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Subcutaneous clinical islet transplantation in a prevascularized subcutaneous pouch – preliminary experience

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Abbreviations: Type 1 Diabetes Mellitus (T1DM), Body Mass Index (BMI), Glycated Hemoglobin (HbA1C), Islet Equivalents (IEQ), Packed Cell Volume (PCV), Panel Reactive Antibody (PRA), 4',6-diamidino-2-phenylindole (DAPI).

Abstract

Despite advances in clinical islet transplantation, intraportal islet delivery is limited by engraftment, neovascularization, immune protection and functional survival. An alternative pre-vascularized, subcutaneous device could solve these issues and be relevant for future transplantation of insulin-producing stem cells. We herein report a first-in-human trial with a newly developed pre-vascularized subcutaneously placed pouch as an innovative approach for human islet implantation. Three longstanding type 1 diabetes subjects underwent subcutaneous implantation of therapeutic and sentinel pouches. After a median delay of 53 days (range 22-130), inner rods were removed and voids filled with purified human islets. In this preliminary experience, the primary endpoint of safety was met, and surviving, vascularized human islets were visualized on histological examination after pouch explantation by 6 weeks post-transplant. Islets retained macro-structure of beta and alpha cells in all cases, and demonstrated neovascularization. The secondary endpoint of insulin independence efficacy was not met, despite transplantation of a substantial islet mass in each case. Early peak C-peptide at 24 hours followed by absence subsequently suggested early functional engraftment failure in all cases.

Introduction

Clinical islet transplantation has advanced beyond 'proof-of-concept' demonstrating that cellular replacement therapy can effectively treat type 1 diabetes mellitus (T1DM) [1]. Currently, islet transplantation into the portal 'black-box' of the liver has clear limitations for engraftment, functional survival, immune protection, monitoring and imaging of grafts, and many subjects require more than one islet infusion to achieve and maintain protection from hypoglycemia or insulin independence[2,3]. The elements of any future widespread cell-based approach to restore beta-cell mass through transplantation beyond cadaveric donation will require a vast supply of compatible and safe insulin-producing cells. If these cells are derived from embryonic or adult stem cell lines, the potential for unregulated growth, teratoma or malignant transformation, will likely dictate a need for graft retrievability, at least in the early phase safety trials[4]. The hepatic portal system is, therefore, likely unsuitable for infusion of stem cell-derived therapies, as a major hepatectomy or liver transplantation would be required if graft retrieval is needed.

Numerous studies have explored alternative suitable sites for islet engraftment[5]. Empirically, the intraportal site is used routinely for clinical islet transplantation, and is currently the only site that has consistently provided protection from hypoglycemia and insulin-independence. Intramuscular[6-8] and bone marrow[9] implantation have generated interest, but no patients have achieved insulin independence with such an approach to date. The subcutaneous site for surrogate beta-cell implantation remains attractive, but has previously failed to offer an adequate milieu for vascularity, oxygen, hormonal and metabolite exchange[10-12]. Furthermore, placement of

non-encapsulated islets or stem cell-derived insulin producing cells within the unmodified subcutaneous space has met with limited success[13].

Over the past six years, Sernova Corp. (London, ON) developed and refined a proprietary, implantable polymer chambered medical device (Cell Pouch™) designed for human cellular replacement therapies[14]. A scaled down Cell Pouch™ prototype for small animal testing demonstrated long-term insulin independence in a marginal mass islet transplant model[15,16]. Initial results suggested the device could provide a critical, unmet need in development of the subcutaneous space for islet, and especially for alternate stem-cell derived therapeutic cell transplantation. The pouch is contract-manufactured from medical-grade materials, under ISO13485, US FDA Quality System Regulations (QSR) 21 CFR 820 standards, and sterilized according to ANSI/AAMI/ISO 11135-1: 2007. The device previously demonstrated a favorable safety profile in multiple animal models and met ISO10993 biocompatibility studies. This human-scaled device is approximately 60 mm x 60 mm and is placed in the deep subcutaneous space, in a minimally-invasive surgical procedure (Figure 1).

Based on safety and efficacy validation in small and large animal islet transplant models (isograft, autograft and allograft), the University of Alberta's Clinical Islet Transplantation Program initiated a pilot phase I/II clinical trial to evaluate safety and efficacy of this device in up to 20 subjects with type I diabetes (Clinical Trials.gov NCT01652911). This study was authorized by the Health Research Ethics Board of the University of Alberta (Protocol number PRO00028097), Data and Safety Monitoring Board (DSMB) and by Health Canada. Therapeutic cells are regulated by the Biologic and Genetic Therapies Directorate and the Cell Pouch™ is regulated by the Therapeutic Products Directorate (TPD) – Medical Devices Bureau of Health Canada. This paper presents our preliminary experience in the first three enrolled subjects and the lessons learned from a first-in-human assessment of the Cell Pouch™ using human islets.

