Leiden University
Medical Center

TRIP Symposium 2025
Eilandjes van Langerhans Transplantatie

Marten A. Engelse, PhD

Associate Professor

Head of Laboratory for Islet Isolation LUMC

Pancreatic Islets

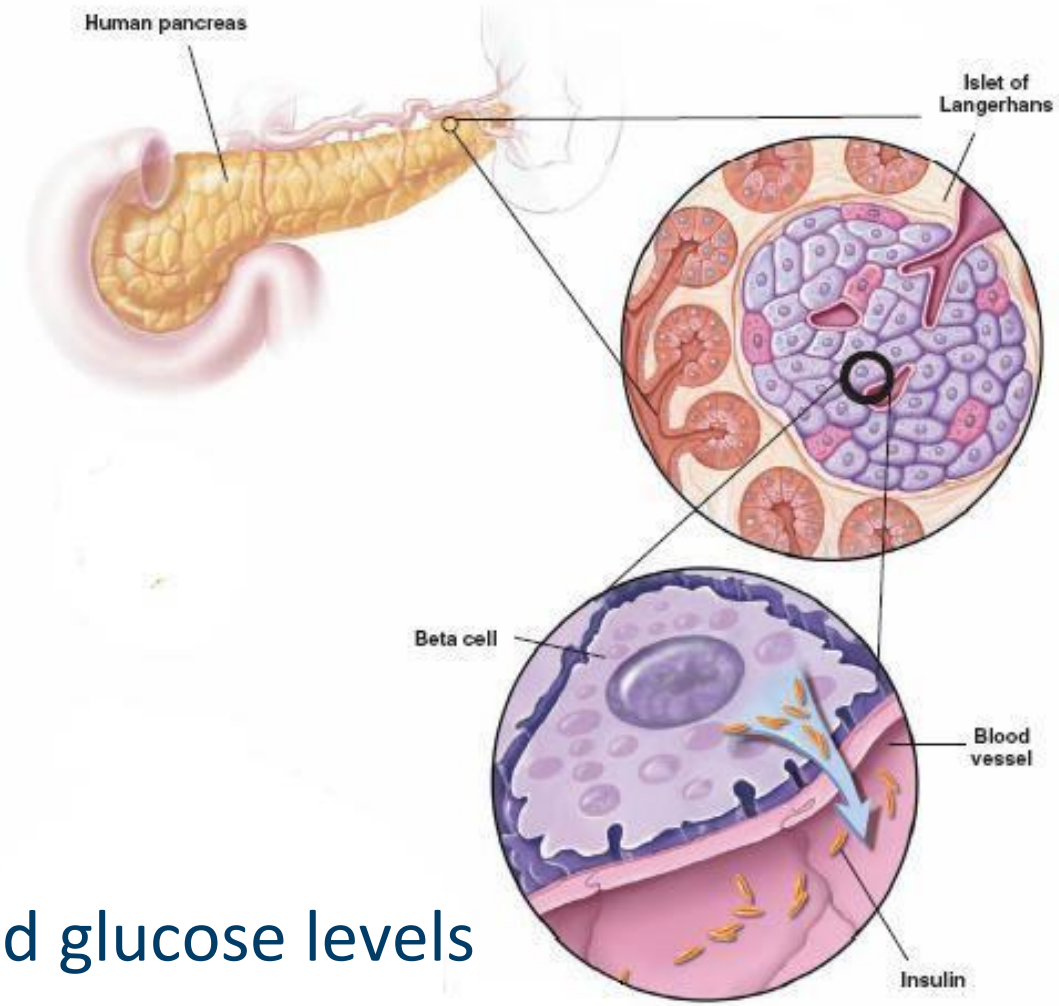
Pancreas

Exocrine

- Digestive enzymes

Endocrine

- Hormones



Pancreatic islets

1 – 2 million islets per organ

1 – 2 % of total organ

α-, β-, δ- and PP-cells

β-cells produce insulin that regulates blood glucose levels

Type-1 Diabetes

422 million people worldwide suffer from diabetes (WHO ‘14)
Approx. 10% diagnosed with type 1 diabetes
Selective auto-immune destruction of β-cells

→ Therapy: exogenous Insulin injections to attain normal glucose levels

To prevent hyperglycaemic complications

- Nephropathy, neuropathy, retinopathy

Risk of hypoglycaemia (unawareness)

- Fainting, coma, death

→ Sometimes a difficult balance……

Beta cell replacement therapy

→ 2 types β-cell replacement therapies:

- Whole-organ pancreas transplantation
  - Invasive procedure

- Islet transplantation
  - Selective transplantation of pancreatic islets
  - Minor surgical procedure

The first recorded human pancreatic transplant was probably performed on December 20, 1893, twenty-nine years before the isolation of insulin by Banting and Best. Dr. P. Watson Williams and his surgical colleague, Mr. Harsant, treated a 15-year-old boy in the Bristol Royal Infirmary by the subcutaneous implantation of 3 pieces of freshly slaughtered sheep's pancreas, each "the size of a Brazil nut."

Williams, P.W.: Notes on diabetes treated with extract and by grafts of sheep's pancreas. Br. Med. J. 2:1303, 1894

Procedures Laboratory for Islet Isolation

- Allogeneic Islets
- Autologous Islets

First isolation December 15th 2006, First Transplantation October 31st, 2007

Diabeet in Leiden krijgt insulinecel

Door onze redactie wetenschap

ROTTERDAM, 11 DEC. Voor het eerst in Nederland is een suikerpatiënt behandeld met de insuline producerende cellen van een donor. Dat maakte het Leids Universitair Medisch Centrum, dat de transplantatie enkele weken geleden uitvoerde, vandaag bekend. De 39-jarige vrouw hoeft nu veel minder van het hormoon insuline te spuiten.

Bijzonder van de behandeling is dat de ziekte bij de bron wordt aangepakt, want defecte insuline producerende cellen zijn de oorzaak van diabetes type 1. Die cellen zijn bij de patiënte nu vervangen. De transplantatie is echter [illegible]

suikerspiegel zo dat zij bewusteloos raken.

Het is een oud idee om de ziekte te genezen door patiënten te behandelen met eilandjes van Langerhans uit de alvleesklier van een overleden donor. Echter, pas in 2000 lukte het Canadese artsen om dat op een betrouwbare manier te doen. Sindsdien is de behandeling wereldwijd bij circa zeshonderd diabetici uitgevoerd. De eilandjes worden uit de alvleesklier geïsoleerd en ingespoten in de poortader van de patiënt. De cellen nestelen zich dan in de lever.

De Leidse internist-endocrinoloog Eelco de Koning is tevreden: hij vertelde dat het heel goed met

October 31st, 2007

Allogeneic islet transplantation:
Donor pancreas derived islets

→ Islets after kidney (Type1-DM)
→ Islets alone (Type-1 DM)
→ Islets after lung (CF)

Pancreatic Islet production

Pancreatic Islet production

In Class A in B cleanroom in GMP environment

DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 31 March 2004
on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

Substances of Human Origin (SoHO)

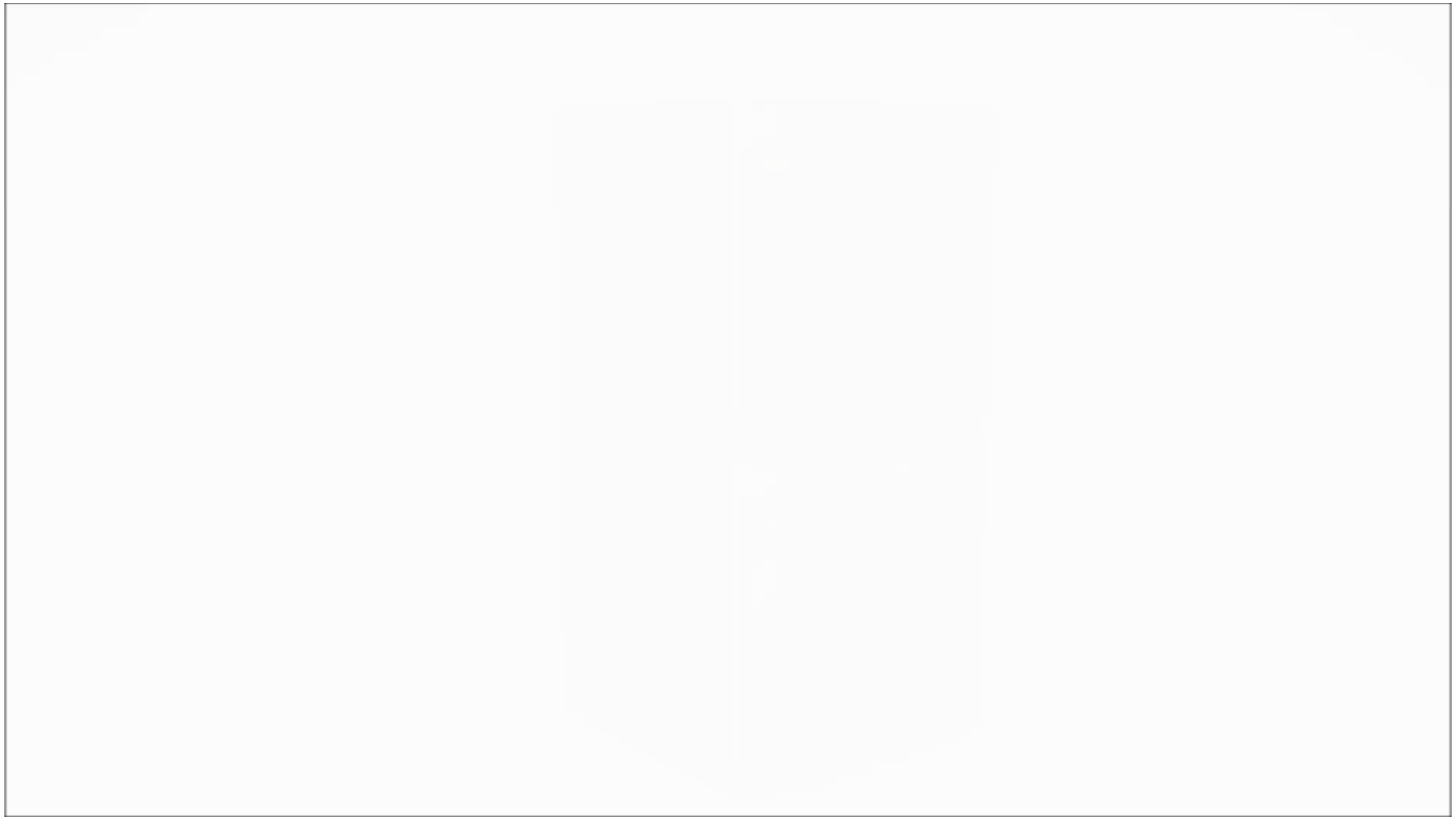
Mandatory start August 7th, 2027

Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC (Text with EEA relevance)

