Chapter

Allogeneic Islet Transplantation and Future

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Abstract

Pancreatic islets contain beta cells which produce insulin based on the blood glucose levels resulting in tight control of blood glucose levels. In type 1 diabetic patients, most of the beta cells are destroyed, therefore, pharmaceutical insulin injection is mandatory to avoid diabetes-related illness and death. Even with recent advanced insulin therapy, hypoglycemia is a critical limiting factor to control blood glucose levels. There is no doubt that hypoglycemia can be fatal. Allogeneic islet transplantation can prevent severe hypoglycemia and provide excellent blood glucose control. On the other hand, allograft donor shortage is the major issue. To overcome donor shortage, xenograft has been used and shown safety and efficacy. Recently stem-cell-derived beta cells are clinically applied. In this chapter, the history and current status of allogenic islet transplantation and future scope are described.

Keywords: islet transplantation, allograft, type 1 diabetes, hypoglycemia, xenogeneic islet transplantation

1. Introduction

Type 1 diabetes is a devastating disease due to its acute and chronic complications.

Acute complications include hyperglycemic ketoacidosis and hypoglycemic attack, and both complications can be life-threatening. Chronic complications include nephropathy which leads to the necessity of hemodialysis, retinopathy which leads to blindness, and neuropathy which causes necrosis of the legs and the necessity of amputation.

Intensive insulin therapy is the gold standard for type 1 diabetic patients, which significantly reduces the risk of chronic complications and mortality rates [1]. However, intensive insulin therapy was associated with weight gain and a threefold increased risk for hypoglycemia [1], and hypoglycemia is a limiting factor for intensive insulin therapy [2]. Indeed, 4–10% of type 1 diabetic patients died due to hypoglycemia [3].

Since the cause of type 1 diabetes is destruction of insulin-secreting beta cells, beta cell replacement therapies are curative treatments [4]. Beta cell replacement therapies include the pancreas and islet transplantation. Allogeneic islet transplantation can

prevent severe hypoglycemia and provide excellent glycemic control. On the other hand, donor shortage is a major issue. In this chapter, the current situation of allogenic islet transplantation and potential resolution of donor shortage is described.

2. History of allogeneic islet transplantation

The idea of isolating islets of Langerhans using collagenase was originally published in 1965 [5]. With this method, Guinea pig pancreas was minced and digested with collagenase resulting in obtaining isolated islets. Washington University group introduced the intra-ductal injection method to improve the islet isolation method [6]. In fact, the Washington University group demonstrated that the first successful reversal of diabetes by islet isolation using diabetic rat model [7]. An important innovation was reported by the Stanford University group. They inject collagenase into pancreatic duct resulting in adequate islets for transplantation from a single donor using a canine model [8]. This method enables to initiate the first clinical trial of allogeneic islet transplantation at the University of Minnesota.

The first clinical trial of allogeneic islet transplantation was performed in 1970s' at the University of Minnesota (**Table 1**), however, did not achieve improving metabolic control [9, 10, 21]. The first successful allogeneic islet transplantation into type 1 diabetic patients was reported by Zurich University group (**Table 1**) [10]. In this first successful case, the patient received simultaneous kidney and islet transplantation, and islets were transplanted into a spleen. The patient achieved insulin independence 8 months after transplantation and maintained it for 10 months. Notably, the age of the donor was 2 years old, and islets from young donor can be suitable for islet transplantation. However, the patient suffered

Year	Events	Authors	Reference
1965	Development of islet isolation with collagenase	Moskalewski S	[5]
1972	First successful islet transplantation in rodent	Ballinger WF, Lacy PE	[7]
1977	First clinical islet transplantation	Najarian JS, Sutherland DER Matas et al.	[9]
1980	First successful islet transplantation	Largiader F, Kolb E, Binswanger U	[10]
1988	Development of automated method for islet isolation	Ricordi C, Lacy PE, Finke EH, Olack BJ, Scharp DW	[11]
1990	First series of successful islet transplantation	Tzakis AG, Ricordi C, Alejandro R, et al.	[12]
1994	First clinical islet xenotransplantation	Groth CG, Korsgren O, Tibell A, et al.	[13]
2000	First clinical encapsulated islet xenotransplantation without immunosuppression	Elliott RB, Escobar L, Garkavenko O, et al.	[14]
2000	Edmonton protocol	Shapiro AM, Lakey JR, Ryan EA, et al.	[15]
2005	First successful living donor islet transplantation	Matsumoto S, Okitsu T, Iwanaga Y, et al.	[16]