Case 1

A 60-year-old male subject with longstanding T1DM of 35 years was listed for clinical islet transplantation based on frequent recurrent hypoglycemia and glycemic lability (Clark score of 5/7, Lability Index 530, Hypo score of 2,704) [17]. Baseline characteristics and glycemic control are shown in Table 1. At the time of device implantation, 1 g cefazolin (Ancef, SmithKline Beecham, Mississau-

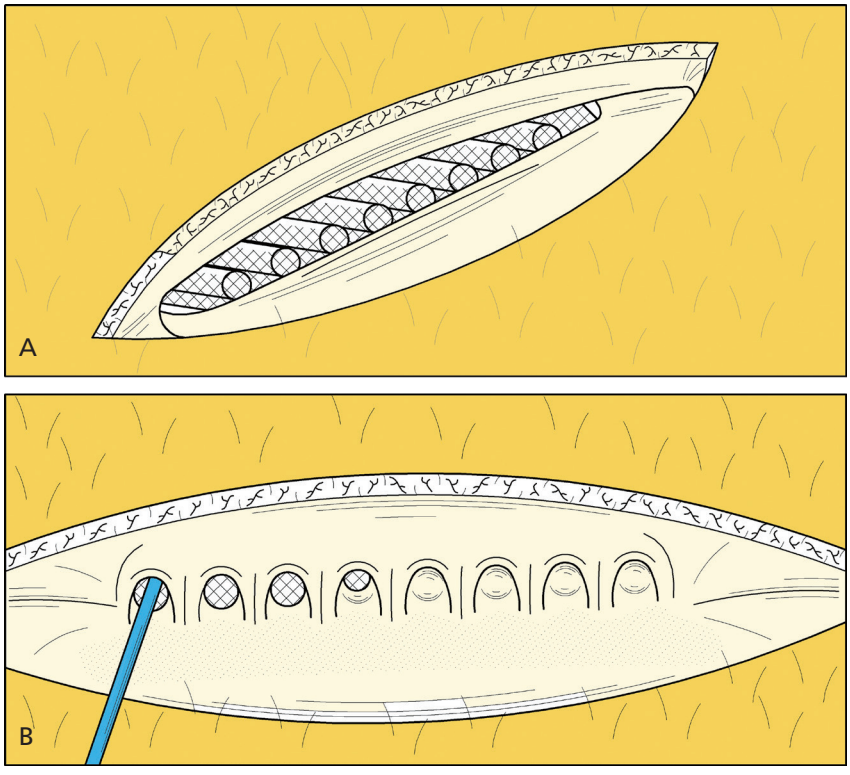

Figure 1. Illustration of the Sernova Cell Pouch™. ***A,*** Plugs in situ within the Cell Pouch™. ***B,*** Illustration of islet infusion within the chambers of the Cell Pouch™.

Table 1. Summarized demographic, glycemic and transplant characteristics of three subjects receiving subcutaneous Cell PouchTM islet transplantation. Islet channel density was calculated by dividing the total islet mass infused (in IEQ) by the total number of therapeutic channels used. Subject 3 received a combination of two islet preparations; aRight-sided therapeutic pouch islet density for subject 3 (first donor); bLeft-sided therapeutic pouch islet density for subject 3 (second simultaneous donor); cOnly sentinel devices were explanted in Subject 3. Therapeutic devices remain in place.

	Subject 1	**Subject 2**	**Subject 3**
Age (years)	60	45	29
Weight (Kg)/BMI	79.3/23.8	83.5/27.4	67.3/26
Basal insulin requirement (U/Kg/day)	0.45	0.37	0.40
Basal HbA1C (%)	7.7	8.3	7.8
Time from implant to transplant (days)	53	22	130
Total islet mass (IEQ)	448,612	506,844	368,696[a] / 794,615[b]
Islet mass per body weight (IEQ/Kg)	5,657	6,070	5,478[a] / 11,807[b]
Islet purity (%)	90	75	40[a] / 57.5[b]
Islet viability (%)	93.5	84	92[a] / 84[b]
Packed cell volume (mL)	1.5	3.0	3.0[a] / 3.0[b]
Number of sentinel devices implanted	1	1	2
Number of therapeutic devices implanted	2	2	4
Number of therapeutic devices transplanted	2	1	4
Islet density (therapeutic channel) (IEQ/channel)	22,430	50,684	46,087[a] / 99,327[b]
Time from transplant to explant (days)	30	14	40[c]

ga, ON, Canada) was administered intravenously, and implantation was accomplished under local anesthesia. Two 10-plug pouches were implanted in the abdominal wall through 2 limited transverse incisions. The devices were positioned lying flat in the deep subcutaneous space. A third small 2-plug pouch, designed as a sentinel, was placed in the volar forearm.

Approximately 13 days post-implant this subject experienced a minor wound seroma, which was aspirated percutaneously. The cultured seroma fluid was initially sterile, but 7 days later ongoing wound discharge was culture positive for *Propionibacterium acnes*, a likely skin contaminant. The seroma resolved completely on clinical inspection, and confirmed by superficial ultrasound interrogation 28 days later.

On day 53 post-implant, and under general anesthesia, the devices were accessed, the inner rods removed, and 448,612 islet equivalents (IEQ) distributed evenly across all channels (Table 1 and Figure 1). Immunosuppression consisted of our local standard alemtuzumab (MabCampath, Genzyme Corp.) 30 mg intravenously induction, etanercept (Enbrel; Amgen Canada Inc., Mississauga, ON, Canada) 50 mg IV on day 0, and 25 mg subcutaneously on days 3, 7 and 10 post-transplant, and anakinra (Kineret, Amgen Canada Inc., Mississauga, On, Canada) 100 mg subcutaneously on day 0 and daily for 7 days. Maintenance twice daily tacrolimus (Prograf, Astellas Pharma Canada Inc., Markham, ON, Canada) was adjusted to provide target trough levels of 10-12 μg/L, together with mycophenolate mofetil (CellCept®, Hoffmann-La Roche Ltd., Mississauga, ON, Canada) up to 2 g per day in divided dose, as tolerated. Cephalexin (Keflex, Eli Lilly Canada Inc. Toronto, ON, Canada) was given at a dose of 500mg 4 times daily, orally for 10 days.