LUMC Islet Isolation Quality system is based on JACIE D annex with a direct oversight by the head of the GMP cleanroom LUMC and local TRIP biovigilance registration.

Audited separately (IGJ), or as part of the LUMC cleanroom.

Islet Transplantation



Pancreatic Islet transplantation

Autologous Islet Transplantation

Islets derived from pancreas after pancreatectomy

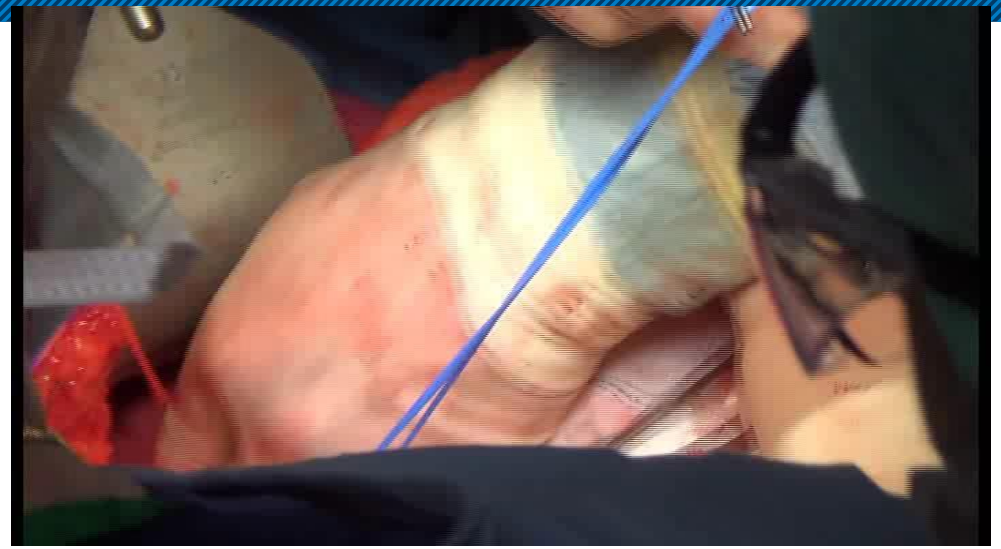
Surgical Indication : severe chronic pancreatitis

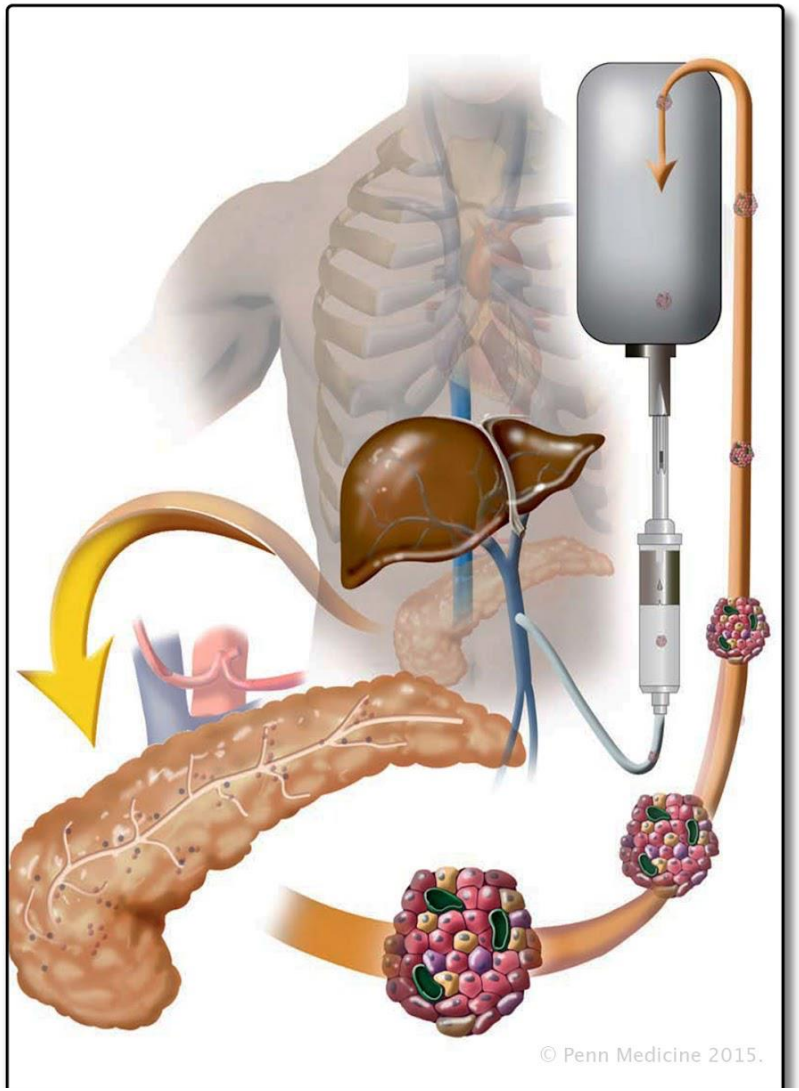
“Total Pancreatectomy and Islet AutoTransplantation”

→TPIAT

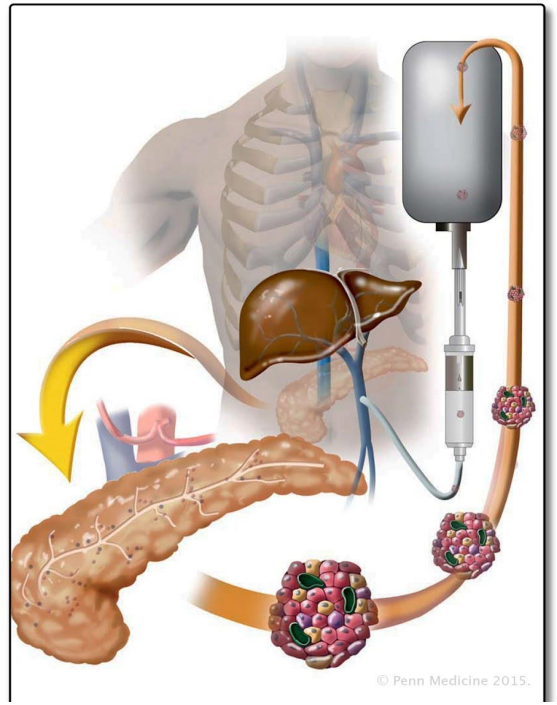
“ Return the islets back to the patient from whom they came ”