Year	Events	Authors	Reference
2006	First series of successful islet transplantation from non-heart-beating donor	Matsumoto S, Okitsu T, Iwanaga Y, et al.	[17]
2016	Phase 3 clinical trial of islet alone transplantation	Hering BJ, Clarke W, Bridge ND, et al.	[18]
2021	Phase 3 clinical trial of islet after kidney transplantation	Markmann JF, Rickels MR, Eggerman TL, et al.	[19]
2021	Stem cell-derived pancreatic endoderm cell implantation	Shapiro AJM, Thompson D, Donner TW, et al.	[20]

Table 1.
History of islet transplantation.

rejection and died after one month of rejection. Intrasplenic pancreatic islets were detected in the necrotic specimens.

A turning point for clinical islet transplantation was the introduction of the automated method of pancreas dissociation by Camillo Ricordi (**Table 1**) [11]. This method consists of a mechanically enhanced enzymatic digestion based on a dissociation-filter chamber (Ricordi chamber) allowing islets freed from gland to be removed promptly from the system to avoid over-digestion while preserving cluster integrity. This method is called Ricordi method. Washington University group performed a clinical trial of islet transplantation for three type 1 diabetic patient using the Ricordi method, however, all patients lost graft function [22].

The first series of sustained insulin independence following islet transplantation with Ricordi method was achieved for the patients after excision of liver and pancreas, and transplant of allogeneic liver and islet from the same cadaveric donors (**Table 1**) [12]. In these cases, 6 out of 10 patients achieved insulin independence for 5 to more than 16 months [23]. The group also conducted the combined liver-islet allograft transplantation for 4 patients with cirrhosis and diabetes, and the combined kidney and islet transplantation for 7 patients with end-stage renal disease due to type 1 diabetes [23]. None of the patients achieved insulin independence although islet graft function was confirmed.

In 1990, Washington University group reported the first case of insulin independence after purified allogeneic islet transplantation for the treatment of type 1 diabetes [24]. Since then insulin independence after islet transplantation was reported by other centers.

In 1994, Justus-Liebig University reported 30% insulin independence after allogenic islet transplantation [25], in 1997, the San Raffaele Institute reported 45% insulin independence after allogeneic islet transplantation [26].

The Islet Transplant Registry reported the outcomes of 267 allogeneic islet transplantation cases from several centers from 1990 until 2001 [27]. Insulin independence rate was 12.4% for periods greater than one week and 8.2% for greater than one year.

3. Edmonton protocol of allogeneic islet transplantation (new era)

In 2000, the University of Alberta group published that 7 out of 7 type 1 diabetic patients became insulin independent one year after allogeneic islet transplantation (**Table** 1) [15]. Their islet transplantation protocol was named

Protocol	Induction	Maintenance
Edmonton protocol	Daclizumab	Sirolimus, low dose tacrolimus
Islet alone transplantation	Anti-thymocyte globulin for the first transplant Basiliximab for the subsequent transplants	Sirolimus, low dose tacrolimus
Islet after kidney transplantation	Anti-thymocyte globulin (ATG) for the first transplant Basiliximab for the subsequent transplants and in a single case of suspected sensitivity to ATG	Calcineurin-based immunosuppression regimen used for the renal transplant. Up to 10 mg of prednisone

Table 2.
Immunosuppression protocol for allogeneic islet transplantation.

the Edmonton protocol. In their clinical trial, patients received two or three islet transplantations to achieve target doses. The average islet doses were 11,547 islet equivalent (IEQ)/body weight (kg). Immunosuppression was initiated immediately before transplantation. Sirolimus and low-dose tacrolimus were used for maintenance immunosuppression. In addition, Daclizumab was given intravenously every 14 days for a total of five doses (**Table** 2). Isolated islets were not cultured and transplanted as soon as possible.