The early posttransplant period was uneventful. In this subject evidence of graft function was not observed at early time points (negative C-peptide on day 7, 14 and 21, with no change of insulin requirement). On day 14 post-transplant, a sterile local wound discharge was observed from the right and left abdominal incision sites, and cultures were positive for anaerobic non-spore forming Gram positive bacilli, a possible skin contaminant. The patient was prescribed cephalexin 500 mg q6h for 14 days and by posttransplant day 23 the discharge was resolving.

On posttransplant day 30, accommodating patient request, all devices were explanted under general anesthesia. The integrity of the pouches was confirmed, and appeared to be vascularized and integrated with surrounding tissues. Tissue

fluid from each of the incisions was cultured and demonstrated no bacterial or fungal growth.

Histology and immunohistochemistry of the excised devices confirmed the devices to be well-integrated with neovascularization (positive staining for von Willebrand factor) and intact, viable islets were present in limited sections with β-cells stained positive for insulin (Figure 2A,B). α-cells, staining positive for glucagon, and δ-cells staining positive for somatostatin were also observed (images not shown). Where islets were identified, their presence was low volume and the distribution was patchy. No evidence of acute cellular rejection or autoimmune infiltrates was seen, without foreign body reaction and no macrophage or monocytic infiltration.

Case 2

A 58-year-old-female was enrolled with T1DM of 45 years (Clark score 7, Lability Index 592, Hypo score 671 (Table 1). The Cell Pouch™ implants were carried out under local anesthesia similar to Case 1 (two 10-plug pouches placed in the lower abdominal wall, and one 2-plug sentinel pouch in the left volar forearm).

There were no local wound complications after device implantation. On day 22 post-implant, under local anesthesia, 506,844 IEQ islets were infused evenly within the left-sided 10-plug pouch and sentinel (Table 1). Since the preparation was very pure, the remaining right-sided device was left *in situ*. Similar immunosuppression was given, and cephalexin prescribed (500 mg 4 times daily orally for 10 days).

The patient did well initially, but subsequently developed superficial cellulitis of the left forearm at day 10 post-transplant, which responded to intravenous ceftriaxone (Sandoz Pharmaceuticals, Sandoz, Boucherville, QC) 2 g daily.

Again, upon patient request, all devices were explanted on day 14 post-transplant. In this patient no detectable C-peptide was evident and no substantive reduction in insulin requirement was detected at this day 10 early time point. She did not reach the protocol defined 3-month posttransplant first efficacy assessment, nor was she offered a second transplant.

Staphylococcus aureus was isolated from the left upper quadrant abdominal site on delayed cultures. Immunohistochemistry of the explanted