Total Pancreatectomy & Islet Auto Transplantation

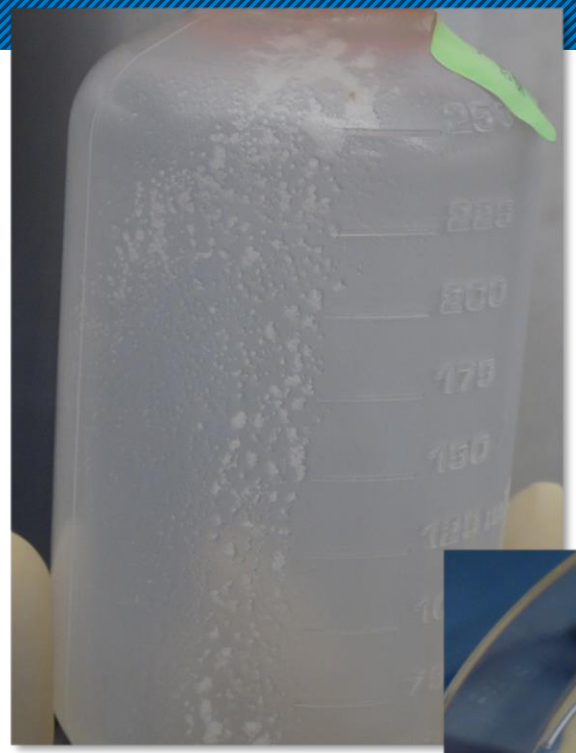


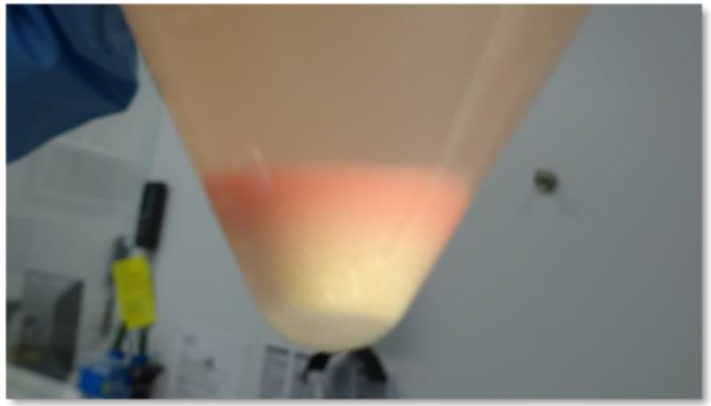


Total Pancreatectomy & Islet Auto Transplantation



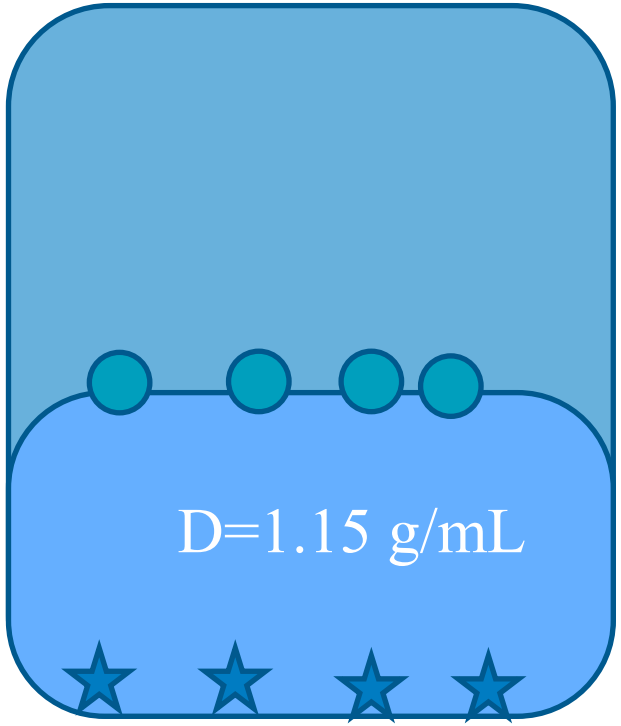
Total Pancreatectomy & Islet Auto Transplantation

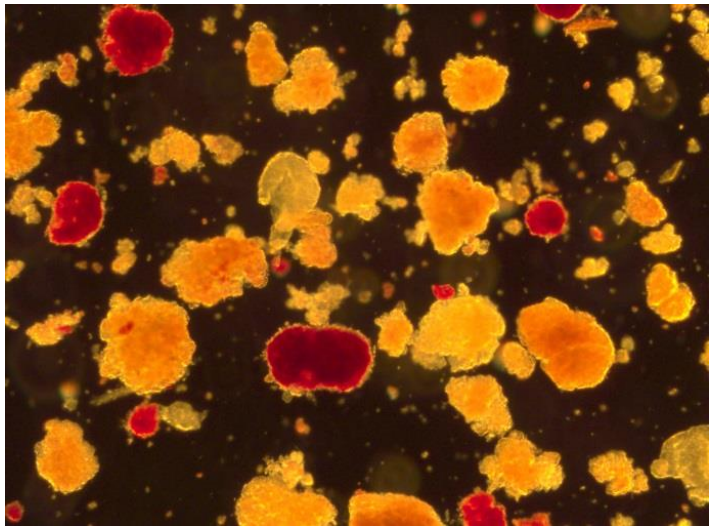


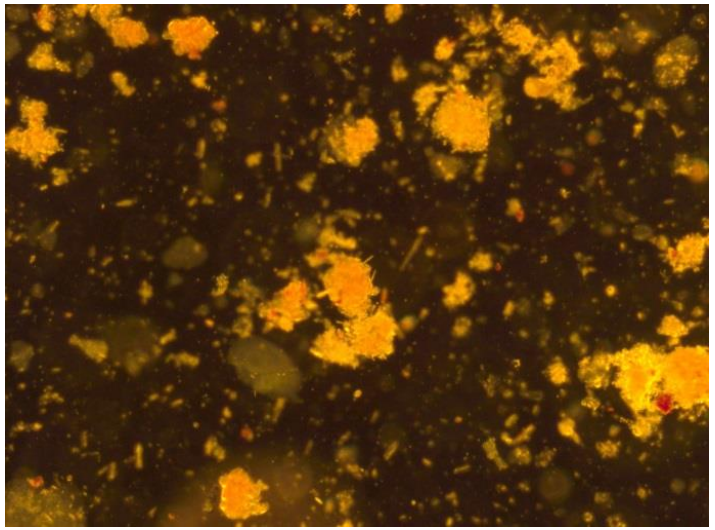


Total Pancreatectomy & Islet Auto Transplantation

How to deal with severe calcifications



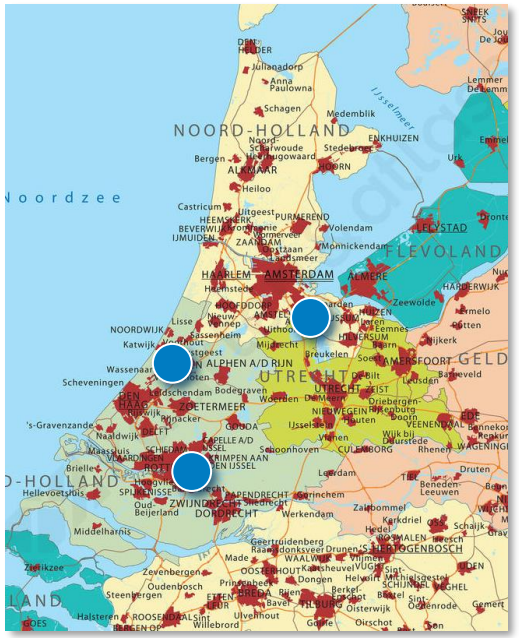




Total Pancreatectomy & Islet Auto Transplantation

→ Transplantation of autologous pancreatic islets after (total) pancreatectomy

- Benign indications (chronic pancreatitis)
- Feasible
- No immunosuppression needed
- (Partial) Insulin independence
- Collaboration LUMC / AMC / Erasmus



→Islet Allo – Autotransplantation

Second chance for vascularized pancreas

Laboratory for Islet Isolation 2025

The Leiden Islet Transplantation Center

LUMC: Nationwide referral for *beta*-cell therapy

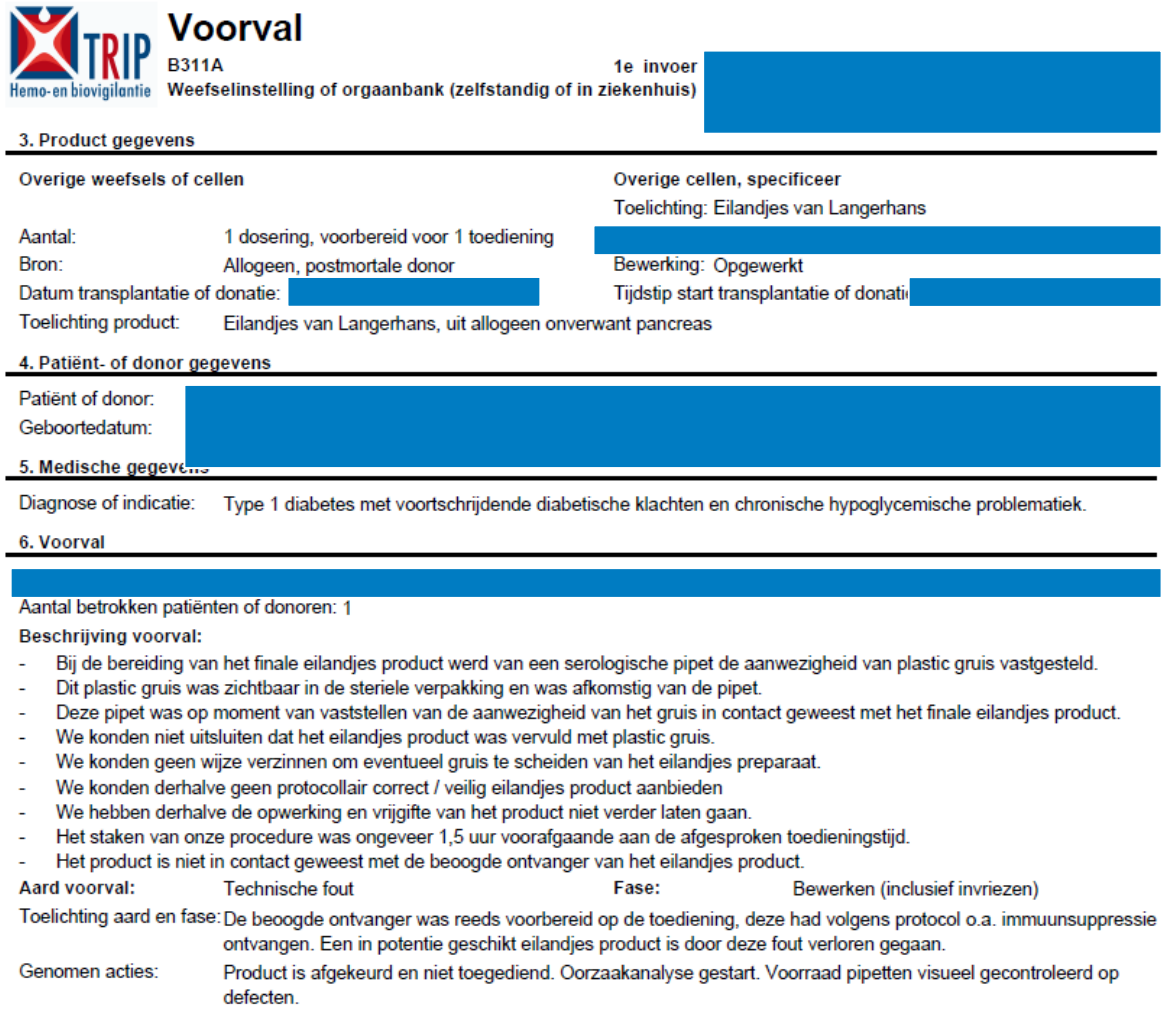
- Previous kidney transplantation (Islets after kidney)
- Pancreas transplantation no option
- Recurrent hypoglycemia (hypoglycemia unawareness)
- Progressive complications

→ Novelties for Leiden Islet Transplantation Center.

