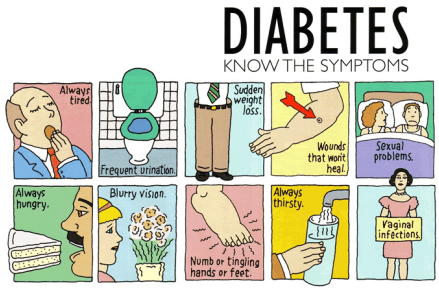
Diabetes

- The number of people with diabetes rose from 108 million in 1980 to 422 million in 2014.
- The global prevalence of diabetes among adults over 18 years of age rose from 4.7% in 1980 to 8.5% in 2014.
- Between 2000 and 2016, there was a 5% increase in premature mortality from diabetes.
- Diabetes prevalence has been rising more rapidly in low- and middle-income countries than in high-income countries.
- Almost half of all deaths attributable to high blood glucose occur before the age of 70 years. WHO estimates that diabetes was the seventh leading cause of death in 2016.
- A healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use are ways to prevent or delay the onset of type 2 diabetes.
- Diabetes can be treated and its consequences avoided or delayed with diet, physical activity, medication and regular screening and treatment for complications.

Diabetes

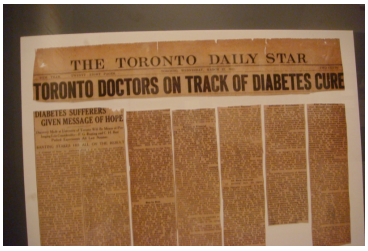
- Diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation.

- Type 1: juvenile-onset diabetes, autoimmune destruction of beta-cells
- Type 2: adult-onset, familiar, insulin-resistance combined with reduced secretion



Current therapy for diabetes

No cure available
Support therapy: insulin (type 1), diet, exercise, oral medications (type 2)
Whole organ transplant requires strong immunosuppression (only in combination with kidney transplant).


THE TORONTO DAILY STAR
TORONTO DOCTORS ON TRACK OF DIABETES CURE
DIABETES SUFFERERS GIVEN MESSAGE OF HOPE

Insulin was discovered over 90 years ago by JJR Macleod at the University of Toronto.

The first patient, Leonard Thompson, at the time of treatment was on a starvation diet that was intended to extend his life for a few years.

He was injected with a crude extract of bovine pancreas in January 1922 with an almost immediate effect on his glycosuria, blood glucose levels and general well-being.

From that moment onward diabetes was no longer a fatal disease.

Current therapy for diabetes

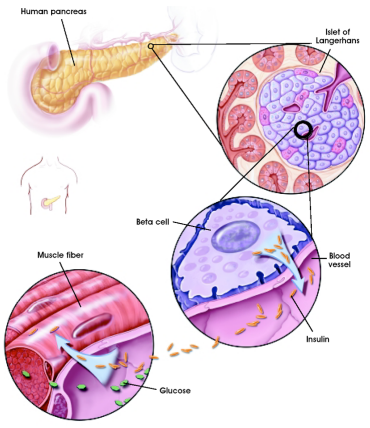
Medscape®	www.medscape.com
1922	First clinical use of insulin
1920s	Short-acting bovine and porcine pancreas extracts
1930s	Improved purification
	Protamine-insulin complexes reported
1940s	NPH (neutral protamine Hagedorn) introduced
1950s	Lente and ultralente insulins
1970s	Highly purified (monocomponent) insulins
1980s	Premixed biphasic insulins
	Insulin pumps for CSII (continuous subcutaneous insulin infusion)
	Biosynthetic human insulin
	Pen injection devices
1990s	Rapid-acting insulin analogues
2000s	Long-acting insulin analogues

Source: Br J Diabetes Vasc Dis © 2004 Sherbourne Gibbs, Ltd.

There have been many major breakthroughs since 1922, but none more important than the cloning and sequencing of the insulin gene in 1980, which brought about the introduction of unlimited supplies of bacterially expressed human insulin and the technology to modify the structure of the protein.

There are now at least 6 rapid- acting or long-acting analogues.