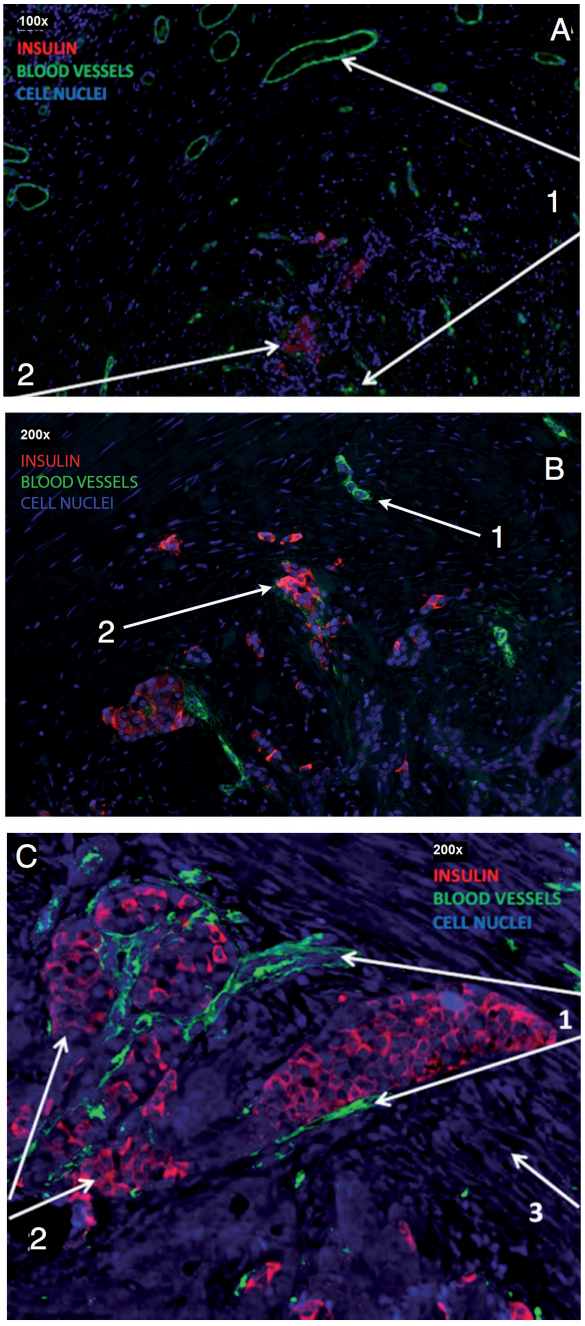

Figure 2. Histology showing surviving islets surrounded by new blood vessels in areas of the therapeutic devices explanted from Subjects 1 and 2 (paraffin embedded, 5 micron sections). *White arrows* (1) highlight strong von Willebrand Factor (vWF) staining in green; *White arrows* (2) demonstrate insulin staining (red) and cell nuclei (3) staining blue with 4',6-diamidino-2-phenylindole (DAPI) ***A,*** Selected section of therapeutic Cell Pouch™ explanted at day 30 post transplant from Subject 1, at 100x magnification to show overview of surrounding large vessels in the graft perimeter together with intra-islet micro vessels; ***B,*** Similar section as 2A, but magnified to 200x; ***C,*** Selected section of therapeutic Cell Pouch™ explanted at day 14 post transplant from Subject 2, at 200x magnification.

devices showed extensive vessel ingrowth by von Willebrand factor staining, and viable islets were identified with a patchy distribution, with β-cells staining positive for insulin (Figure 2C), α-cells positive for glucagon, and δ-cells positive for somatostatin (images not shown). There was no evidence of acute cellular rejection or autoimmune infiltrates, foreign body reaction and no macrophage or monocytic infiltration.

Case 3

Based on our preliminary experience above, we minimized the use of electrocautery during implantation, prolonged prophylactic oral antibiotics, and extended the period from device to cell implantation to 4 months to ensure mature device incorporation. A 29-year-old female with 25 years of T1DM was then enrolled (Clark score 4, Lability Index 610, Hypo Score 501) (Table 1). In this case, we doubled the initial device implant numbers, placing four 8-plug pouches in the deep subcutaneous space of the lower abdominal wall, with two 2-plug sentinel devices placed laterally (Figure 3A). The rationale was to limit exposure to repeated surgeries, and to potentially accommodate simultaneous transplantation of two clinical islet preparations from separate donors. At 3 weeks post-implantation, a large sterile fluctuant seroma developed, extending bilaterally across the dependent lower abdominal wall. There was no pain or discomfort, and no evidence of infection, cellulitis or discharge, and we chose to allow the seroma to resolve fully before proceeding with islet implantation. Complete resolution was confirmed subsequently by superficial ultrasound examination at 3 months.

This subject was transplanted 130 days after pouch implantation, when extensive device incorporation and vascularization was observed. Two donor islet preparations become available simultaneously with cumulative islet mass of 1,294,900 IEQ, and these were distributed evenly across all four major pouches, with a small fraction allocated to the two laterally placed sentinel devices. Approximate comparison of islet density per plug channel is outlined in Table 1. Post-transplant immunosuppression was similar to the previous cases, but antibiotic prophylaxis was extended to 7 days. The transplant procedure concluded without complications.

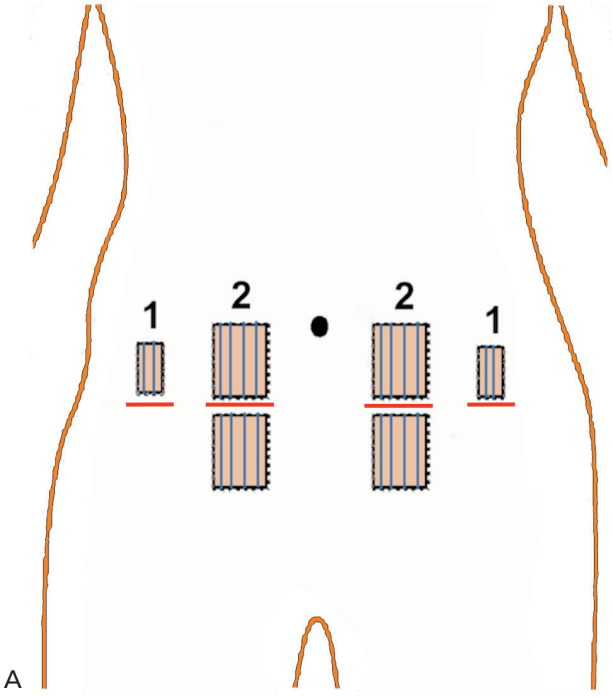

Figure 3. ***A,*** Illustrative diagram showing surgical sites for implantation of Cell Pouch™ devices in subject three. 1. Site of the lateral sentinel pouches placed above the iliac crests. 2. A total of four therapeutic pouches placed in pairs above and below each transverse incision on the lower anterior right and left abdominal wall. Note: Cell Pouches™ are not scaled to size. ***B,*** 2-year post-transplant photograph of the anterior abdominal wall of subject 3.

The two sentinel pouches were excised as per protocol, for histological assessment 6 weeks after transplantation. Histologic and immunohistochemical analysis of the sentinel pouches confirmed neo-angiogenesis and patchy islet fragments present within the device, staining positively for insulin and glucagon (Figure 4A-C) and no evidence of immune cell infiltration by CD3 staining (Figure 5). The examination also identified that exocrine tissue (as identified by pancreatic amylase and CK-19 staining) was abundant to a variable degree (Figure 6).