- Islets alone
- Islets after lung (CF)
- First islets alone of non-heartbeating type-III organ procurement
- Islet auto transplantation
- First Islet allo – auto transplantation in the world

TRIP Reports

TRIP melding



Voorval

B311A — 1e invoer [redacted]

Weefselinstelling of orgaanbank (zelfstandig of in ziekenhuis)

3. Product gegevens

Overige weefsels of cellen

Overige cellen, specificeer

Toelichting: Eilandjes van Langerhans

Aantal: 1 dosering, voorbereid voor 1 toediening [redacted]

Bron: Allogeen, postmortale donor

Bewerking: Opgewerkt

Datum transplantatie of donatie: [redacted]

Tijdstip start transplantatie of donati[redacted]

Toelichting product: Eilandjes van Langerhans, uit allogeen onverwant pancreas

4. Patiënt- of donor gegevens

Patiënt of donor: [redacted]

Geboortedatum:

5. Medische gegev[redacted]

Diagnose of indicatie: Type 1 diabetes met voortschrijdende diabetische klachten en chronische hypoglycemische problematiek.

6. Voorval

[redacted]

Aantal betrokken patiënten of donoren: 1

Beschrijving voorval:

- Bij de bereiding van het finale eilandjes product werd van een serologische pipet de aanwezigheid van plastic gruis vastgesteld.
- Dit plastic gruis was zichtbaar in de steriele verpakking en was afkomstig van de pipet.
- Deze pipet was op moment van vaststellen van de aanwezigheid van het gruis in contact geweest met het finale eilandjes product.
- We konden niet uitsluiten dat het eilandjes product was vervuld met plastic gruis.
- We konden geen wijze verzinnen om eventueel gruis te scheiden van het eilandjes preparaat.
- We konden derhalve geen protocollair correct / veilig eilandjes product aanbieden
- We hebben derhalve de opwerking en vrijgifte van het product niet verder laten gaan.
- Het staken van onze procedure was ongeveer 1,5 uur voorafgaande aan de afgesproken toedieningstijd.
- Het product is niet in contact geweest met de beoogde ontvanger van het eilandjes product.

Aard voorval: Technische fout **Fase:** Bewerken (inclusief invriezen)

Toelichting aard en fase: De beoogde ontvanger was reeds voorbereid op de toediening, deze had volgens protocol o.a. immuunsuppressie ontvangen. Een in potentie geschikt eilandjes product is door deze fout verloren gegaan.

Genomen acties: Product is afgekeurd en niet toegediend. Oorzaakanalyse gestart. Voorraad pipetten visueel gecontroleerd op defecten.

"Broken pipette tip in product. Discovered, Reported, Discussed with islet team and physician,

Not transplanted, patient experienced delay of 4 weeks"

Novelties Laboratory for Islet Isolation 2025

Simultaneous Islet and Kidney Tranplantation (SIK)

Introduction

"Transplantation of a kidney and pancreatic islet from the same donor"

- Same immunological background
- Contribution to glycemic control right after the kidney has been transplanted

Intended Recipient: a person with type-1 diabetes and end stage kidney disease who is in need of a kidney transplant and beta-cell replacement therapy, yet who is not eligible for SPK

Reimbursement of Islet Transplantations @ LUMC

- Per Q3 2025, the Zorg Instituut Nederland has ruled that the islet transplantations should be part of Dutch care that can be reimbursed by health insurance.
  - Uptil now : “academische component” of LUMC

- This is in line with almost all national governments where an islet laboratory is active. Most European partner countries, US, UK, Canada, Australia.

Secondary LUMC cleanroom site for islet isolations

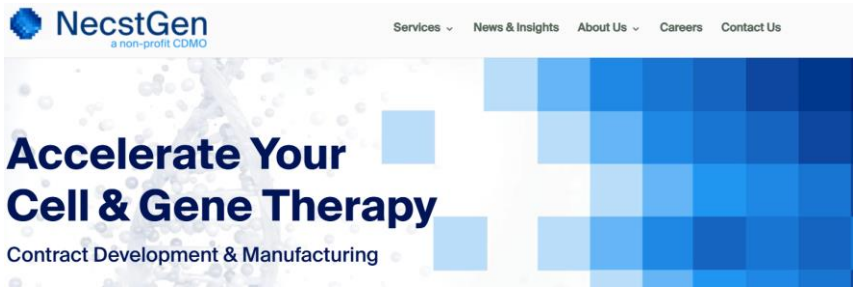
Partnership with NECSTGEN^{Leiden}

new

- Due to major and unforeseen reconstructions at LUMC main cleanroom complex estimated (Q1-Q4 2025).

- The laboratory for islet isolation LUMC requested IGJ for a temporary site to continue the production of pancreatic islets at NECSTGEN^{Leiden}

- The request was approved by IGJ, currently (OCT 2025) our only site for islet isolation, restarting up at LUMC main cleanroom complex soon.



PRISM:PancReactic Islet Separation Method

Team MedTech LUMC
Rutger van Rooden
Jason Doppenberg
Marten Engelse

An Automatic Islet Isolation Machine

The basic concept of PRISM

- Cleanroom Preparation
- Pancreas Preparation
- Enzyme Injection
- Digestion
- Dilution
- Harvest of Digested Tissue
- Density Separation
- Islet Culture

Acme Islet Isolator 3000
W.E. Coyote *et al*

An Automatic Islet Isolation Machine

The basic concept of PRISM

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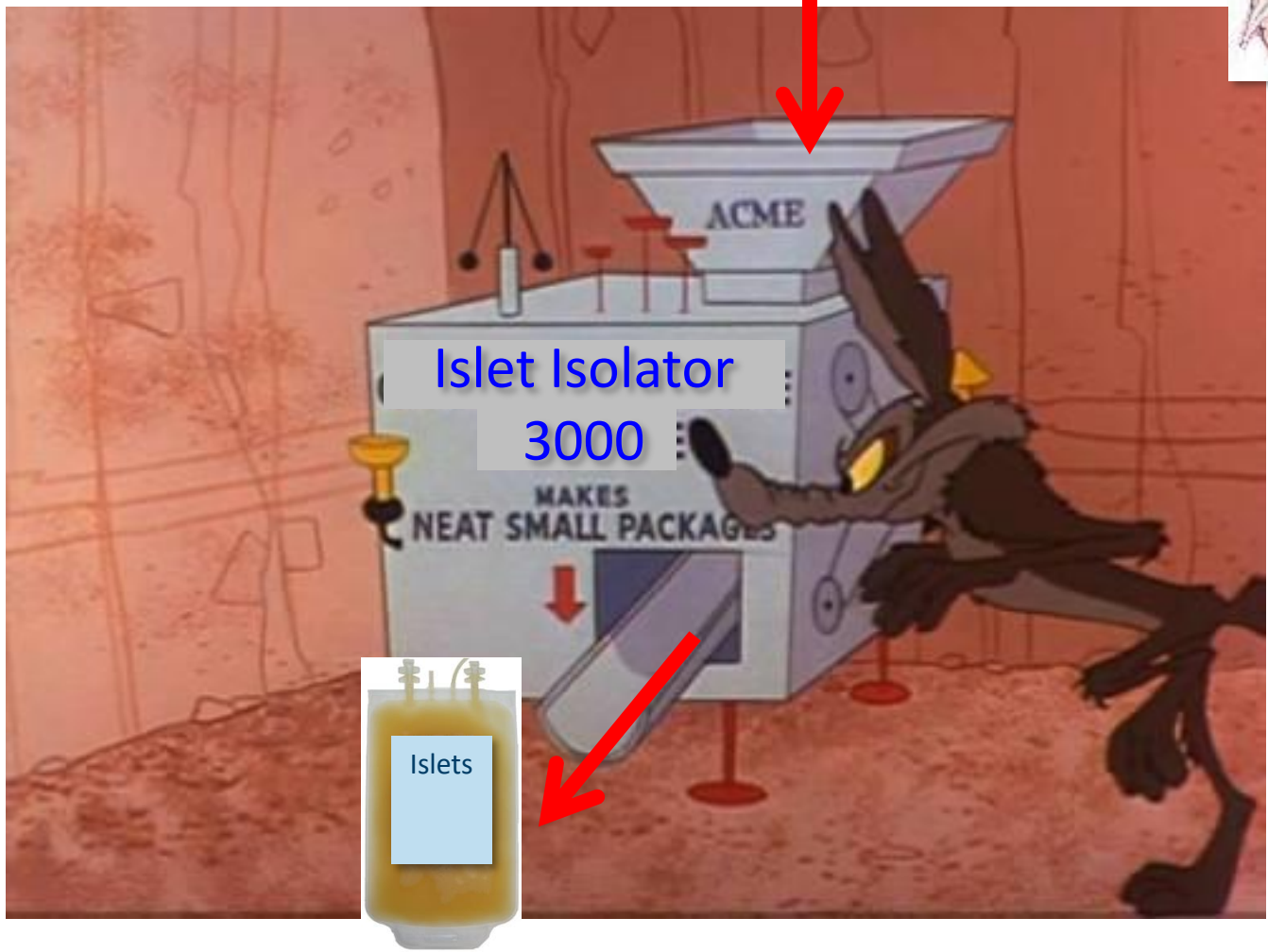
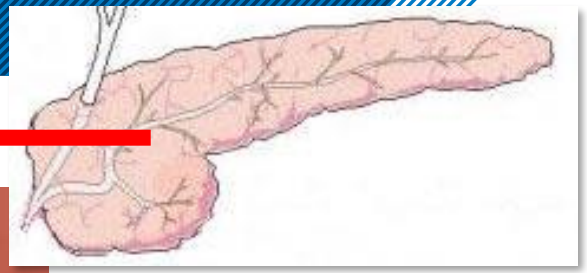


