Research Towards a Cure for T1D

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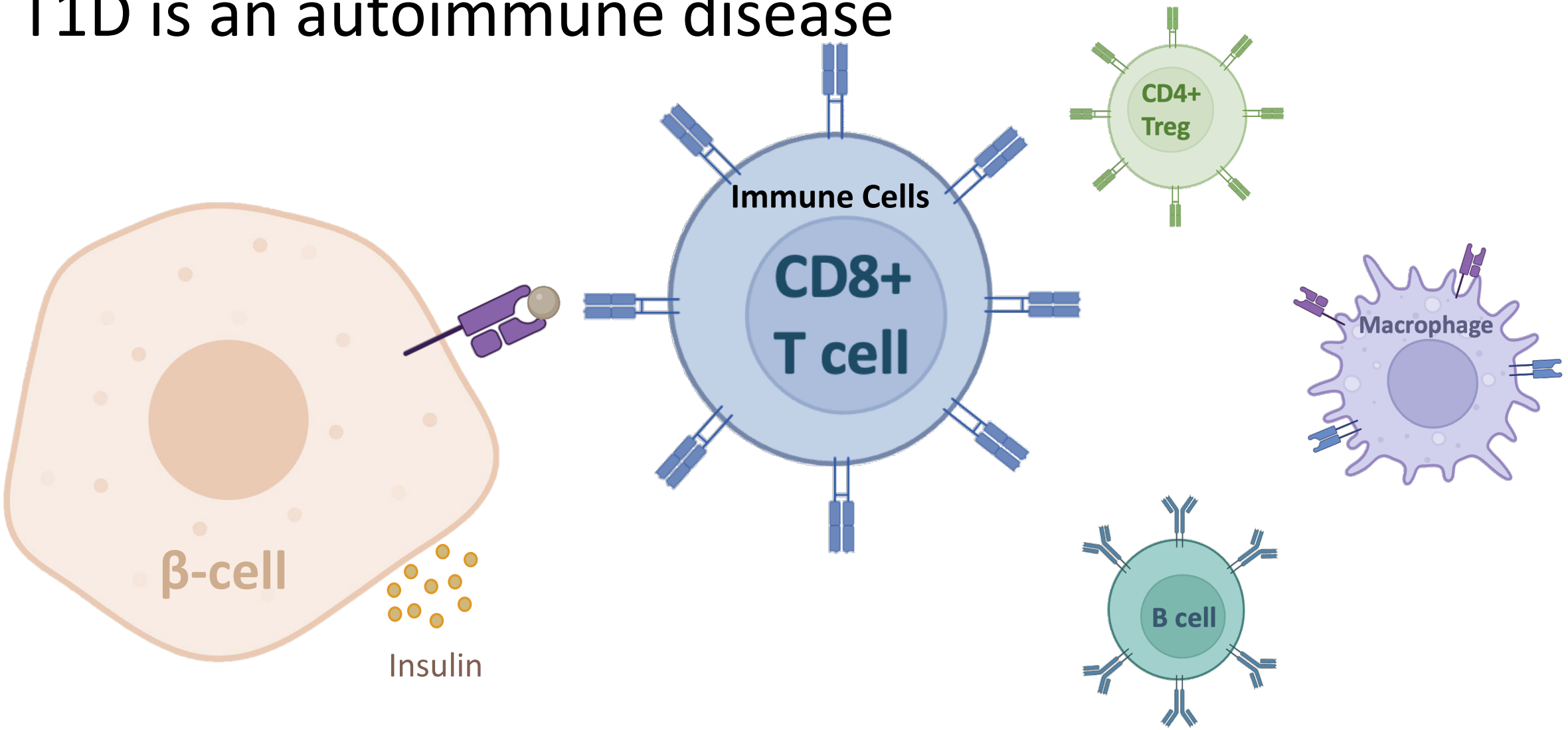