Pancreas structure



Langherans islets:

- Different cell types:
  - Alpha cells producing glucagon (15–20% of total islet cells)
  - Beta cells producing insulin and amylin (65–80%)
  - Delta cells producing somatostatin (3–10%)
  - PP cells (gamma cells) producing pancreatic polypeptide (3–5%)
  - Epsilon cells producing ghrelin (<1%)
- Complex interplay in glucose metabolism regulation
- Digestive enzymes secreted by exocrine pancreatic tissue
- Islet transplantation better than whole organ and beta-cell transplantation

Table 1. Synopsis of Reports of Successful Islet Transplantation in Patients with Type 1 Diabetes.*

Study	Year of Report	No. of Recipients and Size of Transplant	Outcome
Largiader et al.[19]	1980	1 Recipient of pancreas microfragments containing 200,000 islets	Insulin-independent with normal glucose level at 9½ mo
Scharp et al.[22]	1990	1 Recipient of 800,000 islets	Insulin-independent at 22 days
Tzakis et al.[23]	1990	9 Patients with cancer and abdominal exenteration without diabetes received 205,000–746,000 islets	Normal glycosylated hemoglobin values in 5 patients, with some receiving insulin supplementation
Warnock et al.[24]	1991	1 Recipient of 611,000 islets	Insulin-independent with normal glucose levels at 3 mo
Scharp et al.[25]	1991	First 9 patients receiving 6161±911 to 13,916±556 islets/kg of body weight	3 Transplantations failed; 4 had measurable C-peptide levels for up to 10 mo but not insulin-independent; 2 with normal glucose levels and insulin-independent for 1–5 mo
Warnock et al.[26]	1992	4 Recipients of 261,000–896,000 fresh and cryopreserved islets	3 Had measurable C-peptide levels for 1–8 mo, but not insulin-independent; 1 insulin-independent for 1 yr
Gores et al.[27]	1993	2 Recipients of 502,000–528,000 islets	1 Had measurable C-peptide levels but not insulin-independent at 9 mo; 1 with normal glucose levels and insulin-independent at 8 mo
Soon-Shiong et al.[28]	1994	1 Recipient of 678,000 encapsulated islets	Insulin-independent with normal glucose levels at 9 mo
Carroll et al.[29]	1995	1 Patient with cancer and abdominal exenteration without diabetes	Insulin-independent with normal glycosylated hemoglobin values at 3 yr
Luzi et al.[30]	1996	15 Recipients of 98,587–1,294,125 islets	8 Had C-peptide levels >1.4 ng/liter; 4 insulin-independent with glycosylated hemoglobin values of 5.6–7.2 percent at 1–8 mo
Alejandro et al.[31]	1997	8 Recipients of 478,000–1,271,000 islet equivalents	2 Insulin-independent at 1 mo and 2 insulin-independent at 6 yr with normal to near-normal glycosylated hemoglobin values
Secchi et al.[32]	1997	20 Recipients of 3461–14,488 islet equivalents/kg	9 Had measurable C-peptide levels with decreased need for insulin; 6 insulin-independent at 3–11 mo; 1 insulin-independent at 48 mo; all with normal or near-normal glycosylated hemoglobin values
Keymeulen et al.[33]	1998	7 Recipients of 2100–5300 islet equivalents/kg	3 Had measurable C-peptide levels for >1 yr; 2 insulin-independent with normal to near-normal glycosylated hemoglobin values for 1 yr
Oberholzer et al.[34]	2000	13 Recipients of 199,000–863,000 islets	All had measurable C-peptide levels for >3 mo; 5 of 8 had normal C-peptide levels >1 yr; 2 patients insulin-independent at 4 and 36 mo
Shapiro et al.[35]	2000	7 Recipients of 11,546±1604 islets	All insulin-independent at 4–15 mo with 6-month glycosylated hemoglobin values of 5.7±0.2 percent

The New England Journal of Medicine

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VOLUME 343 JULY 27, 2000 NUMBER 4

ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

A.M. James Shapiro, M.B., B.S., Jonathan R.T. Lakey, Ph.D., Edmond A. Ryan, M.D., Gregory S. Korbutt, Ph.D., Ellen Toth, M.D., Garth L. Warnock, M.D., Norman M. Kneteman, M.D., and Ray V. Rajotte, Ph.D.