International trial of the Edmonton protocol for islet transplantation was conducted [28]. The primary endpoint was insulin independence with adequate glycemic control 1 year after the final transplantation. Several secondary endpoints including insulin independence with adequate glycemic control throughout follow-up; improved values for levels of glycated hemoglobin, the mean amplitude of glycemic excursions, and basal and stimulated blood C-peptide levels, and a reduction in the need for insulin. Nine islet transplantation centers participated. The success rate of achieving primary endpoint varies among the 9 centers. The success rates were 100% in one center, 40–80% in five centers and 0% in three centers. They concluded with the Edmonton protocol of islet transplantation, insulin independence is usually not sustainable, however, persistent islet function even without insulin independence provides protection from severe hypoglycemia and improved levels of glycated hemoglobin.

In 2005, five year follow-up after islet transplantation was published by the University of Alberta group [29]. They concluded islet transplantation can relieve glucose instability and problems with hypoglycemia. C-peptide secretion was maintained in the majority of subjects for up to 5 years, although most reverted to using insulin. Since then, islet transplantation is considered a treatment to stabilize blood glucose levels and avoid hypoglycemia, not insulin independence.

4. Phase 3 trial of allogeneic islet transplantation

4.1 Islet alone transplantation

In the United States, allogeneic islet cells are regulated by the FDA as a drug, and expected to be approved under the biological license [18]. In 2016, a license-enabling multicenter phase 3 clinical trial was reported (**Table 1**) [27]. For this study, well-defined islet products were manufactured under Current Good Manufacturing Practices and Current Good Tissue Practices [30]. The collaborative

islet transplantation (CIT) consortium created the protocol for manufacturing islet products. Under CIT protocol, 324 pancreata were processed, and 170 products (52.5%) met the product release criteria. Patients received 75 of 170 successfully manufactured islet products were transplanted. For immunosuppression, they used anti-thymocyte globulin and etanercept for induction for the first transplant, with basiliximab replacing anti-thymocyte globulin at subsequent transplant (**Table 2**). Sirolimus and low-dose tacrolimus were used for maintenance immunosuppression. Twenty-two patients received one transplantation, 25 patients received two transplantation and one patient received three transplantation. The primary endpoint was the achievement of HbA1c < 7% and freedom from severe hypoglycemic events from day 28 to day 365 after the first transplantation. The primary endpoint was successfully met by 87.5% of patients, and it was concluded that islet transplantation should be considered for patients with type 1 diabetic patients and impaired awareness of hypoglycemia in whom other less invasive current treatments have been ineffective in preventing severe hypoglycemic events.

In 2018, improved health-related quality of life in phase 3 islet transplantation in type 1 diabetes complicated by severe hypoglycemia was reported [31]. The Diabetes Distress Scale (DDS), the hypoglycemic Fear Survey (HFS), the Short Form 36 Health Survey (SF-36), and the EuroQoL 5 Dimensions (EQ-5D) were applied before and after islet transplantation at days 75, 365, and 730. DDS measured emotional burden, physician-related distress, regimen-related distress, interpersonal distress, and total score. HFS measured hypoglycemic avoidance behavior, worry about hypoglycemia, and total score.

After transplantation, all items of both DDS and HFS significantly improved in every measure point. This indicated allogeneic islet transplantation can improve the QOL related to diabetes and hypoglycemia from day 75 to day 730.

SF-36 measured physical functioning scale, role physical scale, bodily pain scale, general health scale, vitality scale, social functioning scale, physical component summary (PSC), and mental component summary (MSC) (**Table 3**).