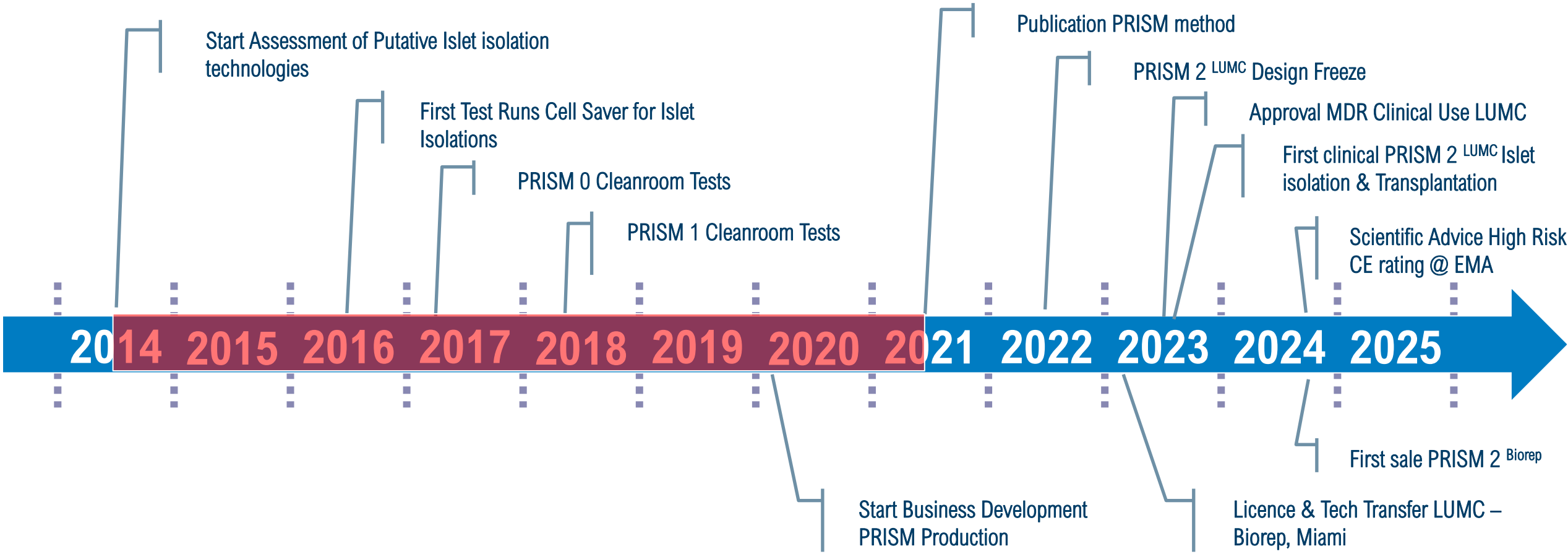


Why to improve the current protocol?

- Less personnel
- Closed system
- No variations

Timeline PRISM development

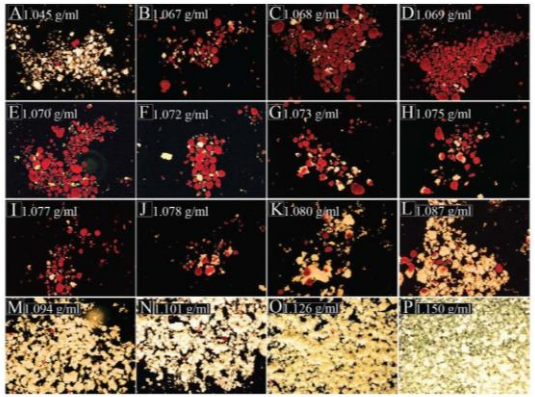
PRISM timeline



PRISM 1 Prototype at cleanroom

Publication

June 2022 ■ Volume 106 ■ Number 6
Official Journal of The Transplantation Society & International Liver Transplantation Society
Transplantation



Wolters Kluwer

www.transplantjournal.com

- Tissue Resident Memory T Cells
- Platelets and Transplant Arteriosclerosis
- Pregnancy and eGFR After Kidney Transplantation
- PRISM Human Islet Isolation

PRISM: A Novel Human Islet Isolation Technique

Jason B. Doppenberg, MSc,[1,2] Marten A. Engelse, PhD,[1] and Eelco J.P. de Koning, MD, PhD[1]

Background. Successful pancreatic islet isolations are a key requirement for islet transplantation in selected patients with type 1 diabetes. However, islet isolation is a technically complex, time-consuming, and manual process. Optimization and simplification of the islet isolation procedure could increase islet yield and quality, require fewer operators, and thus reduce cost. **Methods.** We developed a new, closed system of tissue collection, washing, buffer change, and islet purification termed PancReatic Islet Separation Method (PRISM). In the developmental phase, pump and centrifuge speed was tested using microspheres with a similar size, shape, and density as digested pancreatic tissue. After optimization, PRISM was used to isolate islets from 10 human pancreases. **Results.** Islet equivalents viability (fluorescein diacetate/propidium iodide), morphology, and dynamic glucose-stimulated insulin secretion were evaluated. PRISM could be performed by 1 operator in 1 flow cabinet. A similar islet yield was obtained using PRISM compared to the traditional islet isolation method (431 234 ± 292 833 versus 285 276 ± 197 392 islet equivalents, $P = 0.105$). PRISM islets had similar morphology and functionality. **Conclusion.** PRISM is a novel islet isolation technique that can significantly improve islet isolation efficiency using fewer operators.

(*Transplantation* XXX;00: 00–00).

INTRODUCTION

Pancreatic islet transplantation is a treatment option for selected patients with type 1 diabetes mellitus.[1] It is generally accepted that a higher number of islets of good quality results in better functional outcome including insulin independence.[2] In practice, often 2 or more donor pancreases are required to achieve this goal, but this strategy is associated with an increased risk for HLA sensitization and procedure-related complications and increased costs.[3,4] Costs could be reduced by further automating the islet isolation procedure requiring fewer operators and reducing the complex logistics of islet isolations.

Since the introduction of the semi-automated method of islet isolation,[5] only minor revisions have been broadly incorporated.[6-8] Key in this method is the collection of enzymatically and mechanically digested pancreatic tissue followed by enzyme deactivation via dilution, cooling, and/or the addition of (human) serum or serum albumin.[9] Additional washing steps, requiring several rounds of centrifugation, are necessary to dilute the enzymes to further reduce the risk of islet damage.[10] After pancreas digestion, it is necessary to purify islets from the exocrine tissue to reduce the tissue volume for transplantation. Infusion of >10 mL of tissue is associated with increased procedure-related complications.[11] Isopycnic centrifugation (density gradient separation) has been utilized since the late 1960s to purify islets, mainly using Ficoll variants,[12] since density is the most pronounced physical differential characteristic of islets compared to exocrine tissue. Large scale density gradient separation became possible after the implementation of COBE 2991 cell processors, which are universally used in islet isolation.[13] Still, 15%–51% of islets are reportedly lost during this procedure.[14]

To overcome these issues, we investigated whether closed whole blood processing techniques could be applied to an

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Accepted 28 June 2021.