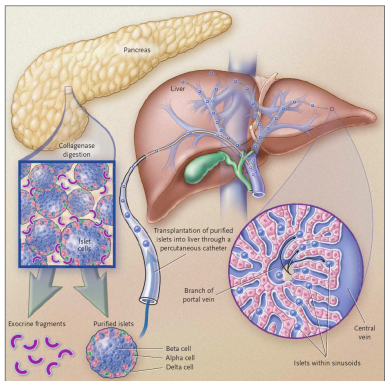
Patient and Procedure No.	Age of Donor	Duration of Cold Ischemia: from cross-clamping to islet isolation	Duration of Cold Ischemia: from cross-clamping to implantation	Total Beta-Cell Mass per Transplant*
	yr	hr		×10⁻⁶
Patient 1				
1	35	4.0	7.5	
2	41	9.5	14.5	
Patient 2				102.2
1	71	1.5	8.0	192.4
2	17	8.5	18.0	
Patient 3				173.6
1	48	3.0	11.4	262.5
2	22	5.0	14.2	
Patient 4				113.8
1	65	2.0	7.0	42.9
2	38	2.5	10.3	
3§	42	5.0	43.0	60.2
3§	39	3.5	21.0	181.3
Patient 5				139.1
1	54	6.5	13.3	193.2
2	57	1.5	7.0	
Patient 6				100.6
1	51	6.0	11.5	166.2
2	44	15.0	18.4	
Patient 7				101.5
1	55	5.0	10.5	31.1
2	41	1.0	6.5	
				50.1
				197.8
Mean (±SD) values	45.0±14	4.8±3	13.9±9	132±67

All patients insulin-free at 1 year !!!!

Important limits:

- 2 donors per transplant
- 11,000 islet equivalents per kilogram body weight
- histocompatibility
- early explant (max 8 hr)

Modern islet isolation technology



- Availability of a healthy pancreas from a brain-dead donor
- Same technique used to procure a pancreas for whole-organ transplantation
- Pancreas duct cannulation and collagenase infusion
- Islet purification by density-gradient centrifugation
- Infusion into the portal vein

The Journal of Clinical Investigation http://www.jci.org Volume 114 Number 7 October 2004

Science in medicine

Challenges facing islet transplantation for the treatment of type 1 diabetes mellitus

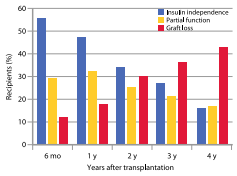
Kristina I. Rother and David M. Harlan

Islet and Autoimmunity Branch, National Institutes of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, Maryland, USA.

Compared to pancreas transplantation, islet transplantation is easier, has lower morbidity and permits storage of the islet graft (cryopreservation for banking)

Yet, islet transplantation does not offer permanent cure of hyperglycemia for all diabetic patients in need

- Only 10% maintain insulin independence after 15 months



- High number of islets is required: 850,000 with Edmonton protocol, 300,000 with autotransplantation after pancreatectomy
- Imbalance between supply and demand. Eligible patients have had T1D for >5 years, are aged 18-65, have poor diabetes control
- Significant side effects due to immunosuppression

Source: Collaborative Islet Transplant Registry (CITR)

Immunosuppressive regimen that avoids the use of diabetogenic glucocorticoids

Table 1

Systemic side effects commonly associated with the immunosuppressive agents typically administered following islet transplant

Immunosuppressant (brand name)	Drug classification	Common and important side effects (Phase of drug administration)
Rapamycin, also known as Sirolimus (Rapamune)	Macrocyclic lactone	Hyperlipidemia, antiproliferation (e.g., anemia, diarrhea) (Maintenance)
FK506, also known as Tacrolimus (Prograf)	Calcineurin inhibitor	Hypertension, nephrotoxicity, CNS effects (e.g., tremor), diabetogenicity (Maintenance)
Daclizumab (Zenapax)	mAb-binding IL-2 receptor α subunit	May increase risk of infections; hypersensitivity (Induction)

The net effect of improved glycemia control produced by the transplant, when balanced against the immunosuppressive-associated hypertension, hyperlipidemia, and decreased renal function, may actually decrease quality of life and increase mortality

Alternative sources of cells for regulated insulin secretion

1. Expanding islet cellular mass in vitro

   Inexorable decline in insulin production
   Islets are mini-organs

2. Islets from species other than humans

   Humans express high titers of antibodies against a galactose residue present on most pig cells (historically pigs were the first source of insulin for diabetes treatment)