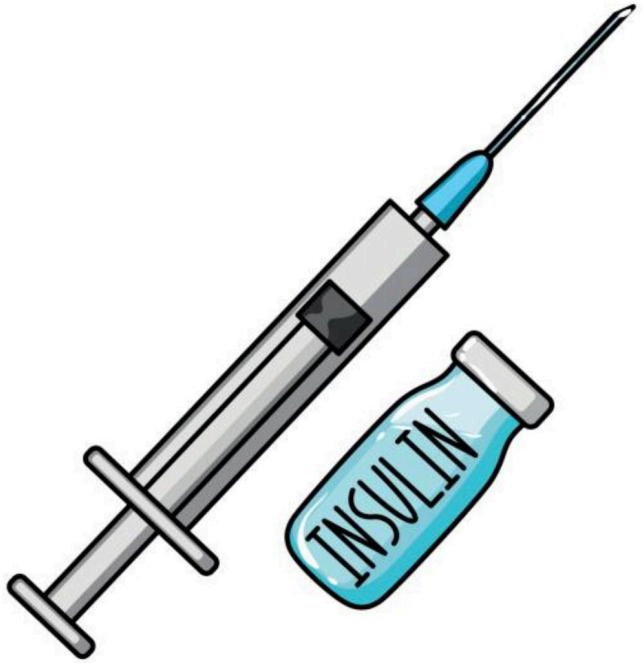
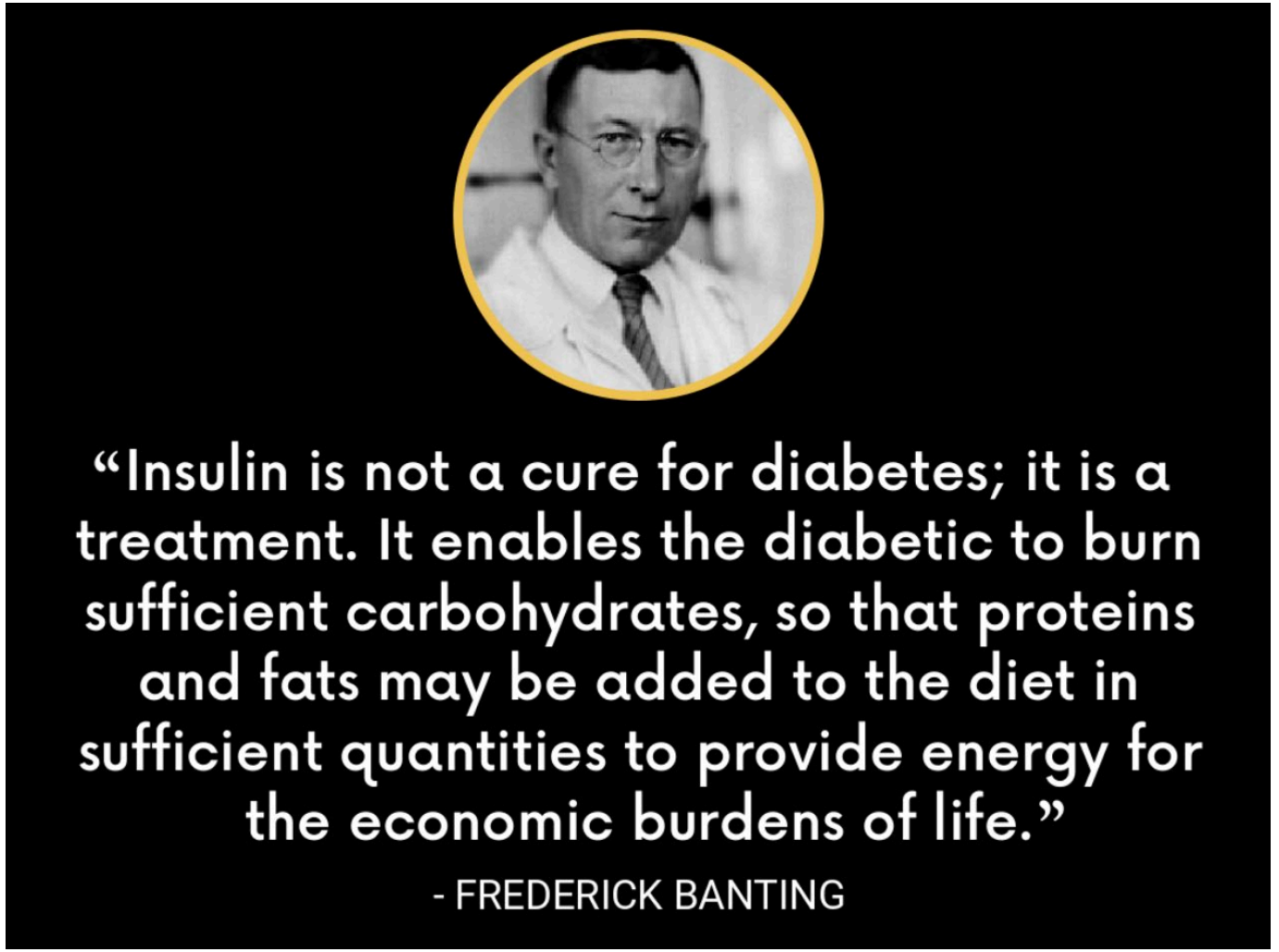
T1D is an autoimmune disease

