Novel extrahepatic sites for islet transplantation

Ekaterine Berishvili
Tbilisi State Medical University, Department of Clinical Anatomy; Georgian National Institute of Medical Research, DRI Federation, Tbilisi, Georgia

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Islet Transplantation

1893 - First attempt of sheep pancreas fragments transplantation. Patrick Watson-Williams, Bristol, UK


1974 - First allogenic transplantation in man. David Sutherland, Minneapolis, USA


2000 - 100% insulin independence in 7 consecutive patients. AM James Shapiro, Edmonton, Canada
Islet Transplant Activity (1999-2011)
Improvement in Outcomes of Clinical Islet Transplantation: 1999–2010

Barton F. B. et al. Diabetes Care 2012;35:1436-1445
Factors limiting islet graft function and survival

Alternative Sites for Islet Transplantation

Considerations/Goals:

- Vascularization
- Oxygenation
- Physiological Insulin Delivery
- Minimal Inflammatory Response
- Mechanical Protection
- Accessibility/Retrievability
Alternative Sites for Islet Transplantation

- Omental pouch
- Gastric submucosa
- Intestinal submucosa
- Subcutaneous tissue
- Anterior eye chamber
- Bone marrow
- Isolated venous sac
- Intrapancreatic
- Intrasplenic
- Renal subcapsule
- Skeletal muscle
Intramuscular Autotransplantation of Pancreatic Islets in a 7-Year-Old Child: A 2-Year Follow-Up


aDepartments of Surgery, bMedicine, cPediatric and bTransplantation Surgery, Karolinska Institutet, Karolinska University Hospital in Huddinge, Stockholm, Sweden
bDepartment of Pediatric Endocrinology at Karolinska University Hospital, Solna, Stockholm, Sweden
cDepartment of Clinical Immunology, Uppsala University Hospital, Uppsala, Sweden

dCorresponding author: Ehab Rafael, ehab.rafael@karolinska.se

A 7-year-old girl with severe hereditary pancreatitis underwent total pancreatectomy. A total of 160,000 islet equivalents (6400 islet/kg) were transplanted to the brachioradialis muscle of the right forearm. Her plasma C-peptide level was undetectable after pancreatectomy but increased to 1.37 ng/mL after 17 days; at this time point, her insulin requirement was 0.75 units of insulin/kg/day. At 5- and 27-months, her hemoglobin A1c (HbA1c) and insulin requirements were 4.5 and 5.3% and 0.3 and 0.18 units/kg/day, respectively. Basal and stimulated C-peptide levels were 0.67 ± 0.07 and 3.36 ± 1.37 ng/mL, respectively. Stimulated insulin levels were 30% higher in the islet-bearing arm compared to the contralateral arm after glucagon stimulation. After surgery and islet transplantation, the quality of life autotransplantation (IAT) is indicated for various pancreatic diseases, including complicated chronic pancreatitis, hereditary pancreatitis and benign tumors of the pancreas (2–5). It is well known that the pancreatectomized patients suffer from brittle diabetes, which is characterized by pronounced blood glucose variability and frequent episodes of hypoglycemia, while ketoacidosis is infrequent (6). Already in 1977, Najarian et al., at the University of Minnesota, reported on the first successful intraportal IAT after total pancreatectomy in a patient with chronic pancreatitis (7). The procedure became successful and well established with insulin independence of up to 13 years in the patient with chronic pancreatitis (8).

Allogeneic clinical islet transplantation is currently explored as a treatment for patients with type I diabetes subjected to recurrent severe hypoglycemic episodes. As such, the procedure is successful, and up to 5 years after transplantation, more than 80% of the recipients are protected from hypoglycemic episodes even though a vast majority of patients are reinstalled on insulin therapy at a low dose after a few years (9). The low efficacy of clinical intrahepatic islet allotransplantation is likely to be related to the procedure of intravascular transplantation leading to activation of the instant blood-mediated inflammatory reaction (10) and exposure of the islets to toxic products from the gastrointestinal (GI) tract, including high concentrations of immunosuppressive drugs in allogeneic situation (11).
The anterior chamber of the eye as a clinical transplantation site for the treatment of diabetes: a study in a baboon model of diabetes

Long-Term Survival of Nonhuman Primate Islets Implanted in an Omental Pouch on a Biodegradable Scaffold

<table>
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<th>ID</th>
<th>Days post-STZ</th>
<th>IEQ/kg</th>
<th>EIR pre-Tx</th>
<th>% Drop EIR on POD 14</th>
<th>POD 50% drop in EIR</th>
<th>Max% drop EIR</th>
<th>C-peptid &gt;0.2/ value/FBG</th>
<th>C-peptide &gt;1.0/ value/FBG</th>
<th>Max C-peptide (ng/mL)</th>
<th>Max elective scaffold explant</th>
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Evaluation of Alternative Sites for Islet Transplantation in the Minipig: Interest and Limits of the Gastric Submucosa

