1 |
| B7-H4 and Ad-LacZ | 1 |
| Anti-rat antilymphocyte serum | 1 |
| No immunosuppression | 9 |

**Table 5 Quantitative analysis of immunosuppressant drugs use**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Immunosuppression** | **Dose** | **Administration frequency** |
| Fotiadis *et al*[9] | MMF and CsA | 12 mg/kg and 23 mg/kg (MMF)5 mg/kg (CsA) | - |
| Merani *et al*[10] | AEB-071 (Protein Kinase C Inhibitory) + CsA, CTLA4-Ig, MMF | 30 mg/kg (AEB-071)2.5 mg/kg and 5 mg/kg (CsA)0.25 mg (CTLA4-Ig Intraperitoneal)10 mg/kg (MMF) | 2 times a day, oral (AEB-071)2 times a day, oral (CsA) 0, 2, 4 and 6 PO, Intraperitoneal (CTLA4-Ig)Once a day, oral (MMF) |
| Nishimura *et al*[11] | Tacrolimus | 0.5 mg/kg | Infused subcutaneously - Daily - for 14 d |
| Makhlouf *et al*[12] | Blockade of CD28:B7 and anti-CD40 L; CTLA-4 | 250 µg | Intraperitoneal - 0, 2, 4 and 6 PO  |
| Wee *et al*[14] | CsA+Tautomycetin (Synergist) | 5 mg/g and 15 mg/kg (CsA) | Once a day for 7 d |
| Watanabe *et al*[16] | Tacrolimus and DHMEQ  | 1.5 mg/kg (Tacrolimus)20 mg/kg (DHMEQ) | Once a day 0 to 3 PO and2 times a day 0 to 14 PO (DHMEQ); 0 to 14 PO (Tacrolimus);Once a day 0 to 3 PO (DHMEQ)+0 to 14 PO (Tacrolimus) |
| Xekouki *et al*[18] | CsA and MMF1 | 5 mg/kg (CsA)12 mg/kg (MMF)23 mg/kg (MMF) | Oral - Daily - 12 consecutive days  |
| Baker *et al*[19] | Monoclonal antibody antiBIP-10  | 300 μg intraperitoneal | Daily - 14 d1 |
| Vieiro *et al*[21] | Tritiated thymidine (preoperative) and CsA | 20 mg/kg (CsA) | N/A |
| Melzi *et al*[23] | Rapamycin+ FK506+ anti–IL-2Ra chain mAbs and rapamycin+IL-10 | 1 mg/kg (Rapamycin)0.05 µg/kg (IL-10) 0.3 mg/kg (FK506)1 mg/kg (mAbs) | Intraperitoneal: Once a day - 30 PO (Rapamycin)2 times a day - 30 d (IL-10)Once a day - 30 d (FK506)0.4 PO (mAbs) |
| Fan *et al*[25] | LTß R-Ig, CTLA4-Ig orLTR mAb anti mouse | 200 µg | Intraperitoneal- days -1, 1, 3, 5, 7 and 9 |
| Jung *et al*[26] | CD154 mAb (MR1) anti mouse + ROS-A  | 250 µg (CD154 mAb (MR1) anti mouse)200 mg/kg of Ros A  | Intraperitoneal injection 0, 2, 4, 6 and 8 PO (CD154 mAb (MR1) anti mouse)8 consecutive days (ROS-A) |
| Påhlman *et al*[27] | AR-C117977 or CsA  | 0.2 mL - 3, 10, 30, or 100 mg/kg(AR-C117977)0.5 mL - 20 mg/kg (CsA) | Subcutaneous - once a day 0 to 9 PO (AR-C117977)Once a day 0-9 PO or 0-39 PO (CsA) |
| Wang *et al*[28] | B7-H4 | 5 plaque-forming units (pfu) of Ad-B7-H4 or Ad-LacZ | N/A |
| Potiron *et al*[32] | CTLA4 Ig or CD40 Ig | 5 × 109 IP of AdCTLA4 IM and/or 5 × 109 IM or 2 × 109 IV of AdCD40Ig;IM administration: 10 µL per point (3 points)IV administration: 150 µL with 0.9% sodium chloride | IM administration - anterior tibialis muscle;IV administration - venile vein |
| Jahr *et al*[33] | Anti-rat antilymphocyte serum | Intraperitoneal administration 0.5 mL | 1 d after islet transplantation |

1First dose administered 4 hours preoperatively. N/A: Not available.