Measures	Visit	Mean (SD)	P value
PSC	Baseline	47.52 (8.77)	–
	Day 75	49.97 (8.05)	N.S.
	Day 365	52.52 (7.69)	<0.0001
	Day 730	52.44 (9.06)	0.0004
MCS	Baseline	49.23 (10.48)	–
	Day 75	53.03 (9.65)	0.0081
	Day 365	51.86 (8.94)	N.S.
	Day 730	54.40 (7.28)	N.S.
Physical Functioning scale	Baseline	50.62 (8.04)	–
	Day 75	53.30 (6.58)	0.0034
	Day 365	53.67 (7.17)	0.0005
	Day 730	52.29 (10.26)	N.S.
Role Physical scale	Baseline	45.69 (10.57)	–
	Day 75	49.17 (9.72)	0.0008
	Day 365	51.70 (7.53)	<0.0001
	Day 730	52.67 (9.04)	<0.0001
Bodily Pain scale	Baseline	50.52 (10.04)	–
	Day 75	49.96 (10.97)	N.S.
	Day 365	52.72 (8.24)	N.S.
	Day 730	53.22 (10.19)	N.S.

Measures	Visit	Mean (SD)	P value
General Health scale	Baseline	44.31 (12.42)	–
	Day 75	50.19 (10.45)	<0.0001
	Day 365	51.57 (9.92)	<0.0001
	Day 730	51.60 (11.57)	0.0064
Vitality scale	Baseline	48.81 (10.94)	–
	Day 75	54.67 (8.92)	0.0001
	Day 365	53.38 (8.53)	0.0029
	Day 730	55.38 (10.62)	0.0015
Social Functioning scale	Baseline	46.99 (10.87)	–
	Day 75	49.38 (9.72)	N.S.
	Day 365	50.98 (8.24)	N.S.
	Day 730	51.70 (10.25)	N.S.
Role Emotional scale	Baseline	48.02 (10.25)	–
	Day 75	51.58 (8.72)	N.S.
	Day 365	50.82 (8.43)	0.0090
	Day 730	52.11 (7.49)	N.S.
Mental Health scale	Baseline	51.54 (9.27)	–
	Day 75	53.83 (9.09)	N.S.
	Day 365	53.69 (8.20)	N.S.
	Day 730	54.30 (8.26)	N.S.

Table 3.
Summary of SF 36 [31].

After transplantation, at day 365 and 730, PCS was significantly improved, and at day 75, MCS was significantly improved. In each item, the physical functioning scale was significantly improved after transplantation at day 75 and 365, role physical scale, general health scale, and vitality scale, were significantly improved at all points, role emotional scale was significantly improved after transplantation at day 365. On the other hand, there was no significant change in the bodily pain scale, social functioning scale, and mental health scale.

EuroQoL measured health preference weight, usual activities, anxiety/depression, mobility, pain/discomfort, self-care, and a visual analog scale of overall health (VAS) (**Table 4**). EuroQoL demonstrated that after transplantation at 365 day VAS was significantly improved, and at 730 VAS and usual activities were significantly improved.

Measures	Visit	Mean (SD) or N no problems (%)	P value
VAS	Baseline	74.13 (14.66)	–
	Day 75	79.06 (15.97)	N.S.
	Day 365	82.86 (14.46)	<0.0001
	Day 730	85.74 (15.36)	<0.0001
Health preference weight	Baseline	0.87 (0.12)	–
	Day 75	0.86 (0.15)	N.S.
	Day 365	0.86 (0.15)	N.S.
	Day 730	0.88 (0.18)	N.S.
Usual activities	Baseline	32 (68.09%)	–
	Day 75	35 (74.47%)	N.S.
	Day 365	33 (78.57%)	N.S.
	Day 730	27 (84.38%)	0.0143

Measures	Visit	Mean (SD) or N no problems (%)	P value
Anxiety/depression	Baseline	32 (68.09%)	–
	Day 75	34 (72.34%)	N.S.
	Day 365	29 (69.05%)	N.S.
	Day 730	23 (71.88%)	N.S.
Mobility	Baseline	38 (80.85%)	–
	Day 75	40 (85.11%)	N.S.
	Day 365	34 (82.93%)	N.S.
	Day 730	26 (81.25%)	N.S.
Pain/discomfort	Baseline	25 (53.19%)	–
	Day 75	27 (57.45%)	N.S.
	Day 365	24 (57.14%)	N.S.
	Day 730	22 (68.75%)	N.S.
Self-Care	Baseline	45 (95.74%)	–
	Day 75	46 (97.87%)	N.S.
	Day 365	39 (92.86%)	N.S.
	Day 730	29 (90.63%)	N.S.

Table 4.
Summary of EuroQOL [31].