R. Calazzo, V. Gmyr, T. Hubert, N. Delalleau, R. Lamberts, E. Moerman, J. Kerr-Conte, and F. Pattou

ABSTRACT

Since the introduction of glucocorticoid-free immunosuppressive regimens, islet transplantation offers a less invasive alternative to pancreas transplantation. However, complications associated with intraportal islet injection and the progressive functional decline of intrahepatic islets encourage the exploration of alternative sites. Herein we evaluated, in the minipig, the use of the gastric submucosa (GS, group 1, n = 5) for islet transplantation compared with the kidney capsule (KC; group 2, n = 5). Subsequently we attempted to improve the vasculization of the submucosal graft (group 3, n = 5) by the addition of an extracellular matrix rich in growth factors (Matrigel). One month after grafting, we evaluated transplanted islet function in vivo and in vitro. Our study showed better function of islets engrafted in the GS than in the KC (P < .05). Despite the growth factors, Matrigel did not offer a more suitable environment to further improve engraftment (group 3, P < .05). Thus, even if the liver remains the gold standard, the GS represents a potential islet engraftment site, confirming the data obtained in vitro and in the rodent. Offering easy access by endoscopy, this site could constitute an interesting alternative for experimental studies in large mammals and, eventually, for clinical application.

Endoscopic Gastric Submucosal Transplantation of Islets (ENDO-STI): Technique and Initial Results in Diabetic Pigs

G. J. Esquivel a,b, K. McGrath a, R. Bottino c, H. Har a, E. M. Dons a,d, D. J. van der Wingt a, B. E. Eckert a, A. Cas a, S. Hous a, M. Ezzelain a, R. Wagner a, M. Trucco e, F. G. Lakki a and D. K. C. Cooper f

a Thomas E. Starzl Transplantation Institute, Department of Surgery, University of Pittsburgh, Pittsburgh, PA
b Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh, Pittsburgh, PA
c Division of Immunogenetics, Department of Pediatrics, University of Pittsburgh, Pittsburgh, PA
d Department of Surgery, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands
e Department of Surgery and Organ Transplantation, University of Padua, Padua, Italy
f Division of Laboratory Animal Resources, University of Pittsburgh, Pittsburgh, PA

Corresponding author: David K. C. Cooper, cooperdk@upmc.edu

The results of transplantation of human donor islets into the portal vein (PV) in patients with diabetes are encouraging. However, there are complications, for example, hemorrhage, thrombosis and an immediate loss of islets through the 'instant blood-mediated inflammatory reaction' (IBMIR). The gastric submucosal transplantation, avoids IBMIR and warrants further exploration.

Keywords: Endoscopy, gastric submucosal space, pig, portal vein, transplantation, islets

Abbreviations: GBMIS, gastric submucosal islets; ENDO-STI, endoscopic gastric submucosal transplantation of islets; IBMIR, instant blood-mediated inflammatory reaction; PV, portal vein; SPF, specific pathogen free

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Introduction

To determine this optimum site for islet transplantation, many anatomic locations have been tested. The liver is the most commonly used site, but survival of islets transplanted into the portal vein (PV) is suboptimal (Table 1). Approximately one third of islet recipients experience at least one adverse event within the first year, with almost half being related to the transplant procedure (2,3); although most resolve without sequelae, almost half require hospitalization (2,7). Occasionally, a mini-laparotomy is required for direct injection into the portal system (8).
Reversal of Diabetes by Pancreatic Islet Transplantation into a Subcutaneous, Neovascularized Device

A. Pileggi et al. Transplantation 2006, 81 (9), 1318-1324
Bone marrow as an alternative site for islet transplantation

![Graphs showing glycaemia levels over time with overlays for intra-BM and intra-Liver transplantation.](graph1.png)

**P = .005**

**H&E**, **Insulin**, **Glucagon**

E. Cantarelli et al. Blood 2009, 114 (20), 4566-4574
Long-term engraftment and function of transplanted pancreatic islets in vascularized segments of small intestine.

Long-term engraftment and function of transplanted pancreatic islets in vascularized segments of small intestine.

Long-term engraftment and function of transplanted pancreatic islets in vascularized segments of small intestine.

Pancreas

SIS
An isolated venous sac as a novel site for cell therapy in diabetes mellitus.

Modifications of islet microenvironment

Modulating Local Environment

- Micro/Nano-scale encapsulation
- Local Drug Delivery
- Biomaterial scaffolds
- Growth factors
- Oxygen carriers
- Stem cells/Vascular precursor cells
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Mesenchymal stem cells forming a beautiful heart shape.
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