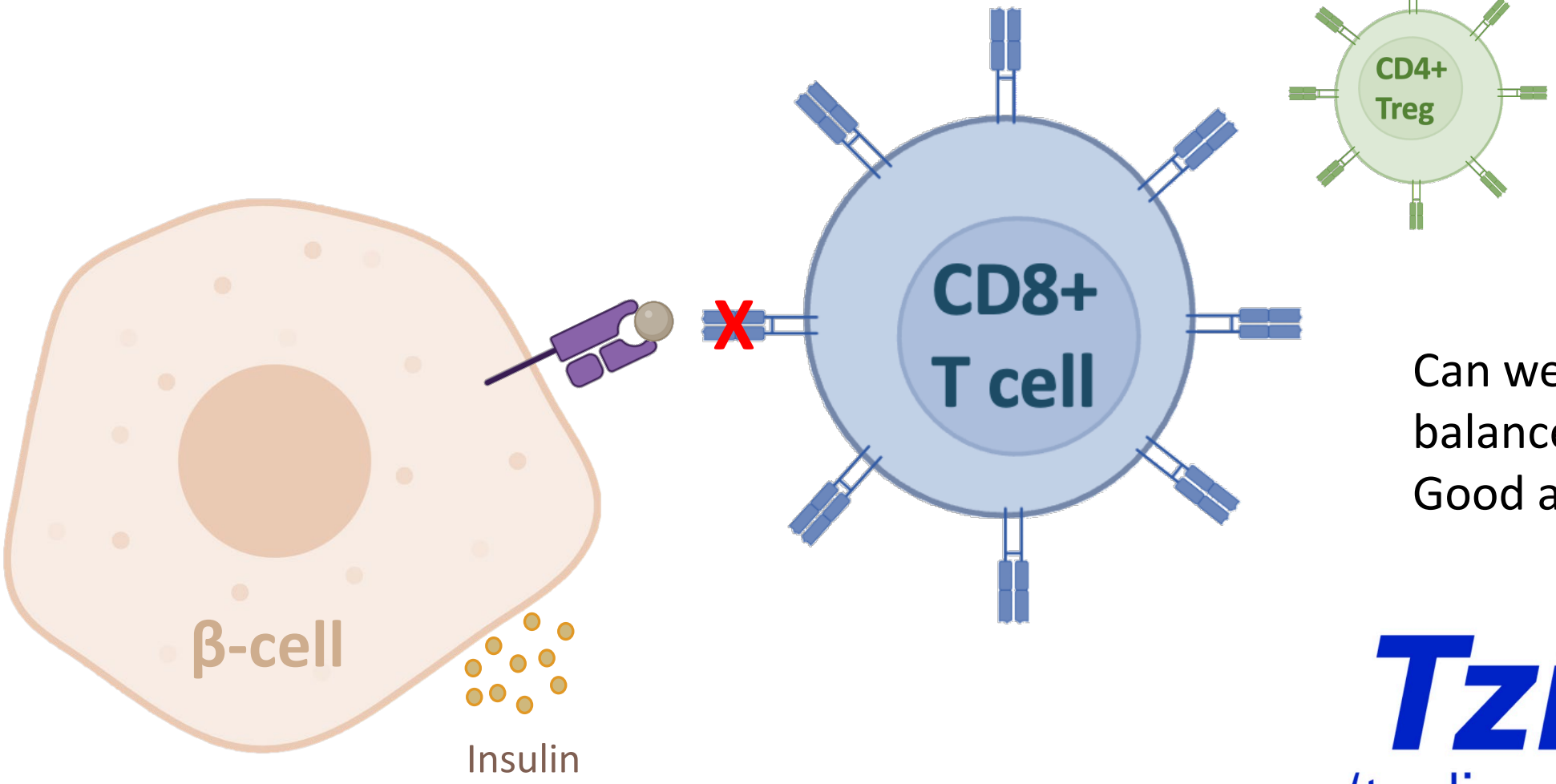


Insulin is the therapy for T1D (>100 years!!)





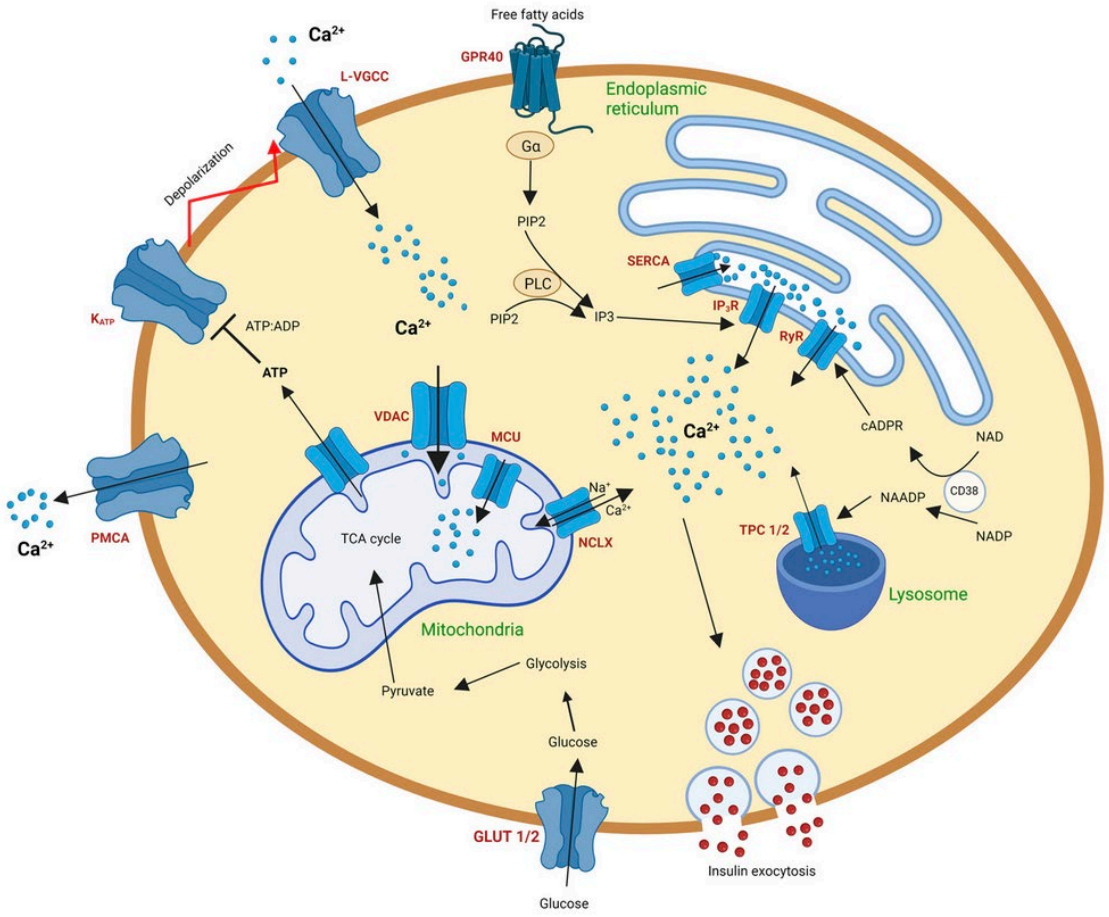
T1D is an autoimmune disease



Can we shift the balance between Good and Bad T cells?

