


# Unsurpassed Intrahepatic Islet Engraftment – the Quest for New Sites for Beta Cell Replacement

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## Abstract

The liver is currently the site of choice for clinical islet transplantation, even though many alternative implantation sites have lately been proposed as more ideal for graft survival. The suggested sites, for example intramuscular space, omentum, bone marrow, and spleen, are sometimes difficult to compare due to differences in animal model, islet isolation procedure, and islet quality. In addition, the variation in transplanted islet mass is vast. The aim of this commentary is to review alternative implantation sites tested experimentally as well as in clinical islet transplantation. Although many sites have been investigated, none have convincingly proved better suited for clinical islet transplantation than intraportal injection to the liver, regardless of whether it is autologous or allogeneic transplantation. However, in order to fully evaluate upcoming bioengineering techniques, such as scaffolds containing insulin-producing cells derived from stem cells, the need of an alternative site has arisen to enable cellular monitoring, which currently cannot be achieved within the liver.

## Keywords

intraportal islet transplantation, type 1 diabetes, beta cell replacement

## Introduction

Islet transplantation (IT) is currently offered to a small subset of type 1 diabetes (T1D) patients to replace destroyed beta cells and thereby avoid glycemic lability. IT is a minimally invasive procedure with increasingly better outcome due to progress in the islet isolation technique and immunosuppressive regime<sup>1</sup>. Allogeneic IT is used for T1D patients, whereas autologous IT is performed in the treatment of chronic pancreatitis or following pancreatectomy<sup>2</sup>. Both types of transplantation are performed by an injection of islets into the portal vein for engraftment into the liver, which has been the site of choice since the beginning of clinical IT<sup>1,3</sup>. The outcome of islet autotransplants demonstrate superior long-lasting graft function even if the transplanted islet mass sometimes is lower than in allogeneic transplantations<sup>4</sup>.

Currently, insulin-independent success rate in allogeneic IT is reported in up to 50% of patients after 5 years<sup>1,5</sup>. Although some patients revert to exogenous insulin therapy, 87.5% achieved freedom of severe hypoglycemic events 1 year after IT and reported improved quality of life<sup>6</sup>.

Clinical IT faces two major challenges. First, it is desirable to decrease the need for immunosuppressive treatment in order to expand the group of patients that could be candidates

for IT. Second, a lack of donors will arise if the only source of islets comes from brain-dead organ donors. New strategies for beta cell replacement might solve both problems, using encapsulation of insulin-producing cells and stem cells. Promising stem cell programs are developed, but clinical translation of such advanced therapy medicinal products requires safety studies with graft monitoring and retrieval possibilities. Questions regarding the liver as the future implantation site of choice have therefore been raised on several occasions over the last decades. We have previously demonstrated engraftment difficulties after intraportal transplantation, including reduced vasculature, hypoxia, and amyloid formation, which contribute to islet mass reduction and loss of function<sup>7</sup>. The aim of this commentary is to highlight the conditions of alternative sites for future beta cell replacement.

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## Advantages of the Intrahepatic Site for Clinical Transplantation

The clinical procedure of percutaneous intraportal infusion of islets into the liver is associated with low morbidity and low risk of adverse events, such as bleeding (7%) and portal thrombosis (3.7%)<sup>8</sup>. In order to further reduce the risk of complications, it is recommended to restrict the total volume of transplanted tissue and to avoid rapid increases in portal pressure<sup>9</sup>. At the same time, islet volume is a known predictor that positively correlates to transplantation outcome<sup>10</sup>. A unique consequence of intraportal injection is the scattering of islets throughout hepatic sinusoids, avoiding clusters, which form in every other transplant site and may initially impair diffusion of oxygen and nutrients. On the other hand, this makes the graft very difficult to monitor by imaging techniques, and means that biopsies are difficult to obtain<sup>11</sup>.