**Table 6 Analysis of induction and treatment of diabetic process with islet transplantation**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Number of transplanted islets** | **Diabetes induction method** | **Hyperglycemia induction (preoperative)** | **Normalization of hyperglycemia (postoperative)** | **Graft rejection** | **Criteria for Primary Graft Dysfunction (PGD)** |
| Fotiadis *et al*[9] | 1812 ± 145 | Streptozotocin (60 mg/kg) + PBS-Solution (Phosphate Buffer Solution) - 10 mg/mL (pH 4,5);  | 7 d | 3 d | 12 d (MMF)10 d (CsA) | Glucose above 200 mg/dL; after 2nd PO 2 consecutive times |
| Merani *et al*[10] | 1500 | Streptozotocin (75 mg/kg) intraperitoneal | 5 d | 3 d | 22 d | Glucose above 324 mg/dL after 2 consecutive days |
| Nishimura *et al*[11] | 2-10/dorsal skinfold chamber | - | - | - | N/A | - |
| Makhlouf *et al*[12] | 350 (Balb/c)700 (NOD) | Streptozotocin and spontaneously (225 mg/kg in peritoneal cavity) | 2 wk | 3 d  | 10 d (Balb/c)5 d (NOD) and 7 days complete rejection (NOD) | 200 mg/dL - 2 to 3 consecutive days |
| Salazar-Bañuelos *et al*[13] | 840 (of Wistar) | - | - | - | N/A1 | N/A |
| Wee *et al*[14] | 4000 | Streptozotocin (35 mg/kg) | N/A | N/A | Untreated - 5.2 days (± 0.5)TMC - 5,1 days (± 0,9) TMC (0.03 mg/kg) + CsA (5 mg/kg) - >41 days TMC (0.1 mg/kg) + CsA (5 mg/kg) - 103.8 days ± (56.8) | 200 mg/dL after 2 consecutive days |
| Plesner *et al*[15] | 550 | Streptozotocin (375 mg/dL) intraperitoneal | 3-5 d | 5 d1 | 60 d | ≥ 198 mg/dL after 2 consecutive days |
| Watanabe *et al*[16] | 600 or 300 | Streptozotocin (180 mg/kg) intraperitoneal | 5-7 days | N/A | 69 d (Tacrolimus)100 d (DHMEQ 3 d and Tacrolimus 14 d) | > 350 mg/dL for 2 dconsecutive days  |
| Gysemans *et al*[17] | 300 | Alloxan (90 mg/kg) | 24 h  | N/A | N/A - 23% | Glucose level > 200 mg/dL more than 3 consecutive days  |
| Xekouki *et al*[18] | 2000 | Streptozotocin (60 mg/kg) diluted in phosphated solution 10 mg/mL | 1 wk | N/A | 7 d (MMF × 1) | - |
| Baker *et al*[19] | 300 | Streptozotocin (220 mg/kg) | N/A | N/A | 7 d | - |
| Li *et al*[20] | 400 (200/Kidney capsule) | Streptozotocin (220 mg/kg) | N/A | N/A | 8.36 ± 1.67 (islets of FVB)16.2 ± 2.52 (islets of MT) | Glucose levels > 250 mg/dL - 2 consecutive measurements |
| Vieiro *et al*[21] | 200 | Streptozotocin (270 mg/kg) intraperitoneal | N/A | N/A | 3-7 d | ≥ 250 mg/dL - 3 consecutive measurements |
| Neuzillet *et al*[22] | 550 | N/A | N/A | 4 h | PEG-Solution 8 kDa 27.50 ±3.70 d; PEG PEG-Solution 20 kDa 23.13 ± 4.39d; PEG-Solution 35 kDa 13.80± 3.49 d | > 199.8 mmol//L - 2 consecutive measurements |
| Melzi *et al*[23] | 400 | 175 a 200 mg/kg intravenous | 1-2 weeks | 5 d | 29 d (mouse with Glucose levels < 450 mg/dL) and 16 d (mouse with Glucose levels > 450 mg/dL) | > 250 mg/dL - 2 consecutive measurements on postoperative |
| Fiorina *et al*[24] | NA | Streptozotocin | N/A | N/A | 14 d | N/A |
| Fan *et al*[25] | 500 | Streptozotocin(200 mg/kg) | N/A | N/A | 27 d (LT[α] R-Ig)55 d (CTLA4-Ig)After 100 days or more (LT[β] R-Ig and CTLA4-Ig) | > 300 mg/dl - after 2 consecutive days |
| Jung *et al*[26] | 300 IEQ | Streptozotocin (180 mg/kg) | N/A | 1 d | ROS-A - 53 dMR1 - 82 dROS-A+MR1 - > 160 d | > 200 mg/dL - 2 consecutive measurements on the same week |
| Påhlman *et al*[27] | 500-600 | AlloxanIntravenous | N/A | N/A | CsA - 16 daysAR-C117977, 10 mg/kg - > 100 dAR-C117977, 30 mg/kg -29,33 d | N/A |
| Wang *et al*[28] | 400 | Streptozotocin (200 mg/kg) | 3-4 d | 3 d | B7-H4 - approximately 60 dAd-LacZ - approximately > 20 d | > 250 mg/dL after primary graft success |
| Chen *et al*[29] | 3000 IEQ | Streptozotocin dissolved in saline (50 mg/kg) | N/A | 1 wk | 13 wk (SGA - microencapsulated)7 wk (ABa- microencapsulated)5 wk (APA- microencapsulated) | N/A |
| Giraud *et al*[30] | 1400 IEQ | Streptozotocin (250 mg/kg), intraperitoneal | N/A | N/A | SCOT + PEG - Solution20 kDa ³10 g/L - 20 d,CMRL-1066 + 1% BSA - Solution 17.5 ± 1 d,UW-Solution - 17.2 ± 0.4 d, SCOTwithout PEG -14 ± 0.9 dHBSS + 0.5% BSA - Solution - 14 ± 0.7 d | > 200 mg/dL - 2 consecutive measurements |
| Qi *et al*[31] | 1940(± 39) | Streptozotocin (55 mg/kg) | 7 d | N/A | N/A | N/A |
| Potiron *et al*[32] | 800-1000 | Streptozotocin (180 mg/kg) | 1 wk | 4 d | 24.3 ± 9.7 d | 250 mg/dL on 2 successive measurements |
| Jahr *et al*[33] | 700-900 | Streptozotocin (55 mg/kg) | 7-10 d | Right after transplantation | 1 wk | > 300 mg/dL after 8.9 ± 0.7 d |