3. Promotion of β-cell differentiation from stem cells

XENOTRANSPLANTATION

Prolonged diabetes reversal after intraportal xenotransplantation of wild-type porcine islets in immunosuppressed nonhuman primates

Bernhard J Hering[1], Martin Wijkstrom[1], Melanie L Graham[1], Maria Hårdstedt[2], Tue C Aasheim[1], Tan Jie[1], Jeffrey D Ansite[1], Masahiko Nakano[1], Isaac Cheng[1], Wei LP, Kathleen Moran[1], Uwe Christians[3], Colleen Finnegan[4], Charles D Mills[1], David E Sutherland[1], Pratima Bansal-Pakala[2], Michael P Murtaugh[4], Nicole Kirchhof[5] & Hauk-Jan Schuurman[2]

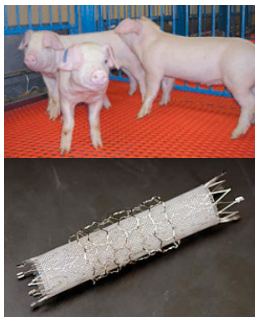
NATURE MEDICINE VOLUME 12 | NUMBER 3 | MARCH 2006

Problem of immune rejection

- use of transgenic pigs that do not express xenogenic surface antigens

- islet embedding in alginate microcapsules

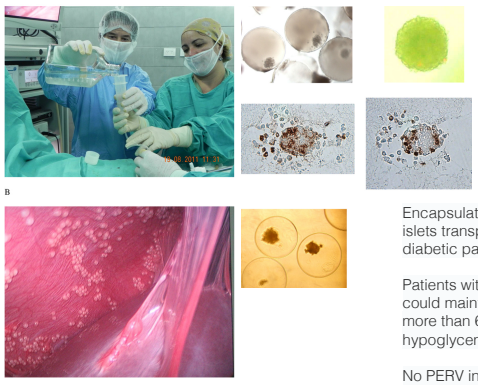
- influence the recipient's immune system



Clinical Benefit of Islet Xenotransplantation for the Treatment of Type1 Diabetes

Shinichi Matsumoto MD[a,*], Adrian Abalovich MD[b], Carlos Wechsler MD[b], ShaunWynyard PhD[c], Robert B. Elliott MD[c,d]

EBioMedicine 12 (2016) 255–262

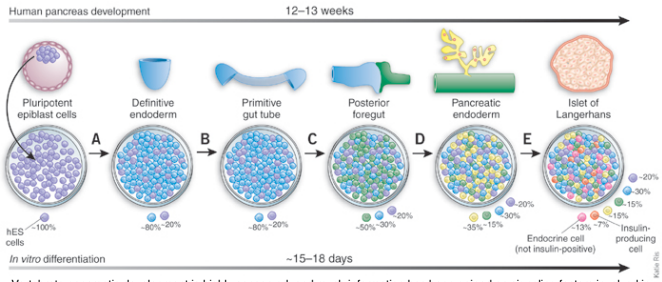


Encapsulated porcine neonatal islets transplanted into type 1 diabetic patients (8 patients).

Patients with high dose group could maintain HbA1c < 7% for more than 600 days with reduced hypoglycemic events.

No PERV infection in all patients

Directed differentiation of hES or iPS cells to insulin-producing cells by mimicking embryonic development



Vertebrate pancreatic development is highly conserved, and much information has been gained on signaling factors involved in patterning of the early gut tube toward the pancreas. This information can be translated into a stepwise differentiation protocol that includes sequential exposure to:

(i) FGF10 and the hedgehog-signaling inhibitor cyclopamine, and removal of activin A (inducing the primitive gut-tube markers HNF1B and HNF4A)

(ii) retinoic acid inducing the posterior gut-tube markers HNF6, PDX1 and HLXB9

(iii) exendin-4 with DAPT-mediated inhibition of Notch signaling inducing pancreatic epithelial markers including endocrine progenitor markers such as NKX6-1, NKX2-2, NGN3 and PAX4

(iv) exendin-4, IGF1 and HGF (inducing PAX6, NEUROD1, ISL1 and hormone-gene expression).