The liver is the main target organ for insulin, and intrahepatic islets can therefore mimic the physiological pancreatic insulin secretion as opposed to systemic insulin release<sup>12</sup>. In experimental studies, the liver also appears to be more efficient than bone marrow<sup>13</sup> and kidney subcapsular site<sup>14</sup> due to immunological factors. Islets grafts within the liver lasted a longer time before rejection compared with islet grafts at the kidney subcapsular site in rats<sup>13</sup>. Likewise, a lower count of recruited lymphocytes has been reported in islet grafts in liver than in islet grafts in bone marrow<sup>14</sup>.

## Challenges with the Intrahepatic Site for Clinical Transplantation

After transplantation, beta cell survival can be impaired by acute and/or chronic factors. Immediately when islets are injected, direct contact with the vascular system exposes them to an instant blood-mediated reaction (IBMIR) which contributes to early graft loss<sup>15–17</sup>. In addition, there is a substantial risk of beta cell death due to acute hypoxia. Even after revascularization, oxygen delivery to intrahepatic islets is inferior compared with native islets in the pancreas, leading to prevailing hypoxia<sup>18–21</sup>. Better outcomes have been demonstrated with selective transplantation of smaller islets, which exhibit a lower oxygen demand<sup>10</sup>. Amyloid formation, which is associated with type 2 diabetes, has been found in intraportal islet grafts<sup>22</sup>. In our recent study, 27% of islets contained amyloid 1 month after transplantation<sup>7</sup>. Furthermore, gluco-lipototoxicity from surrounding hepatocytes has been shown to damage transplanted islets<sup>23–25</sup>. Although there are controversial findings, Robertson et al. have demonstrated how glycogen metabolism and glucose flux in the hepatic site inhibit secretion of glucagon by transplanted alpha cells, which leads to hyperinsulinemia and hypoglycemia in both autologous and allogeneic settings<sup>26–28</sup>. Kupffer cells are specific to the liver site and have also been shown to be detrimental for islet allograft survival at this site<sup>29</sup>. Another concern regarding the hepatic site which has been postulated is that portal blood contains

potentially harmful concentrations of immunosuppressive agents<sup>30</sup>. Notably, however, intrahepatic islets only sense to glucose stimulation through the hepatic artery after their revascularization; therefore, the relevance of drug-related effects due to increased concentrations in portal blood can be debated<sup>31</sup>.

## Alternative Implantation Sites and Comparative Studies

Comparing engraftment efficacy for different transplant sites is challenging due, for example, to variations in transplanted islet mass, especially when using human islets. Table 1 lists experimental studies comparing alternative sites to the liver in the commonly used C57Bl/6 mouse model.

**The kidney subcapsular site** appears to provide one of the best engraftment environments, at least for experimentally transplanted islets, and has therefore been used routinely in research. The only clinical trial, however, reports failed graft function despite an increased number of transplanted islets<sup>38</sup>. Besides the described immunological reasons for failure<sup>13</sup>, another problem when scaling up to humans is the need of much larger number of islets, which cause clustering in a restricted volume space, thereby impairing the diffusion of oxygen and nutrients to the highly metabolically active tissue. Furthermore, patients with T1D risk developing diabetic nephropathy that could deteriorate the kidney as a possible site.

**The muscle** has, in mice, been demonstrated capable of providing a superior islet revascularization and function when compared with the liver<sup>35</sup>. Autotransplantation has generated good long-term function in humans<sup>35</sup>. Meanwhile, clinical allotransplantation has unfortunately terminated in graft loss after 3–4 months<sup>39</sup>.

**The omentum** appears to provide more rapid revascularization compared with intrahepatic islets<sup>36</sup>. In humans, patients receiving autologous IT due to chronic pancreatitis have partially been transplanted to the omental pouch, in cases when increased portal pressure prevented complete intraportal transplantation<sup>40</sup>. However, results are so far disappointing, with only a small number of patients that have been rendered insulin independent, while the majority of grafts have failed. Ongoing clinical trials have reported a functional decline 1 year after transplantation, for unknown reasons<sup>41</sup>.