1Rodents that had normalized blood glucose in 5 d were included in the study.

N/A: Not available. IEQ: Islet equivalents.

**Table 7 Analysis of the parameters of hyperglycemia**

|  |  |
| --- | --- |
| **Ref.** | **Blood Glucose Levels: hyperglycemia (mg/dL)** |
| Fotiadis *et al*[9] | 180 on 2 consecutive measurements |
| Merani *et al*[10] | 180 on 3 consecutive days |
| Makhlouf *et al*[12] | Moderate diabetes: between 240 and 350 Severe diabetes: between 351 and 550 Very severe diabetes: more than 550  |
| Wee *et al*[14] | 200 |
| Plesner *et al*[15] | ≥ 360 |
| Watanabe *et al*[16] | 200 on 2 consecutive days |
| Gysemans *et al*[17] | 200 on 2 consecutive days |
| Xekouki *et al*[18] | 300 |
| Baker *et al*[19] | 300 on 3 consecutive days |
| Li *et al*[20] | 350 to 500 after 2 consecutive measurements |
| Melzi *et al*[23] | 250 on 2 consecutive measurements |
| Fan *et al*[25] | 300 on 2 consecutive measurements |
| Jung *et al*[26] | 300 on 2 consecutive days |
| Påhlman *et al*[27] | 288 on 2 consecutive measurements |
| Wang *et al*[28] | 300 after 2 consecutive days |
| Chen *et al*[29] |  302.4 on more than 3 consecutive days |
| Giraud *et al*[30] | 350 after 2 consecutive days |
| Qi *et al*[31] | 450 |
| Potiron *et al*[32] | > 200 |