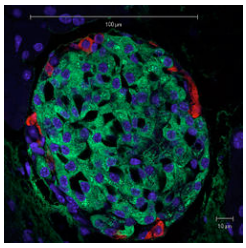
Protocol for the differentiation of pluripotent cells in functional islets

- D0-2: induce formation of Definite Endoderm by high concentrations (100 ng/ml) of activin A, which mimics the effects of nodal signaling in the early embryo

- D2-4: specification of the pancreas, by adding retinoic acid and inhibiting endogenous sonic hedgehog signaling with cyclopamine

-D4-6:formation of the pancreatic cell types by adding FGF and inhibiting the actions of activin A, which at this stage would push the cells towards liver lineages

- D7-9: inhibit Delta/Notch signaling, by use of a γ-secretase inhibitor, to enrich for a population of endocrine progenitors



To date it has not been possible to differentiate these progenitors further into fully functional β-cells; however when placed under the kidney capsule or epididymal fat pad of immunocompromised mice, the progenitors, after 12 weeks or so, secrete human C-peptide in a manner that responds to a glucose tolerance test and can rescue hyperglycemia if the mice are subsequently treated with streptozotocin, which kills mouse but not human β-cells

Markers of functional β-cells

MAFA: a basic leucine zipper transcription factor expressed in mature β cells and absent in pancreatic progenitors and other cell types

NEUROD1: downstream factor of NGN3 expressed in most pancreatic endocrine cells, including β cells)

PDX1/NKX 6.1: restricted coexpression in β cells

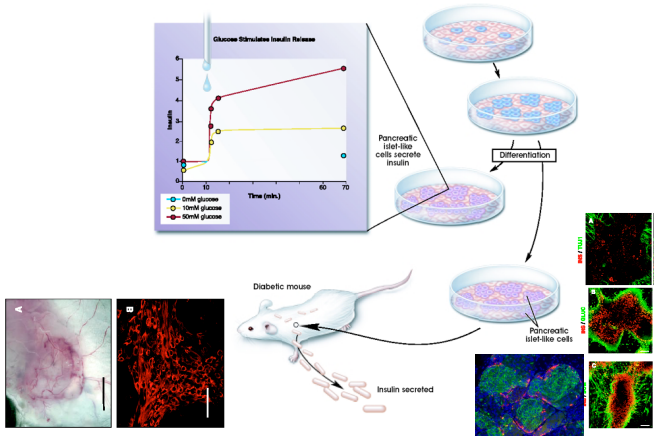
Functional features of β-cells

Glucose-stimulated insulin secretion (GSIS)

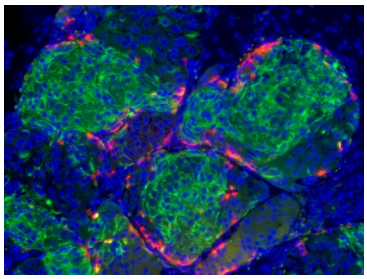
C-peptide secretion

Glycemia control in diabetic mice

Islet cells transplantation for diabetes



From stem cells to billions of human insulin-producing cells



The generation of insulin-producing pancreatic β cells from stem cells in vitro would provide an unprecedented cell source for drug discovery and cell transplantation therapy in diabetes. However, insulin-producing cells previously generated from human pluripotent stem cells (hPSC) lack many functional characteristics of bona fide β cells. Here, we report a scalable differentiation protocol that can generate hundreds of millions of glucose-responsive β cells from hPSC in vitro. These stem-cell-derived β cells (SC-β) express markers found in mature β cells, flux Ca^{2+} in response to glucose, package insulin into secretory granules, and secrete quantities of insulin comparable to adult β cells in response to multiple sequential glucose challenges in vitro. Furthermore, these cells secrete human insulin into the serum of mice shortly after transplantation in a glucose-regulated manner, and transplantation of these cells ameliorates hyperglycemia in diabetic mice.