**The gastric submucosa**, like the omentum, exhibits favorable portal drainage, and case reports have shown promising results for both types of transplantation<sup>42,43</sup>.

**The bone marrow** has demonstrated promising results for autotransplantation, in both preclinical<sup>44</sup> and clinical studies<sup>45,46</sup>. However, allogeneic transplantation was not successful, which the authors suspected to be caused by autoimmunity<sup>46</sup>. A markedly increased destructive inflammatory process occurred in the grafts despite immune suppression of the recipients.

**The spleen** is highly vascularized and has portal drainage. Its immunological function has been assumed

**Table 1.** Experimental Studies Comparing Alternative Islet Transplant Sites to Liver in C57Bl/6 Mice.

Author (reference)	Animal model	Implantation sites	Transplant type	Islet type	Islet volume tx	Major outcome	Comments
Korsgren O et al. 1993 <sup>32</sup>	C57Bl/6	Liver, spleen and kidney	Syngeneic	Murine	300 islets	Better nerve in growth in kidney compared to liver and spleen	Not diabetic recipients
Lau J et al. 2007 <sup>33</sup>	C57Bl/6 nu/nu and YC-3.0	Pancreas vs. liver	Allogeneic to immunodeficient mice	Murine	200 islets	Glucose stimulated insulin release and oxidation rates were markedly decreased in liver	Intraportally transplanted islets were retrieved after mechanical digestion of liver tissue and picked under a stereomicroscope
Kim HJ et al. 2010 <sup>34</sup>	C57Bl/6	Kidney, liver, muscle and omentum	Syngeneic	Murine	Marginal mass (subcurable dose of 100–600 IEQ) calculated for each site	Kidney, liver, muscle, and omentum required 100, 600, 600, 200 islets to cure 50% of engrafted diabetic mice, respectively. Kidney had shortest time to reach euglycemia (3 days), muscle the longest (27 days)	Different islets volume. High perioperative mortality for liver transplants
Christofferson G et al. 2010 <sup>35</sup>	C57Bl/6 and C57Bl/6 nu/nu	Muscle vs. liver	Syngeneic and xenogeneic to immunodeficient mice	Human and murine	300 islets	Improved revascularization and response to glucose challenge in intramuscular transplantation, on par with intrahepatic transplantation	Vascular density of human islets transplanted to muscle same as murine islets
Espes D et al. 2016 <sup>36</sup>	C57Bl/6 and C57Bl/6 nu/nu	Omentum vs. liver	Syngeneic and xenogeneic to immunodeficient mice	Human and murine	200-300 islets	Normalized vasculature and better response to IVGTT 1-month post-transplant in the omentum	200 islets not sufficient to restore euglycemia to intraportally transplanted diabetic recipients
Stokes RA et al. 2017 <sup>37</sup>	C57Bl/6	Kidney, muscle, liver, spleen capsule, liver capsule	Syngeneic and xenogeneic to immunodeficient mice	Human and murine islets	220-250 islets (syngeneic) and 2000 IEQ human islets	Kidney best site for murine and human islet transplantation (Kidney used as control). Muscle and intraportal site had similar cure rate for human islets, however both inferior to kidney	Large transplant volume. Improvement of graft survival when increasing islet number to muscle
Cantarelli E et al. 2017 <sup>13</sup>	C57Bl/6 and Balb/c	Bone marrow vs. liver	Allogeneic	Murine (two different strain)	450 IEQ	Treating the animals with anti-CD3, islet rejection is prolonged when transplanted to liver compared with bone marrow	No difference when no immunosuppressive treatment was given