[1] *Department of Internal Medicine, Leiden University Medical Center, Leiden, the Netherlands.*

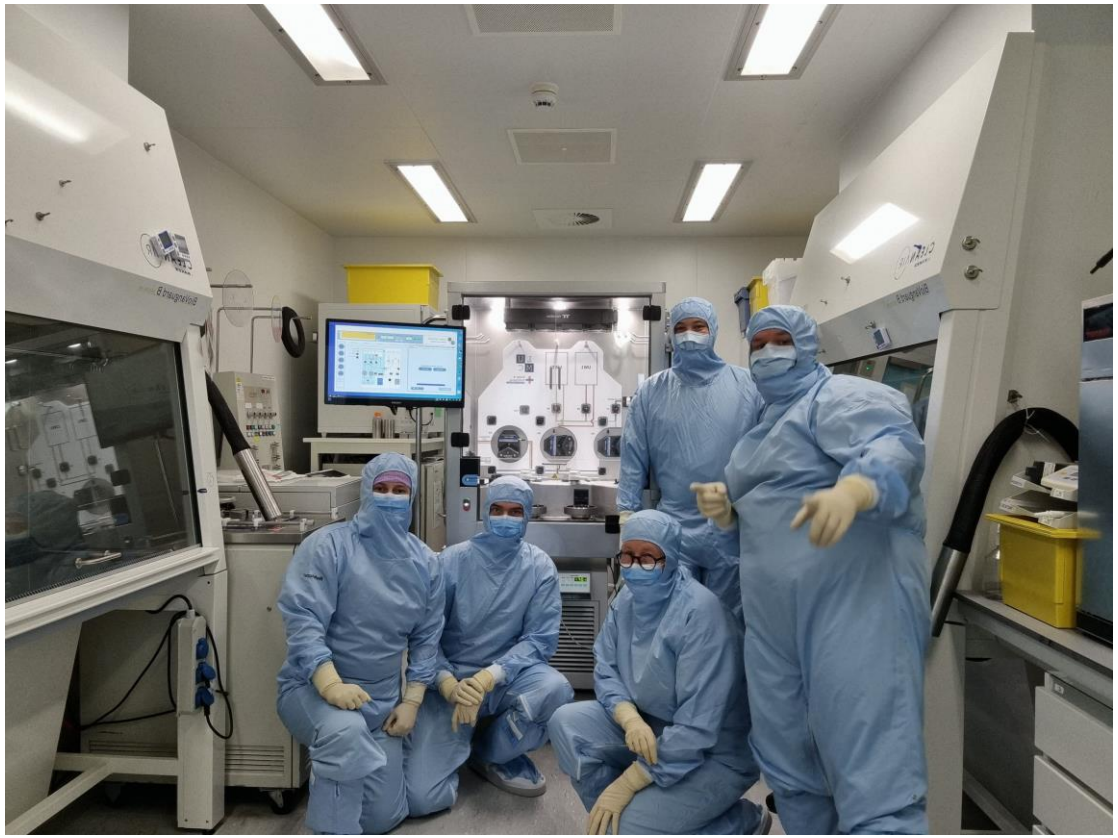
[2] *Transplantation Center, Leiden University Medical Center, Leiden, the*

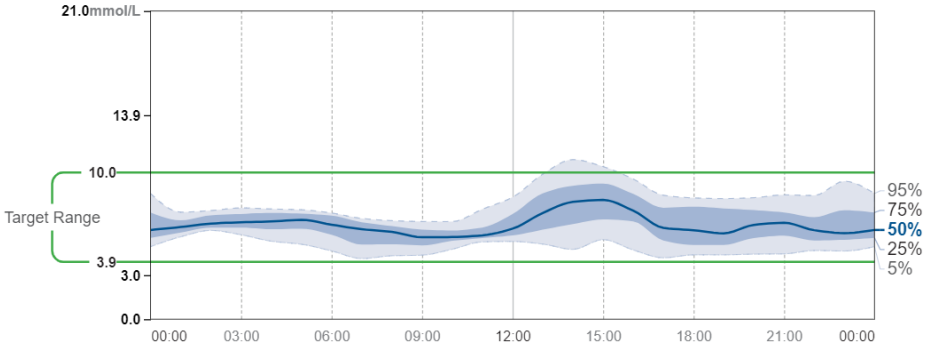
4 years later…..
PRISM prototype 2

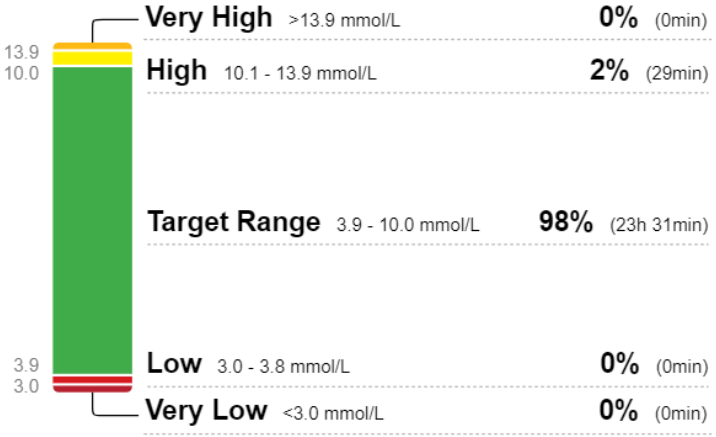
→ **FULL MDR Workup**

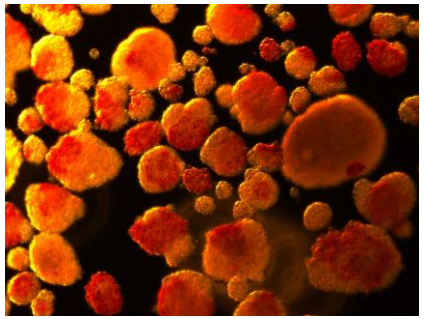
→ **New design envelope**

First Islet transplantation using PRISM



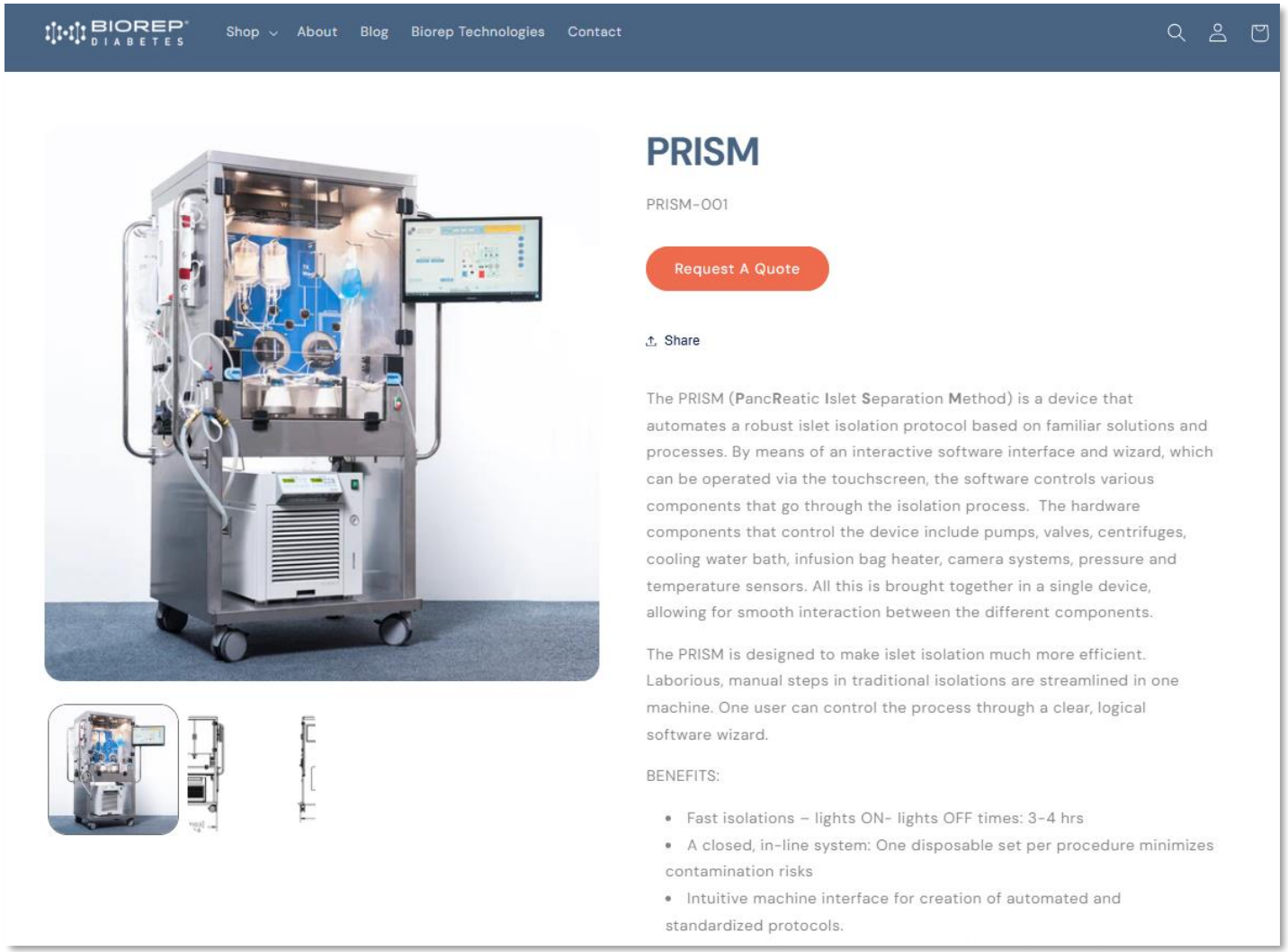






Average Glucose	6.5 mmol/L
Glucose Management Indicator (GMI)	6.1% or 43 mmol/mol
Glucose Variability	21.3%