Tzield®
(teplizumab-mzwv)

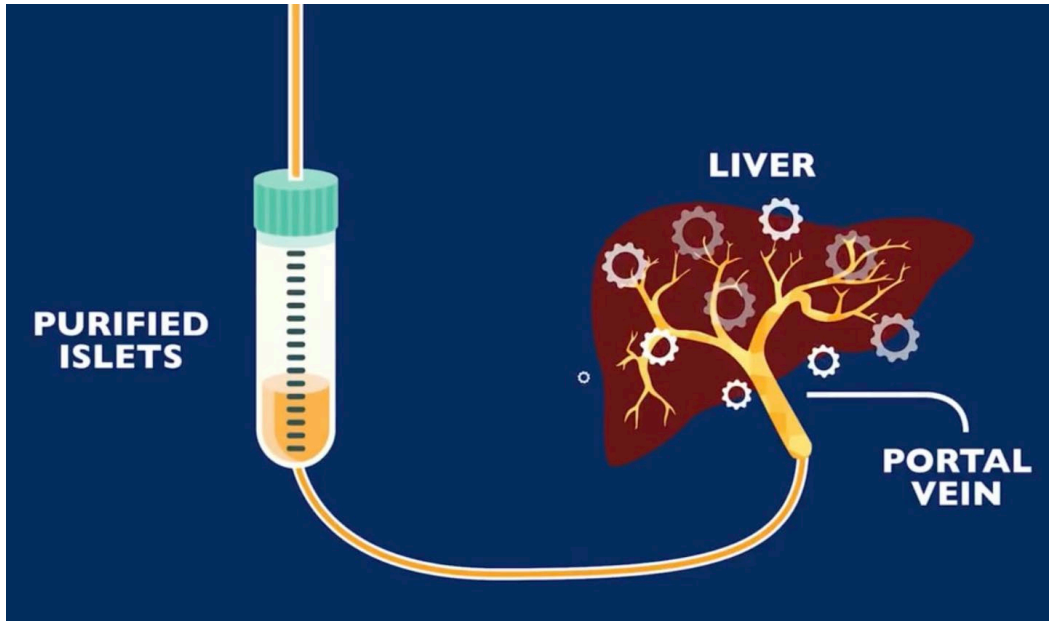
Beta cell replacement therapy



Islet transplantation as a therapy (25 years ago)

Recipients remain insulin independent for >5-10 years

- Reduced hypoglycemic episodes
- Improved quality of life



Challenges:

- Multiple donors for each patient
- Limited donor tissue
- Substantial graft failure
- Immunosuppression required

Historical milestones of pancreatic islet transplantation

1965 — **Pancreatic islet isolation from guinea pig utilizing collagenase** first described by Stanislaw Moskalewski

1966 — **First successful pancreas transplantation** performed by surgeons Richard Lillehei and William Kelly

1988 — **The Ricordi Chamber** was created by Dr. Camillo Ricordi, allowing for more efficient pancreatic islet isolation

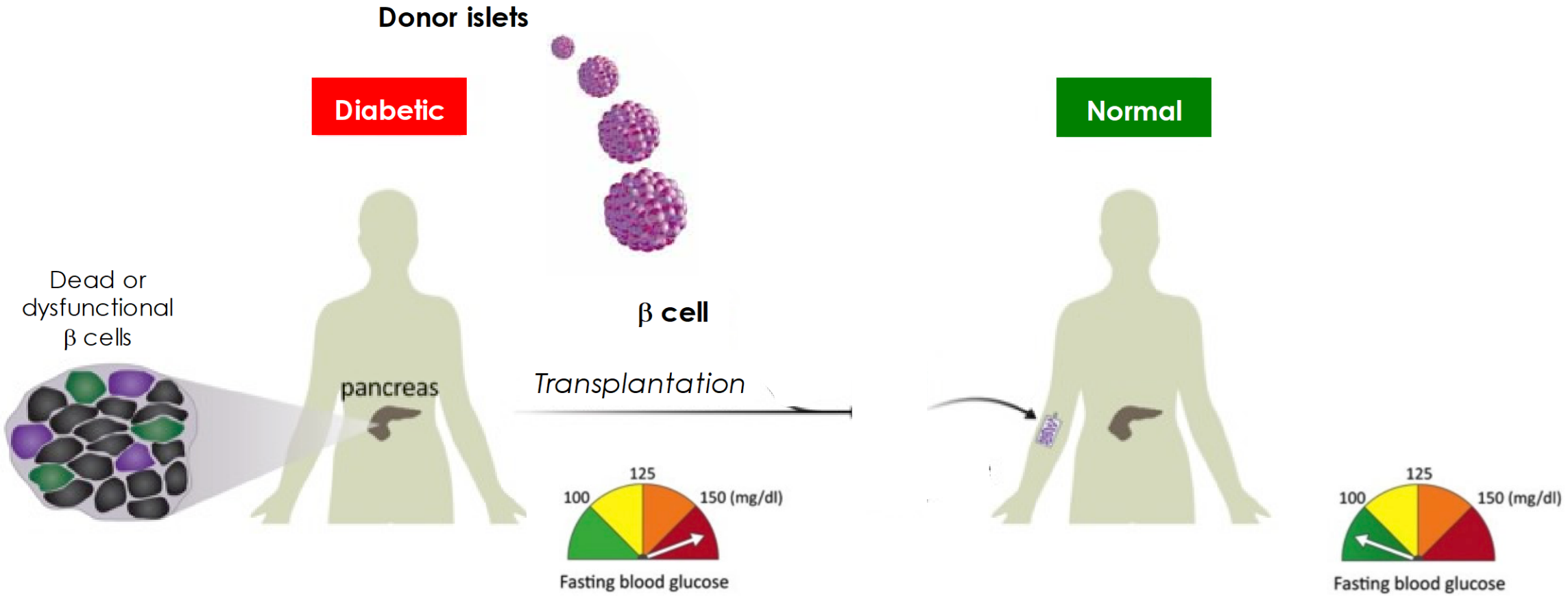
2000 — **The Edmonton Protocol** was developed by Dr. James Shapiro, allowing successful restoration of long-term endogenous insulin production and glycemic stability in subjects with type 1 diabetes by introducing a steroid-free immunosuppressive regimen