**Table 2.** Implantation Sites Used in Clinical Allogeneic and Autologous Islet Transplantation.

Transplant site	Transplantation type	Advantages	Disadvantages	Comments	References
Liver	Allogeneic & autologous	Low complication rate Physiological insulin secretion	IBMIR Restricted islet volume Difficult to monitor Thrombosis and bleeding adverse effects	To date, 50–60% of patients reach 3-year post-transplantation insulin independence	Barton FB et al. 2012 <sup>1</sup> Bellin MD et al. 2012 <sup>5</sup> Sutherland et al. 2008 <sup>4</sup>
Muscle	Allogeneic & autologous	Minimally invasive Safe Easy to monitor	Systemic insulin release	Allotransplant clinical trial by Betruzzi demonstrated a decline after 3–4 months in 75% of patients	Betruzzi F et al. 2018 <sup>39</sup> Rafael E et al. 2008 <sup>51</sup> Christofferson G et al. 2010 <sup>35</sup>
Omentum	Allogeneic	Minimally invasive Portal drainage Retainable graft	Few clinical trials	Transplantation to combined sites. 12–36% of islet volume to omental pouch, rest to liver	Stice MJ et al. 2018 <sup>40</sup> Baidal DA et al. 2017 <sup>41</sup>
Bone marrow	Allogeneic & autologous	Minimally invasive	Less immunologically favorable vs. liver	Allogeneic transplantation failure	Maffi P et al. 2013 and 2018 <sup>45,46</sup>
Gastric submucosa	Allogeneic & autologous	Endoscopic procedure No volume limitation Portal drainage Easy access to the graft	Difficulty with monitoring and retrieval? Demand large islet volume	Case studies. Detectable c-peptide levels 3-year post-autotransplantation to gastric wall. Allotransplant partially to the gastric wall, partially to the liver Three patients received islets under kidney capsule, two showed c-peptide production but not sustainable	Wszola M et al. 2018 <sup>42,43</sup> Jindal RM et al. 1998 <sup>38</sup>
Kidney	Allogeneic				White SA et al. 2000 <sup>48</sup>
Spleen	Autologous	Immunologically favorable	Complications with splenic infarction	Five patients, two received splenic transplantations alone, the other three combined intraportal and splenic	
Anterior chamber of the eye	Allogeneic	Immunologically favorable	Tissue volume	FDA approval for clinical trial	Shishido A et al. 2016 <sup>52</sup>

advantageous and immune tolerance has been demonstrated in dogs<sup>47</sup>. The only human trial was marred by splenic infarctions, splenic rupture, and thrombosis<sup>48</sup>. In Minnesota, there was even one fatal incident following a splenic injection when islets after reflux ended up causing a pulmonary embolism through a porto-systemic anastomosis.

**The anterior chamber of the eye** has, alongside testis, cerebral ventricles, and thymus, been investigated because it is considered “immune privileged.” The anterior chamber of the eye has been used for in vivo imaging as well as in large animal models, preceding an ongoing clinical trial (IND017007)<sup>49,50</sup>.

Table 2 gives a summary of alternative sites used in the clinical setting, for both allogeneic and autologous IT.

## Concluding Remarks

Many different sites have been evaluated for beta cell replacement in the experimental setting and found superior in different aspects when compared with intraportal IT. Also, in the clinical setting a number of sites have been evaluated, but so far none have reported improved outcome when compared with the intrahepatic site. Even though IT is minimally invasive, especially compared with whole pancreas transplantation, the different sites used are associated with specific technical complications and different volume capacities. Upcoming bioengineering techniques of stem cells and scaffolds, including the use of auxiliary stem cells such as mesenchymal stem cells, neural crest stem cells, or endothelial progenitor cells, may be used to advance the field of beta cell replacement<sup>53–57</sup>. However, monitoring possibilities and safety issues make the intrahepatic site inappropriate for this purpose. Changing site could contribute to better graft survival by avoiding, for example, IBMIR and lipotoxicity. However, solutions to obtain scattering of graft tissue are then needed. We consider scattering of the tissue at implantation to be the most important reason why the liver works so well clinically.

## Ethical Approval

This study was approved by our institutional review board.

## Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

## Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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