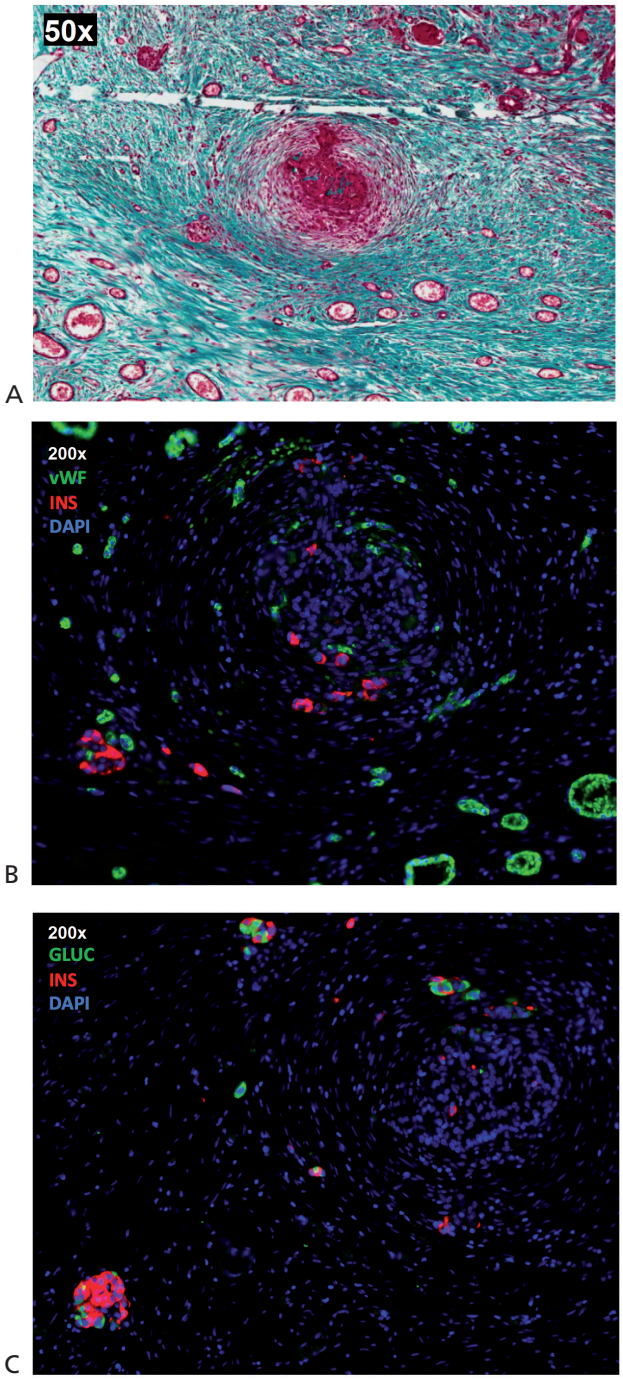

Figure 4. Selected histology and immunohistochemistry from the sentinel devices explanted at 30 days post transplant in subject 3, showing surviving islets surrounded by tissue and new blood vessels within the device. ***A,*** Masson's trichrome stain at 50x magnification showing location of the transplanted cells within the channel lumen; ***B,*** Positive immunofluorescence staining for insulin/vWF/DAPI at 200x magnification (insulin red (INS), von Willibrand Factor green (vWF), 4',6-diamidino-2-phenylindole blue; ***C,*** Glucagon green (GLUC), INS (red) and DAPI (blue) at 200x magnification. /DAPI antibodies.

Serial C-Peptide monitoring and Subsequent Course

All three subjects experienced acute, short-lived peaks in serum C-peptide levels within the initial 24h post transplant, most evident in subject 3 that received the largest islet mass (Figure 7A,B). All three subjects remained C-peptide negative after post-transplant day 2.

The three subjects made a complete recovery without long-term sequelae, and the second and third subject were relisted for 'standard-of-care' intraportal islet transplantation outside of this research protocol. Subject 1 chose not to participate in further islet transplants, remained C-peptide negative, and has not been followed actively (Figure 8A,B). Subject 2 received a first intraportal islet transplant 11 months after the subcutaneous procedure and promptly attained positive C-peptide status with reduction in exogenous insulin requirement and correction of HbA1C. A second intraportal islet infusion was given at 16 months, which rendered her insulin free (Figure 8C,D). Subject 3 was the only patient in the study to reach the 3-month efficacy assessment. Evidence of graft function was not observed at any time point up to and beyond 4 months post transplant in this subject, as determined by serial measurement of mixed meal stimulated C-peptide (Ensure^{TM}), decrease in insulin requirement, insulin independence at any time-point preceding intraportal transplantation, or protection from hypoglycemia. While a decrement in HbA1C was noted, in the absence of C-peptide this is consistent with more optimized glycemic and insulin monitoring rather than graft function *per se* (Figure 8E,F).

Subject 3 underwent two subsequent intraportal islet infusions on day 131 and 202 after the subcutaneous intervention, and promptly achieved attained C-peptide status, correction of HbA1C and periods of insulin independence (Figure 8E, F).

All subjects remained non-sensitized with negative panel reactive antibody (PRA) following device transplantation, and there were no donor-specific antibodies identified directed against any of the subcutaneous donors.

Finally, other than minor superficial scars, no major aesthetic concerns were apparent as a consequence of the pouch implantation, cell transplants or sentinel retrievals. Indeed, subject 3 still has four 8-plug pouches *in situ* at 24 months post surgery with no safety sequelae (Figure 3B).