BIOREP Diabetes USA Miami



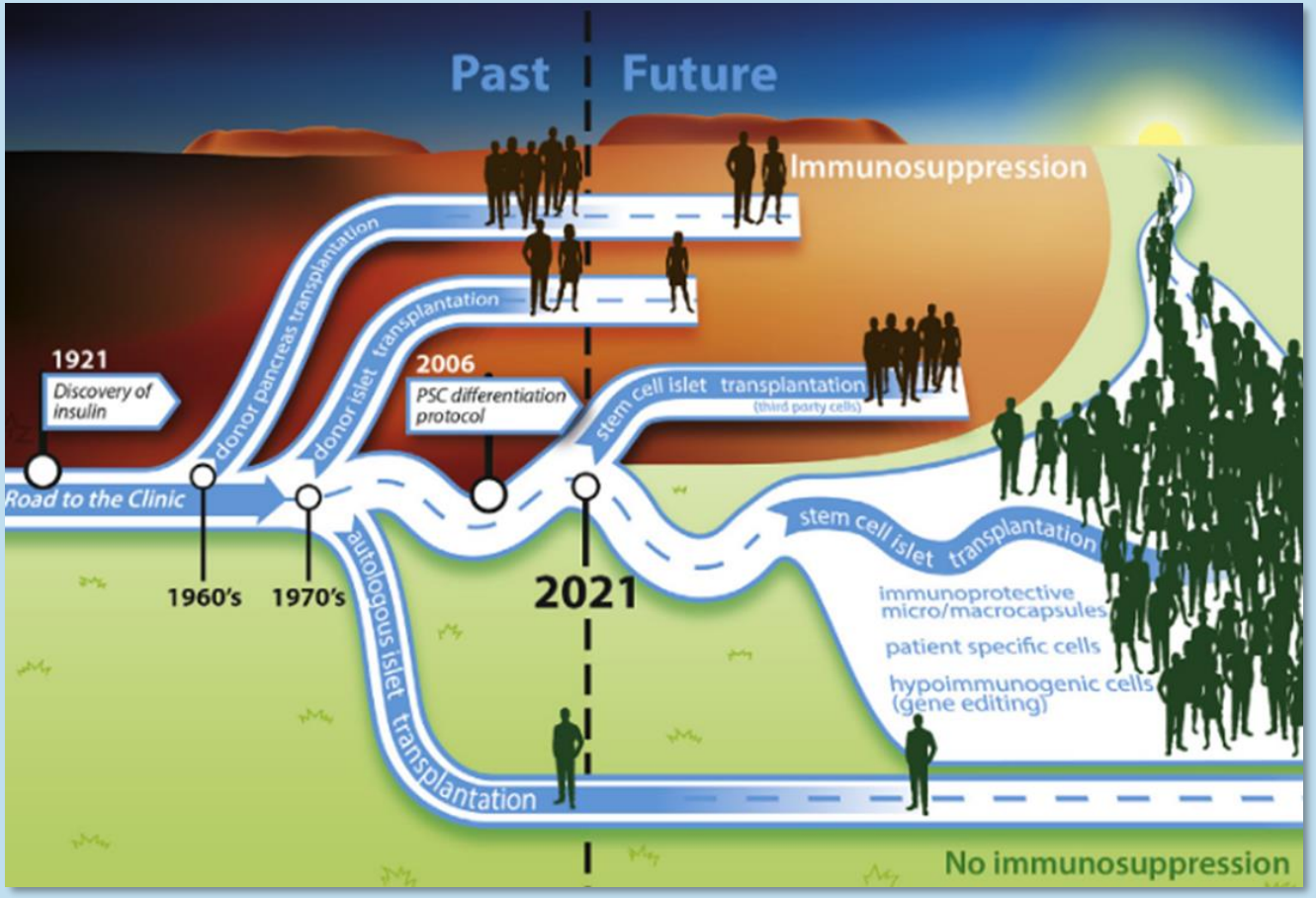
new

→ **Tech Transfer LUMC → Biorep**

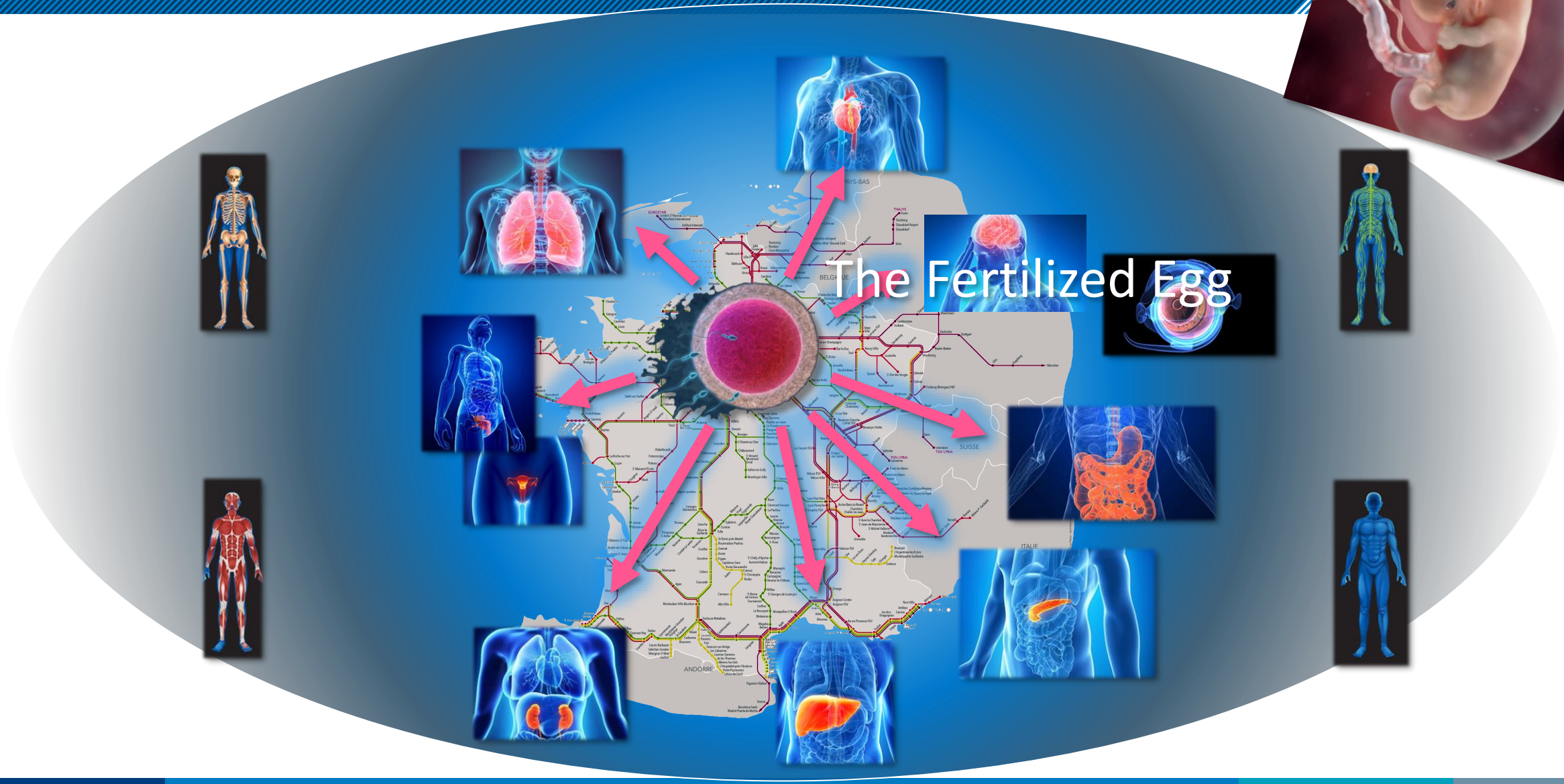
- Integration into their production line

→ **First thirdparty use of PRISM and PRISM disposable tubing sets**

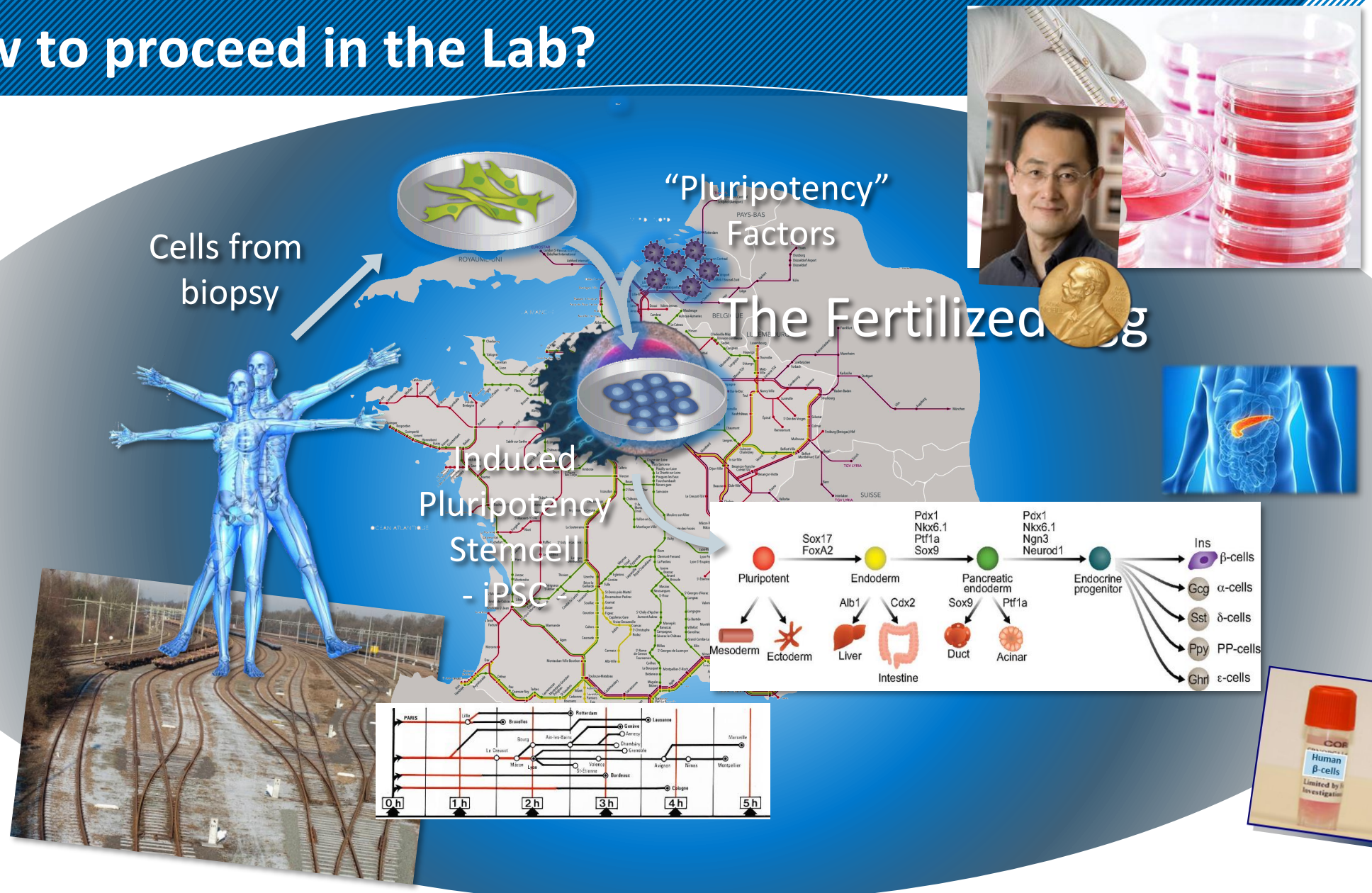
Stem Cells: The future? The Future !