However, all other measurements had no significant improvements. Allogeneic islet transplantation dramatically improved hypoglycemia-related QOL.

4.2 Islet after kidney transplantation

In 2021, a phase 3 trial of human islets after kidney transplantation in type 1 diabetes was reported (**Table 1**) [19]. This was an open-label, single-arm study involving subjects with type 1 diabetes who had previously received kidney transplantation conducted at 10 centers in North America. The primary endpoint was achieving HbA1c level equal to or less than 6.5%, or reduction in HbA1c of at least 1 point from baseline to day 365, and freedom from severe hypoglycemic events from day 28 to day 365 after the initial islet transplant. For immunosuppression, induction immunosuppression consisted of rabbit anti-thymocyte globulin (ATG) and etanercept for the first transplant, with basiliximab replacing ATG for subsequent transplant and in a single case of suspected sensitivity to ATG (**Table 2**). The calcineurin-based maintenance immunosuppression regimen used for the renal transplant was continued after the islet transplant. Up to 10 mg of prednisone was allowed as part of maintenance immunosuppression.

Twenty-four patients who experienced kidney transplantation received allogeneic islet transplantation. Elven patients received single transplantation, 11 patients received two transplantations, and 2 patients received 3 transplantations. After islet transplantation at 365 days, 15 patients (62.5%) met primary endpoints. They also measured DDS and HFS before and after islet transplantation at day 75, 365, 730, and 1095. Both DDS and HFS demonstrated improved QOL after islet transplantation in type 1 diabetic patients who previously received kidney transplantation at all time points. This study also indicated that islet transplantation is effective treatment for patients with type 1 diabetes and unstable glucose control despite intensive insulin treatment, supporting the indication for islet transplantation in the post-renal transplant setting.

More general QOL was assessed with Euro QOL Visual Analog Scale (VAS). EuroQOL VAS from baseline to day 75, day 365, day 730, and day 1095 following islet transplantation were statistically analyzed. The P-values at day 75 were 0.1016 at day 75, 0.0002 at day 365, 0.0952 at day 730, and 0.0327 at day 1095.

In 2022, long-term outcomes with islet-alone transplantation and islet-after-kidney transplantation for type 1 diabetes in the clinical islet transplantation consortium were reported [32]. Islet alone (n = 48) and islet-after-kidney (n = 24) transplant recipients were followed up to 8 years after allogeneic islet transplantation. The primary endpoint is duration of sustained islet allograft function as determined by evidence from MMTT of c-peptide production at each anniversary of the final transplant. A c-peptide level greater than or equal to 0.3 ng/mL at 0, 60, or 90 minutes will be considered evidence of islet allograft function.

Among them, 26 islet patients and 8 patients for islet-after-kidney patients completed long-term follow-up with islet graft function, 15 and 7 withdrew from follow-up with islet graft function, and 7 and 9 experienced graft failure, respectively.

5. Efforts to improve the efficacy of allogeneic islet transplantation

Phase 3 clinical trial of allogeneic islet transplantation demonstrated the benefit of the islet transplantation, on the other hand, the success rate of production was 52.5%. Improving the success rate is critically important to utilize precious human donor pancreas.

Baylor Research Institute group demonstrated seven consecutive successful clinical islet isolations using the pancreatic ductal injection technique [33]. The average islet yield was 588,566 ± 64,319 islet equivalent (IEQ), and 6 islet products were implanted into 3 type 1 diabetic patients. All three patients achieved insulin free. They demonstrated that ductal injection immediately after pancreas procurement could enhance the delivery of collagenase resulting in the high success rate of islet isolation [34]. The group also analyzed the 100 human islet isolation, then revealed that in addition to the ductal injection, pancreas procurement by the islet isolation team, two-layer pancreas preservation, and short cold ischemic period had a significant impact to improve the success rate of islet isolation [35]. Among them, the two-layer pancreas preservation was created by Dr. Takashi Kawamura and Dr. Yoshikazu Kuroda (**Figure 1**) [36]. The two-layer method consists of an organ preservation solution and perfluorocarbon. During the preservation by the two-layer method, oxygen is continuously supplied through the perfluorocarbon, and the pancreas can be oxygenized. This method provided the longest preservation period before whole pancreas transplantation using canine model [37] and high islet yield [38]. The first clinical trial of the two-layer preservation before pancreas transplantation and islet isolation was both conducted at the University of Minnesota [39, 40]. Oxygen charged two-layer method was developed to eliminate bringing an oxygen tank for continuous oxygenation [41]. The two-layer pancreas preservation was used for clinical islet transplantation using a non-heart-beating donor (**Table 1**) [17] and the first successful living donor islet transplantation (**Table 1**) [16].