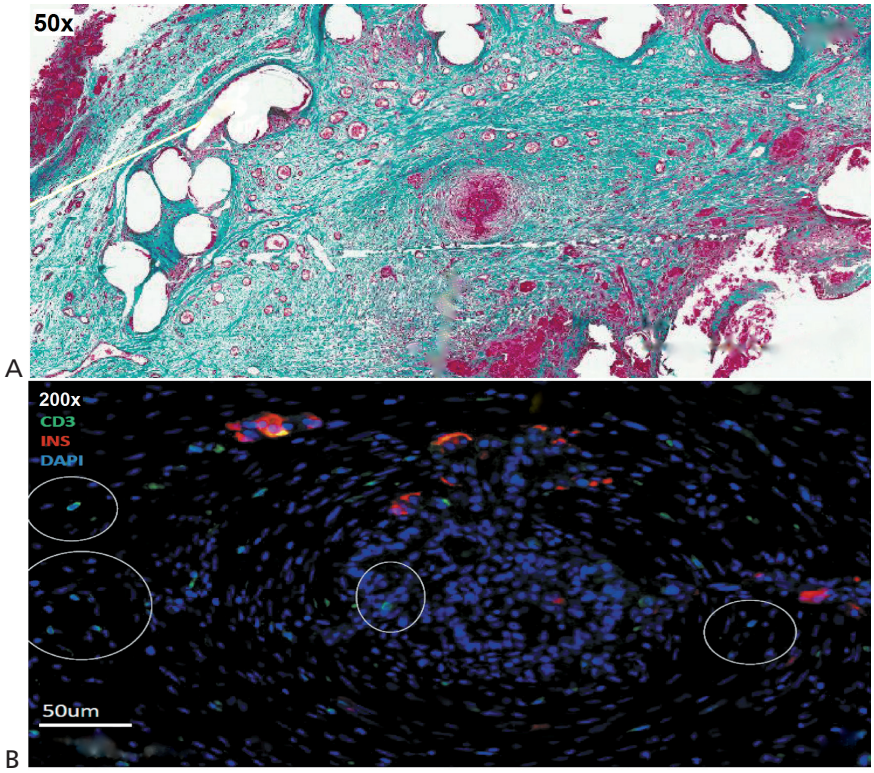

Figure 5. ***A,*** Masson's trichrome stain of a selected histology image of a Cell Pouch™ explanted after day 30 post transplant from subject 3, showing outer device tines (large white voids in upper portion of slide) with a portion of an islet graft seen centrally (50x magnification); ***B,*** Immunofluorescence staining for CD3 (green); insulin (INS, red) and DAPI (blue), demonstrating no evident T-cell infiltrate (200x magnification). White circles highlight occasional CD3 positive cells.

Discussion

We herein report our initial first-in-human experience with a pre-vascularized subcutaneous islet transplant device, Sernova's Cell Pouch™, in a single center phase I/II study. The results clearly show the device and surgical approach to be relatively safe. Minor wound complications occurred in all 3 cases, including cellulitis and seroma, and either resolved spontaneously over time (third subject) or following device explantation (first and second subject). An important observation was the histologic identification of human islets staining positively for insulin, glucagon and somatostatin within the pouch, with incorporated neovascular ingrowth in all cases at different time points. Although the human islet distribution was patchy and found only in limited sections, where present, cells were surrounded by viable stroma and demonstrated no features of immune rejection or infection.

While the device materials have been shown by the manufacturer to be biocompatible in small and large animal models, the occurrence of seroma in human subjects was not predicted in previous studies, perhaps suggesting attenuated foreign-body reaction responses in human subjects with longstanding diabetes[18]. Based on our preliminary observations especially in subject 3, we would advocate delaying implantation of viable cellular material until the devices have become fully incorporated.

The lack of demonstrable graft functionality evidenced by detectable C-peptide, decrement in insulin requirement or insulin independence preceding intraportal transplantation in this preliminary experience, an important secondary endpoint, is disappointing. We have closed enrollment of further subjects based on this observation. In our own preclinical studies with a sentinel-sized Cell Pouch™, it took approximately 20 days with full islet mass, and 40 days with a marginal mass to fully reverse diabetes in mice[16]. However, a steady improvement in glycemic control was observed within the initial 5-10 days of transplantation in these mice[16]. These findings contrast with routine clinical experience with intraportal islet transplantation in diabetic patients, where measurable C-peptide function, marked decrease in insulin requirement or insulin independence with stabilization of hypoglycemic events occur within days of transplantation (Figure 8). Due to pre-emptive device explantation within 15 and 30 days in the first two cases, insulin independence was not expected, but a decrement in insulin requirement and the presence of detectable C-peptide was anticipated. Further developmental work will be required to determine the functional utility of this approach. Subject 3 maintained thera-