Embryology, Organogenesis; What do we know?



How to proceed in the Lab?



→ Moving toward full GMP compliant stem cell derived beta cell production at the LUMC with the intent to transplant people with type-1 diabetes

How to transplant (stem cell) islets without immune suppression ?

Research performed together with Maastricht University

→ Maybe the future is already here??

VERTEX

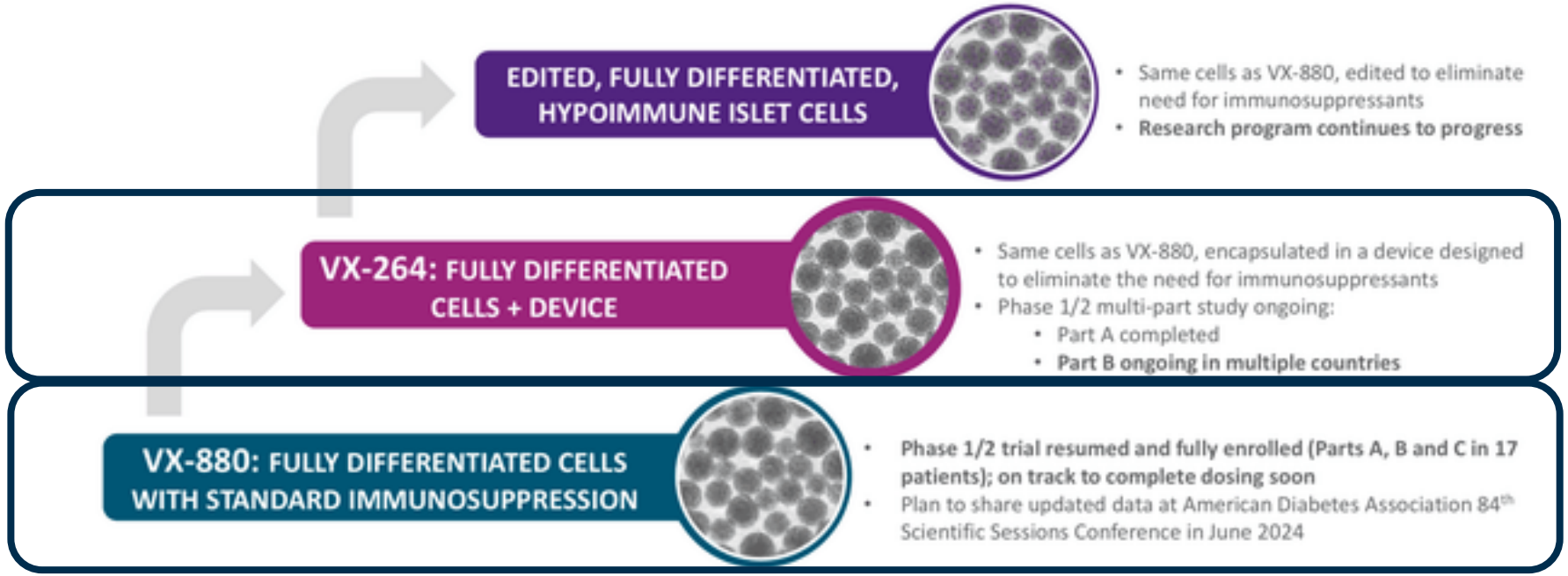
Phase ½ trial using stem cell derived beta cells

new

VERTEX
THE SCIENCE of POSSIBILITY

TYPE 1 DIABETES: ADVANCING POTENTIALLY CURATIVE TREATMENTS FOR ~3.8M PATIENTS IN NORTH AMERICA & EUROPE

VX-880 PHASE 1/2 TRIAL RESUMED; GLOBAL 17-PATIENT STUDY IS FULLY ENROLLED



10

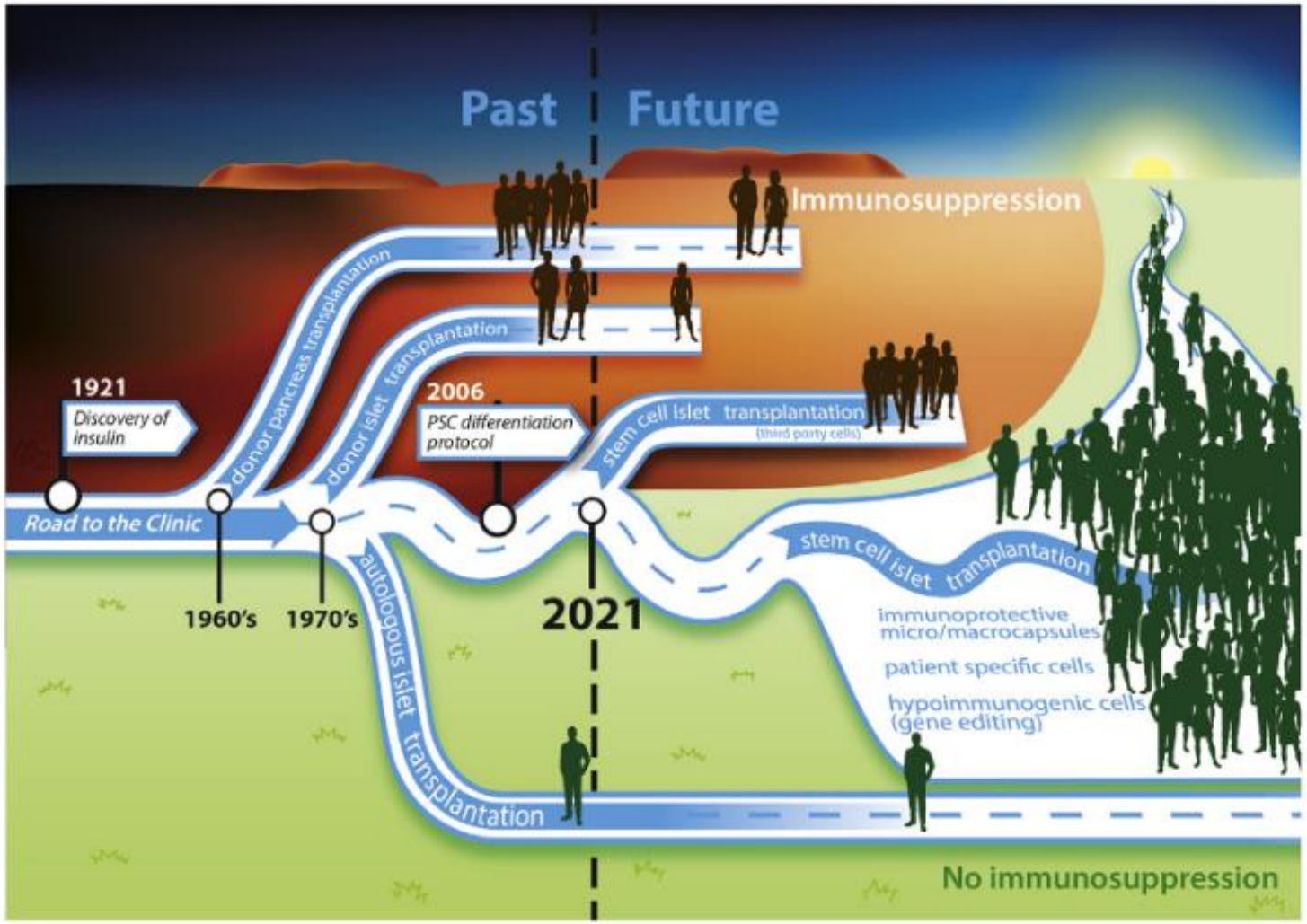
Zimislecel product

- VX 880 safe, feasible
- Already function seen

Game changer ? !

Beta cell replacement therapy

Getting as many insulin producing cells to those who need them



De Koning E and Carlotti F, *Cell Stem Cell* 2021

Acknowledgements

LUMC Transplantatie Centrum