2014 — **First stem cell-derived islets** enter a phase 1/2 clinical trial. Developed by ViaCyte (VC-01)

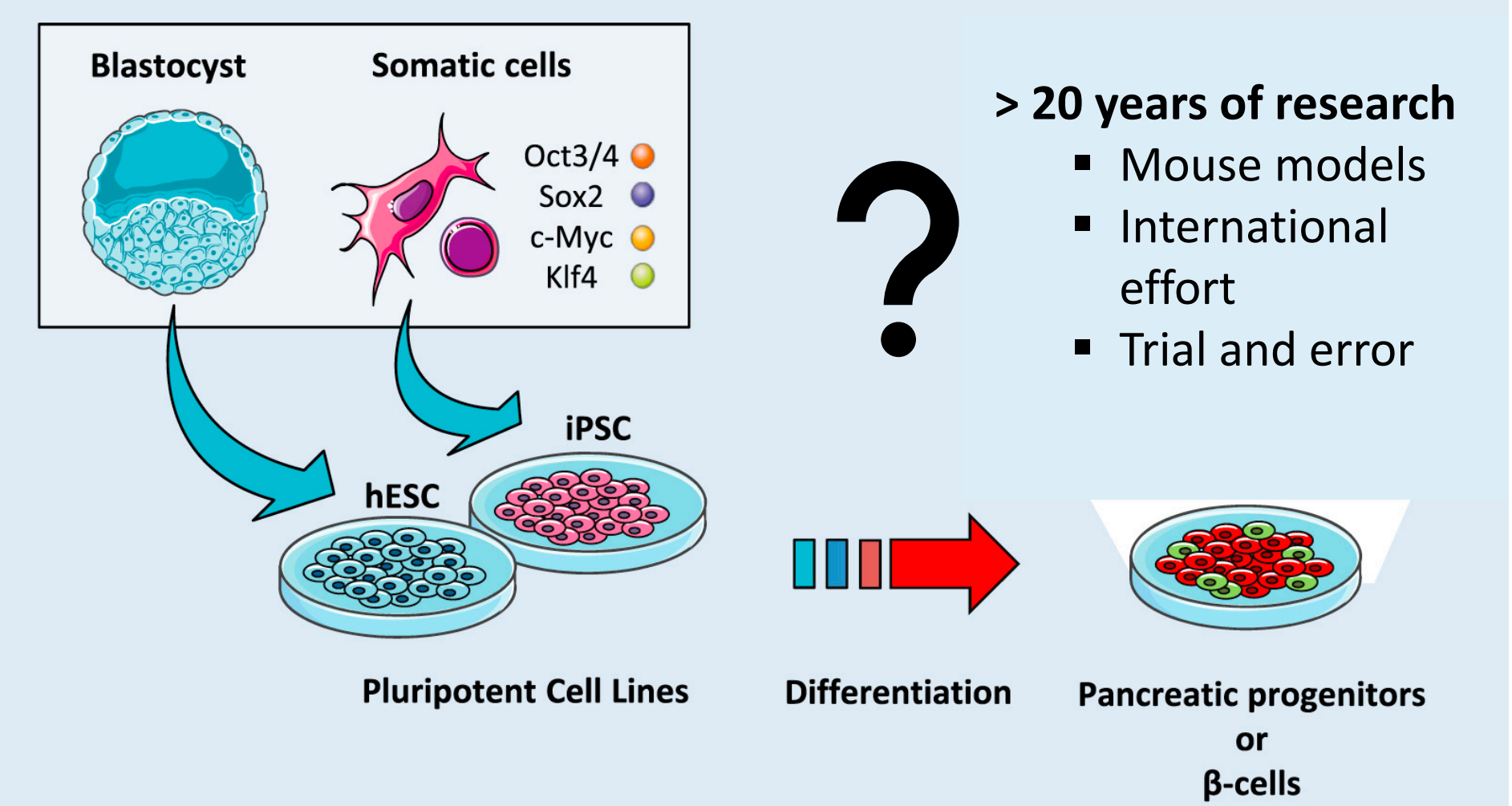
2016 — **Phase 3 clinical trial** of allogeneic human islets in Type 1 diabetes patients suffering from severe hypoglycemia

2023 — **First cellular therapy** for type 1 diabetes patients is approved by the US FDA. Lantidra (CellTrans) consists of allogeneic pancreatic islet transplantation from deceased donors

Can there be an unlimited source of β cells?



How do we generate β cells in a dish?



Vertex Clinical Trial

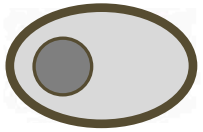
November 2021

The New York Times

A Cure for Type 1 Diabetes? For One Man, It Seems to Have Worked.