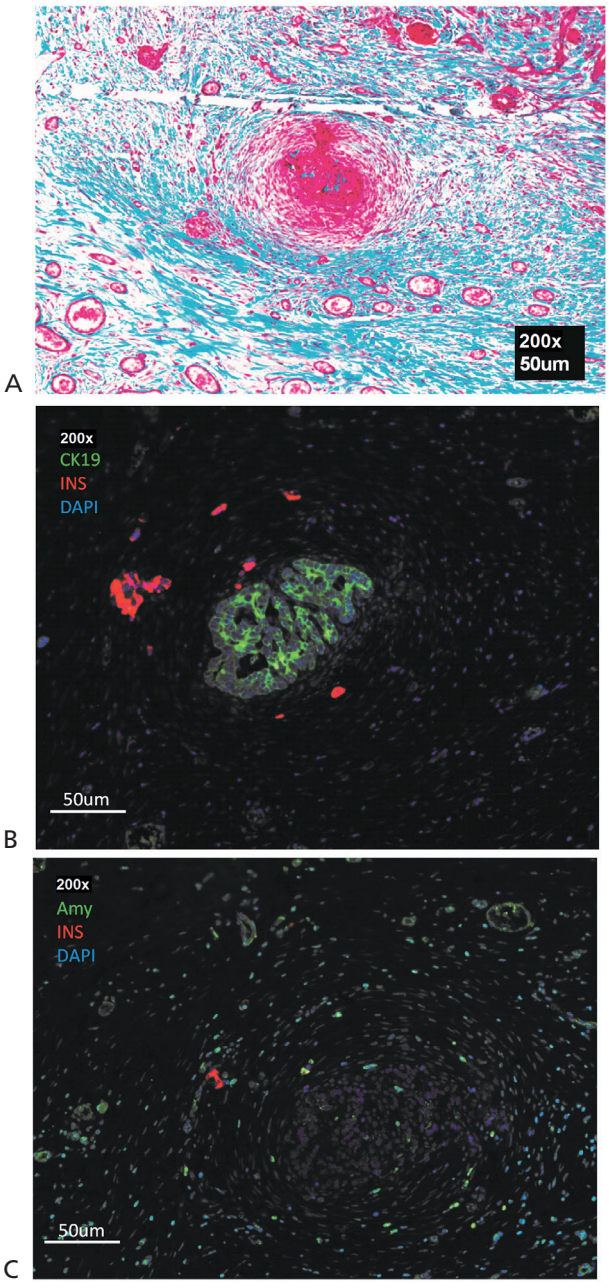

Figure 6. Evidence for survival of pancreatic exocrine tissue and ductal elements (CK19 positive) within the sentinel devices explanted from subject 3. ***A,*** Masson's trichrome stain of a selected histology image of a Cell Pouch™ explanted after day 30 post transplant from subject 3 (200x magnification); ***B,*** Selected section stained by immunofluorescence for CK-19 (green), insulin (INS, red) and DAPI (blue) (200x magnification); ***C,*** Immunostaining for Amylase (Amy (green), insulin (INS, red) and DAPI (blue) (200x magnification).

peutic Cell Pouches™ containing a substantial islet mass for 131 days before intraportal islet transplantation intervened (Figure 8). The presence of measurable C-peptide in all 3 subjects within the initial 24 hours, and the high peak observed in subject 3 (Figure 7), is consistent with acute islet demise during the initial engraftment period, with passive insulin and C-peptide release.

The contrast between lack of detectable function and histologic survival is consistent with the majority of the transplanted islets failing to survive following introduction to the device, especially in the light of the acute C-peptide release at 24 hours. The observation of occasional islet patches in histological examination is consistent with this. The study was not designed to assess precise, longitudinal, histological quantification of islet cell survival, but there was a marked discrepancy between the number transplanted and number observed following histological examination. The optimal islet density per device channel still remains to be defined for human islets in patients, and it is contemplated by the authors that in these three cases we may have overwhelmed the capacity of the Cell Pouch to provide oxygen and nutrient exchange (Table 1).

The presence of contaminating exocrine and ductal components may be an important differentiating factor between Cell Pouch™ studies in mice and patients. The human islet preparations selected for subjects 1 and 2 were of high purity. The third subject received a larger islet mass distributed across almost twice as many channels, but also contained more substantial exocrine pancreatic tissue (Table 1). While such a preparation is generally accommodated within the intraportal space, this may have further contributed to cellular hypoxia and demise within the limited confines of the device. Of interest, subject 3 was found to have surviving exocrine tissue in the sentinel Cell Pouch™ (Figure 6), in contrast to intraportal islet transplantation where exocrine tissue is not routinely found [19].

The pre-vascularized subcutaneous Sernova Cell Pouch™ approach offers a potentially retrievable site for human islet implantation, and future application of embryonic or adult stem cell-derived beta cells in diabetes. Based on our limited preliminary experience, and acknowledging technical challenges in our early learning curve, the current device and surgical techniques likely require further modification to optimize accommodation of functional cells. Prevascularization of the subcutaneous site through a variety of approaches may transform a non-favorable site for therapeutic cellular engraftment, thereby broadening future potential cell transplant approaches in regenerative medicine.