Even improving the efficacy of islet transplantation is important, as long as donor source is human, it is not possible to treat all type 1 diabetic patients who need islet transplantation.

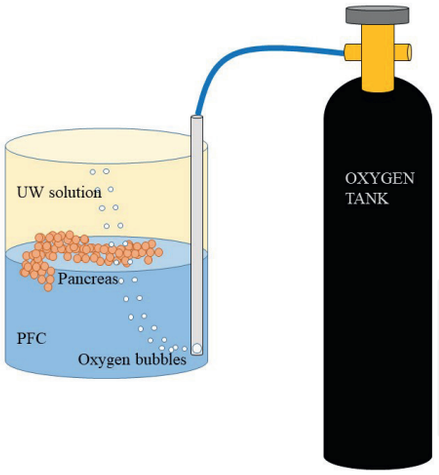

Figure 1.
Two-layer preservation method consists of perfluorocarbon (PFC) and organ preservation solution (for example University of Wisconsin (UW) solution). PFC is unsolvable in the water therefore, PFC and organ preservation solution clearly created the two-layer. The procured pancreas locates between the PFC and organ preservation solution. Oxygen has been provided to PFC for the original two-layer method. For oxygen static charged two-layer method, before using the two-layer preservation method, PFC was fully oxygenated. Fully oxygenated PFC could reserve adequate oxygen concentration for up to 18 hours. During preservation by the two-layer method, pancreas has been oxygenated and maintained high energy status. The two-layer pancreas preservation enabled the longest preservation period before canine whole pancreas transplantation and improved islet yield after human islet isolation.

6. Overcome the issue of donor shortage

6.1 Clinical porcine islet xenotransplantation

In 1994, transplantation of porcine islet-like cell clusters (ICCs) was implanted into 10 insulin-dependent diabetic kidney transplant patients (**Table 1**) [13]. Among the 10 patients, 8 patients received ICCs into the portal vein and the other two patients received ICCs under the kidney capsule. Four patients who received ICCs into portal vein secreted porcine C-peptide for 200 to 400 days. A biopsy was conducted on one patient who received ICCs under kidney capsule, and ICCs with positive insulin and glucagon stains were detected. On the other hand, insulin reduction was not achieved.

In 2000, two cases of encapsulated neonatal porcine islet transplantation were reported (**Table 1**) [14]. The first patient was a 41-year-old male who had type 1 diabetes for 18 years and required 50 units insulin per day. He received total of 13,000,000 IEQ encapsulated porcine islets. The second patient was a 39-year-old female who had type 1 diabetes for 24 years. She required 49 units of insulin per day. She received kidney transplantation two years before this islet transplantation; therefore. She took maintenance immunosuppression with cyclosporine, azothiaprine, and prednisone. She received 930,000 IEQ-encapsulated porcine islets. Both patients experienced a significant reduction in frequency of severe hypoglycemic reactions. Porcine C-peptide had been detected over 14 months, and improved HbA1c and 8–40% reduction of insulin were confirmed until 27 months post-transplantation.

More than 9 years after transplantation, the first patient was followed. Oral glucose tolerance test revealed positive porcine insulin. Laparoscopic biopsy demonstrated that the alginate capsule included insulin and glucagon-positive cells [42].