Generation of Functional Human Pancreatic β Cells In Vitro

Felicia W. Pagliuca,[1,3] Jeffrey R. Millman,[1,3] Mads Gürtler,[1,3] Michael Segel,[1] Alana Van Dervort,[1] Jennifer Hyoje Ryu,[1] Quinn P. Peterson,[1] Dale Greiner,[2] and Douglas A. Melton[1,*]
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http://dx.doi.org/10.1016/j.cell.2014.09.040

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VERTEX

Vertex Announces Positive Day 90 Data for the First Patient in the Phase 1/2 Clinical Trial Dosed With VX-880, a Novel Investigational Stem Cell-Derived Therapy for the Treatment of Type 1 Diabetes

October 18, 2021

- First patient dosed with VX-880 demonstrated restoration of insulin production and achieved C-peptide of 560 pmol/L in response to Mixed Meal Tolerance Test (MMTT) at Day 90 Visit -

- 91% decrease in daily insulin requirement and simultaneous robust improvements in glucose control as measured by HbA1c -

- Treatment was generally well tolerated -

BOSTON--(BUSINESS WIRE)--Oct. 18, 2021-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced positive Day 90 data for the first patient from the Phase 1/2 clinical trial of VX-880, an investigational stem cell-derived, fully differentiated pancreatic islet cell replacement therapy for people with type 1 diabetes (T1D). This is the first demonstration of a patient with T1D achieving robust restoration of islet cell function from such a cell therapy.

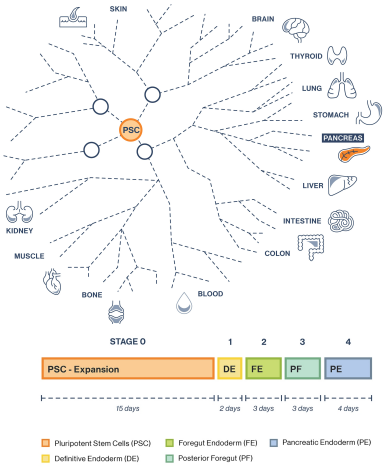
The patient was treated with a single infusion of VX-880 at half the target dose in conjunction with immunosuppressive therapy. The patient achieved successful engraftment and demonstrated rapid and robust improvements in multiple measures, including increases in fasting and stimulated C-peptide, improvements in glycemic control, including HbA1c, and decreases in exogenous insulin requirement. VX-880 was generally well tolerated.

"These results from the first patient treated with VX-880 are unprecedented. What makes these results truly remarkable is that they were achieved with treatment at half the target dose," said Bastiano Sanna, Ph.D., Executive Vice President and Chief of Cell and Genetic Therapies at Vertex. "While still early, these results support the continued progression of our VX-880 clinical studies, as well as future studies using our encapsulated islet cells, which hold the potential to be used without the need for immunosuppression."

VIACYTE
Regenerating Health™

The process mimics the natural development of the human pancreas. During each step, prescribed types and amounts of growth factors, growth media, and supplements direct pluripotent stem cells to progress along the differentiation pathway until they become pancreatic precursor cells (PEC-01).

Once implanted under the skin of a patient, PEC-01 cells, which are contained within an implantation device, have been designed to mature into functional beta cells and other cells of the islet that control blood glucose levels.



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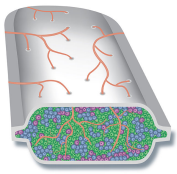
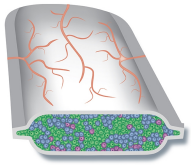
PEC-Direct (VC-02)



Pouch designed to allow blood vessels to enter the device and directly interact with PEC-01 cells. Vascularization allows for robust and consistent engraftment but necessitates immune suppression therapy because implanted cells are not hidden from the immune system.

PEC-Encap (VC-01)



Pouch designed to fully contain the implanted cells but still allows vital nutrients (oxygen, glucose, insulin) to travel between the cells inside the device and blood vessels, which grow along the outside of the device.

This device is designed to prevent immune cells from directly contacting the implanted cells.

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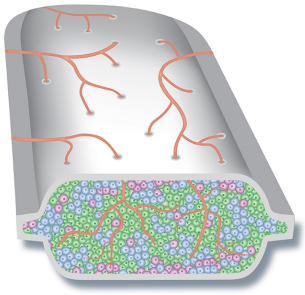
PEC-QT (VCTX210)



Using gene editing on the pluripotent stem cell protects implanted cells from immune system by ex vivo editing of immune-modulatory genes (collaboration between ViaCyte and CRISPR Therapeutics)