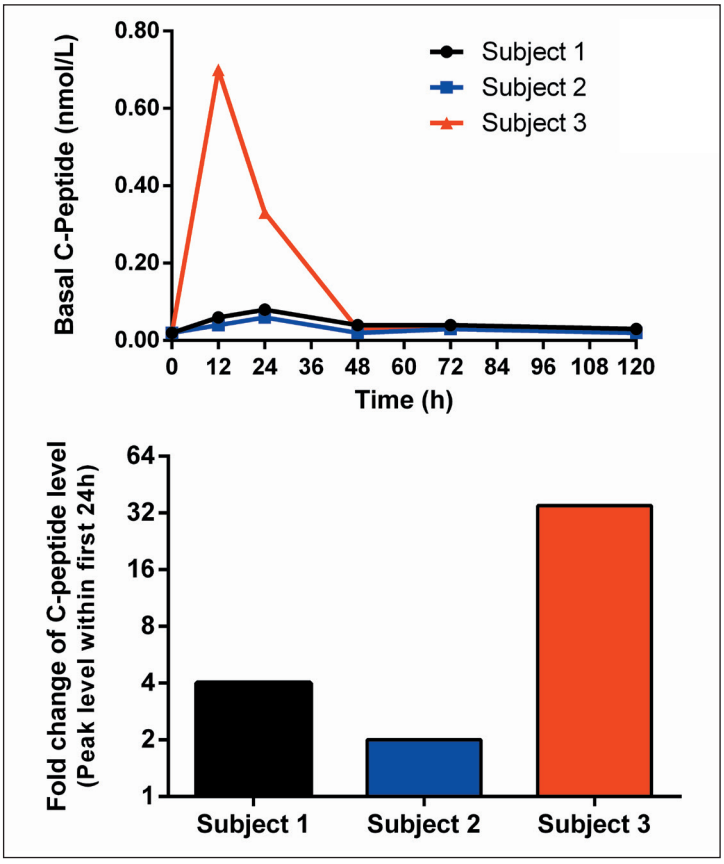

Figure 7. Early post-transplant basal levels of C-peptide. ***A,*** Post-transplant levels of C-peptide for all three subjects showing peak increase within the first 24h, most substantial in subject 3 who received a larger transplant dose; ***B,*** Corresponding fold-change in basal C-peptide levels for all subjects seen within the initial 24h post-transplant.

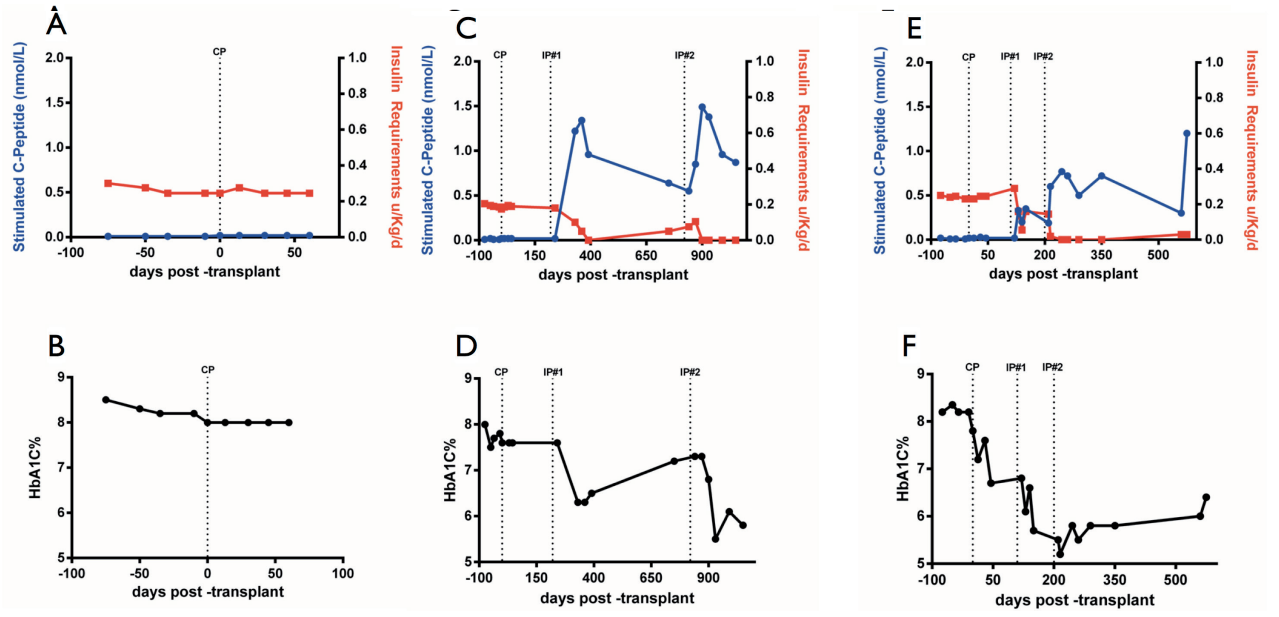

Figure 8. Pre and post-transplant function of the 3 study subjects as determined by stimulated C-peptide response to a mixed meal challenge (Ensure™), daily insulin requirement and glycated hemoglobin over time. There was no detectible C-peptide secretion beyond the first 48 hours, decrement in insulin requirement, protection from hypoglycemia, and nor was insulin independence achieved at any time point preceding intraportal islet transplantation in any case following Cell Pouch™ transplantation, despite transplantation of a substantial islet mass. Subjects 2 and 3 subsequently received two intraportal islet infusions and both became promptly C-peptide positive, insulin independent for a period, and corrected hemoglobin A1C (HbA1C). ***A-B,*** Data from Subject 1; ***C-D,*** Data from subject 2; ***E-F,*** Data from subject 3. CP: Cell Pouch™; IP#1: first intraportal transplant; IP#2: second intraportal transplant. HbA1C: hemoglobin A1C.

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Disclosure

AMJS serves on the Scientific Advisory Board of Sernova Corp. AP was a former employee of Sernova Corp, and has been supported in part by a MITACS award funded through Sernova.

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