In 2005, twelve adolescent diabetic patients received neonatal porcine islet combined with porcine Sertoli cell transplantation using a subcutaneous device. Eleven patients received second transplantation and 4 patients received third transplantation. At 4 years, half of the patients achieved reduction of insulin doses. Notably, two patients achieved insulin independence [43]. The same group reported long-term follow-up study outcomes of 21 type 1 diabetic patients [44]. The median time post-transplantation was 5.7 years. More than half of the patients reduced insulin doses by more than 30% compared with pre-transplantation. Before transplantation 14 patients had chronic complications of diabetes including neuropathy (n = 5) evidenced by abnormal speed of nervous conduction, non-proliferative diabetic retinopathy (n = 5), and microalbuminuria (n = 8). At the follow-up, only two patients had chronic complications. No patients had neuropathy, 1 patient had retinopathy and 2 patients had microalbuminuria.

In 2011, Wang et al. reported that 22 patients received neonatal porcine islets in the hepatic artery [45]. The first 14 patients were treated with cyclosporine, mycophenolate mofetil (MMF), and prednisolone, the following 2 patients were treated with cyclosporine and MMF, and the next 6 patients were treated with OKT. The first 14 patients required less insulin and improved HbA1c after transplantation. In the 2 subsequent patients did not have any metabolic change and porcine C-peptide was negative. The last 6 patients reduced insulin requirements, and HbA1c was normalized 3 months after the transplantation.

In 2011, Matsumoto et al. reported that 14 patients in received encapsulated neonatal porcine islets in the abdominal cavity without immunosuppressive drugs in New Zealand [46]. Patients received 5000 (n = 4), 10,000 (n = 4), 15,000 (n = 4), and 20,000 (n = 2) IEQ/kg islets. There were no apparent differences among the groups. Patients experienced reduction of unaware hypoglycemia and minimal change in HbA1c and insulin doses one year after transplantation. In 2016, the same group reported 8 patients who received encapsulated neonatal porcine islets in the abdominal cavity without immunosuppressive drug in Argentina [47]. Four patients received 10,000 IEQ/kg and the other 4 patients received 20,000 IEQ/kg. All patients improved HbA1c, and high dose group demonstrated a significant reduction in the number of unaware hypoglycemia. They also demonstrated no zoonosis after 5–7 years of islet xenotransplantation [48]. Recently, they reported 21 patients' opinions who received encapsulated neonatal porcine islet transplantation after approximately 10 years [49]. Importantly, no patients suffered zoonosis, and no patients suffered cancer. Compared with pre-transplantation, the majority of patients still improved glycemic control, diabetic management, and reduced severe hypoglycemic events and hyperglycemia required hospitalization even after 10 years of transplantation. All patients considered this treatment adequate and majority of patients wanted to recommend this treatment to the other patients and desired to receive booster transplantation.

6.2 Stem cell-derived beta cell transplantation in clinic

In 2021, stem cell-derived pancreatic endoderm cell transplantation was reported (**Table 1**) [20]. Stem cell-derived pancreatic endoderm cells within the device were transplanted into 17 type 1 diabetic patients. Since the device has no immune protective property, the patients received immunosuppressive drugs. The induction immunosuppression was anti-thymocyte globulin up to 6 mg/kg iv over 5 days, TNF alpha blocking etanercept 50 mg iv pre-implant followed 25 mg subcutaneous x 3 doses

after transplant. Maintenance immunosuppression was tacrolimus (target 10–12 ng/mL for the first 3 months; 7-9 ng/mL there-after) and mycophenolate mofetil up to 2 g per day as tolerated.

Primary efficacy endpoint was C-peptide measurements. A total of 6/17 subjects (35.3%) demonstrated stimulated C-peptide at varying time points. Adverse events were related to side effects of immunosuppressive drugs (33.7%) followed by surgical procedures (27.9%).

7. Conclusions

Allogeneic islet transplantation has become the standard therapy for unstable type 1 diabetic patients for avoiding severe hypoglycemia. Considering a large number of type 1 diabetic patients, donor shortage is an issue for allogeneic islet transplantation. To overcome the donor shortage, xenogeneic islet transplantation had been conducted for more than 10 years, and recently stem cell-derived pancreatic endoderm cell transplantation began. With advanced technology, we wish type 1 diabetes will become a curable disease.

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Conflict of interest

Shinichi Matsumoto is a chief scientific officer at Otsuka Pharmaceutical Factory Inc. and an adviser at PorMedTec Inc.

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