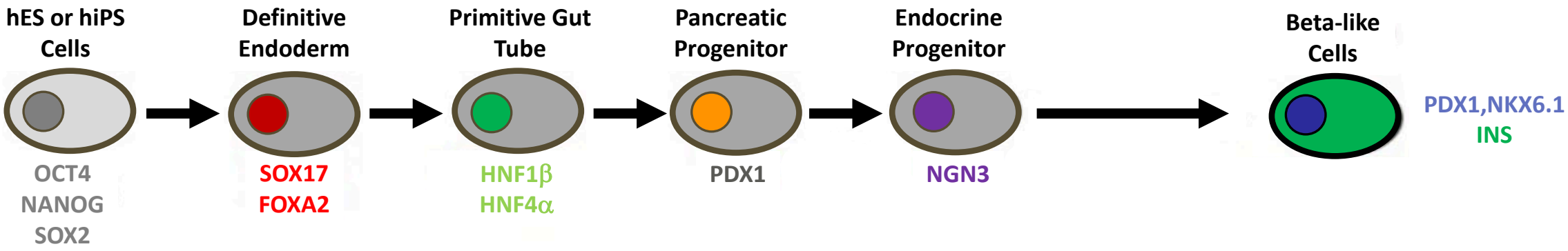
Challenges with differentiating β cells

hES or hiPS Cells



OCT4
NANOG
SOX2

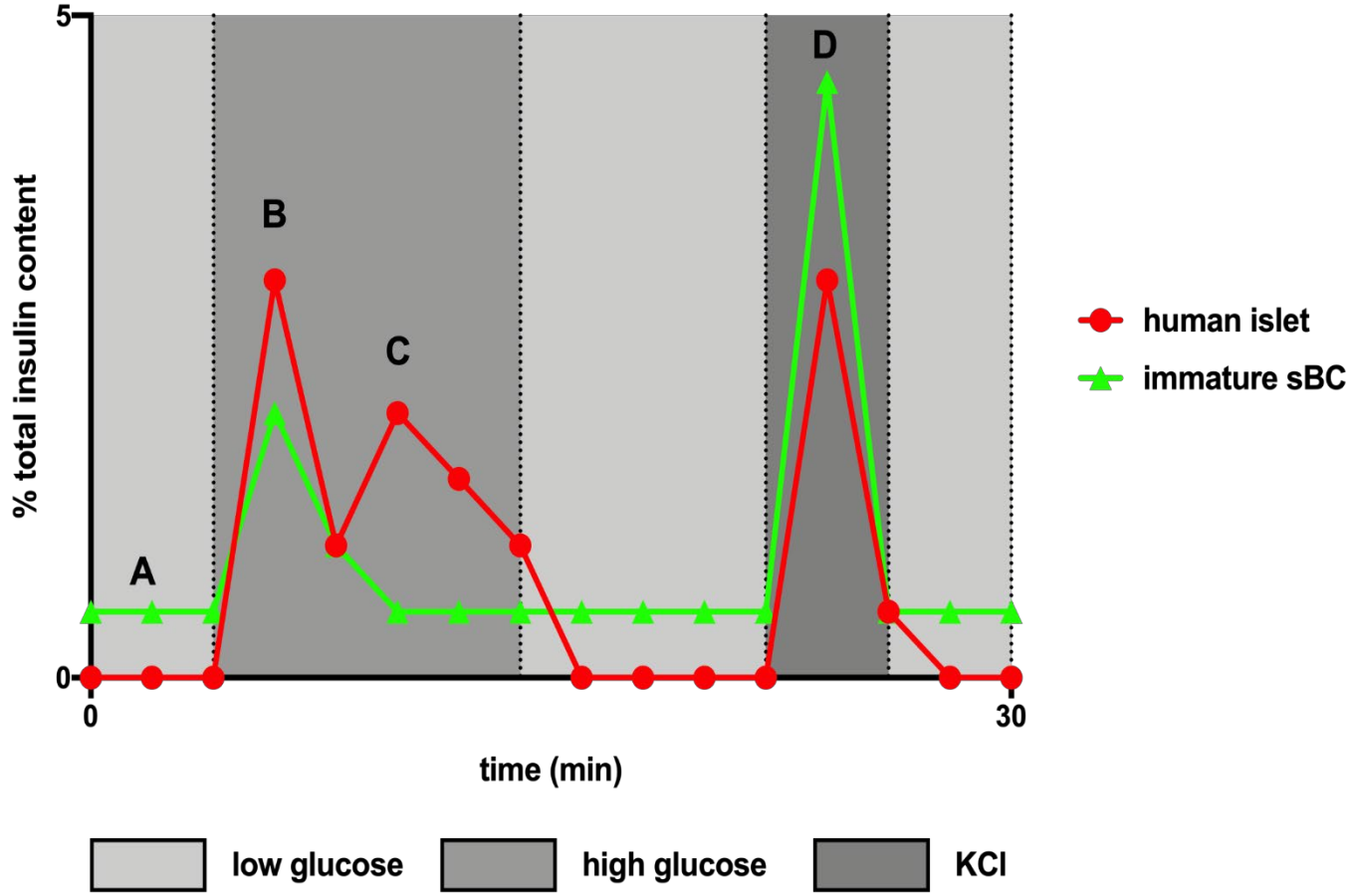
Challenges with differentiating β cells



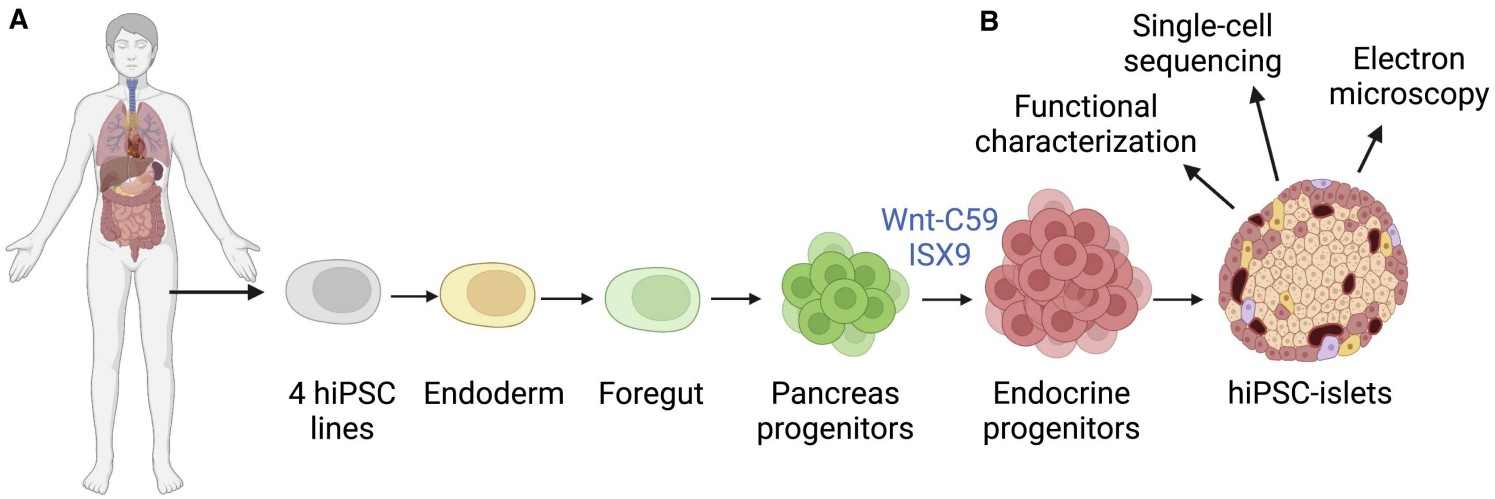
Summary: hPSC-derived β -like cells

Remaining issues:

- Derived β cells are still "β – like"
- Differentiation isn't strictly directed → α, β and δ cells
- Differentiations are highly variable
- β cells are immature
- We still have to block the immune system

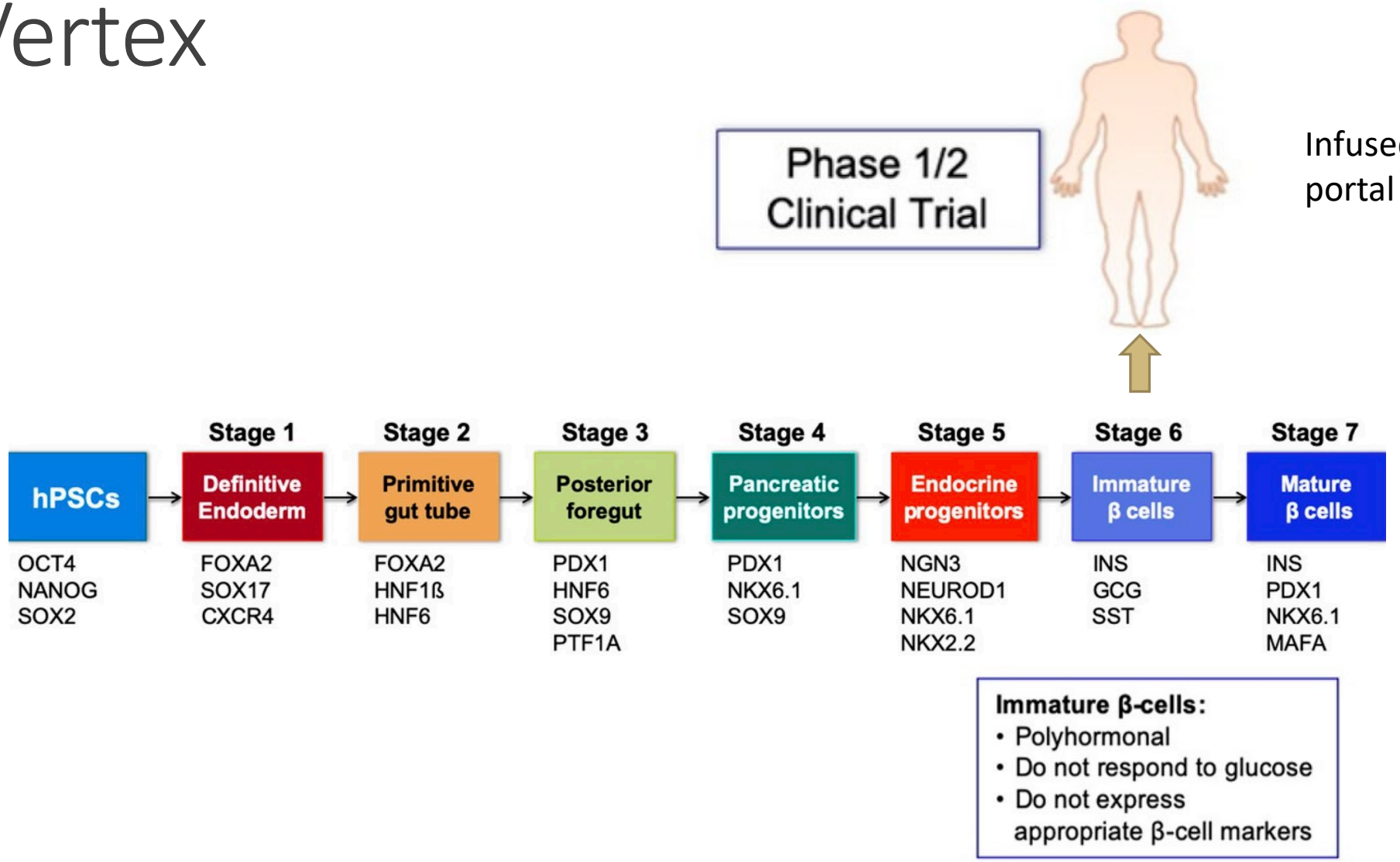


Preclinical trials



Grapin-Botton and Ludwig, Cell Stem Cell, 2022

Vertex


Phase 1/2
Clinical Trial
Infused into the portal vein
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Stage 6
Stage 7
hPSCs
Definitive Endoderm
Primitive gut tube
Posterior foregut
Pancreatic progenitors
Endocrine progenitors
Immature β cells
Mature β cells
OCT4
NANOG
SOX2
FOXA2
SOX17
CXCR4
FOXA2
HNF1ß
HNF6
PDX1
HNF6
SOX9
PTF1A
PDX1
NKX6.1
SOX9
NGN3
NEUROD1
NKX6.1
NKX2.2
INS
GCG
SST
INS
PDX1
NKX6.1
MAFA
Immature β-cells:
• Polyhormonal
• Do not respond to glucose
• Do not express appropriate β-cell markers

American Diabetes Association®

2024/2025

Vertex Releases New Data on Potential Cure for Type 1 Diabetes

- 12 Participants (0 levels detectable insulin/severe hypoglycemic episodes)
- All 12 had a reduction in A1C *<7.0% and >70% time-in-range (70-180 mg/dL)* and did not experience severe hypoglycemic events
- 11/12 had reduced need for exogenous insulin within 90 days of treatment
- 3/3 participants past the 2 year mark are insulin independent

Vertex Trial (ongoing)

Participant 1

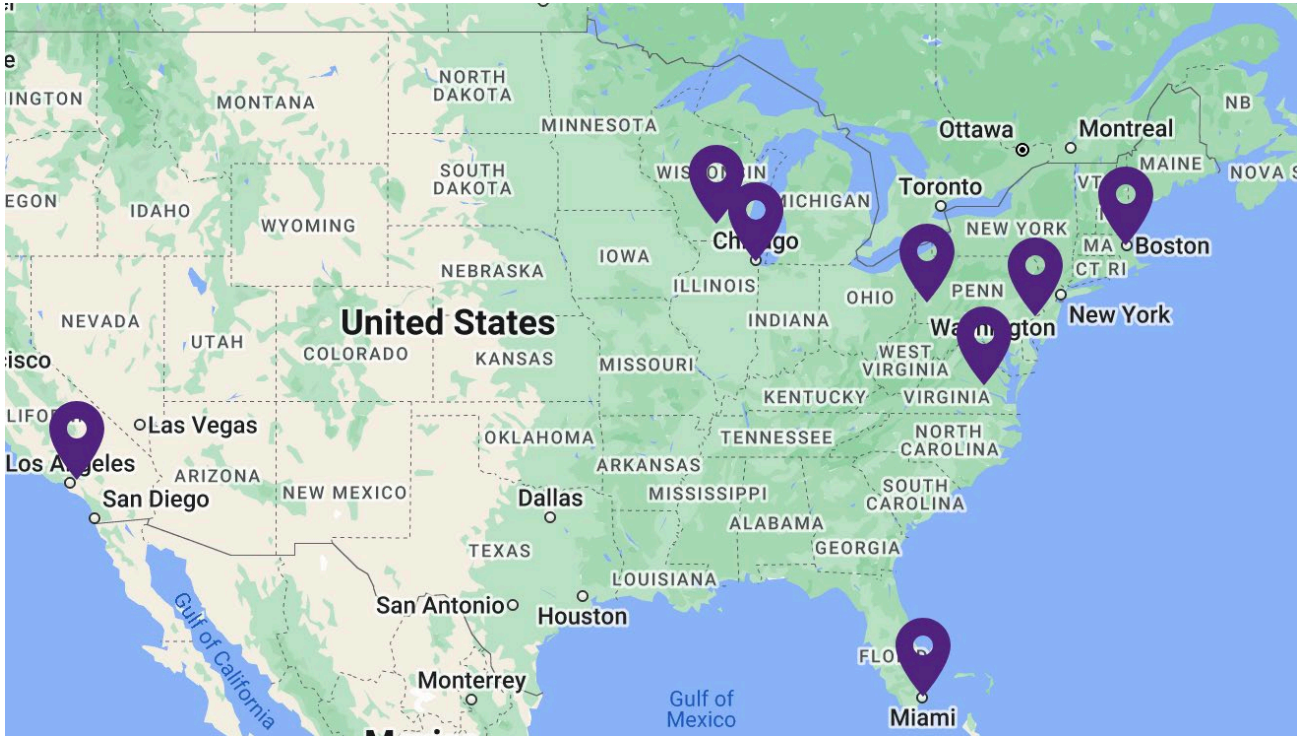
Study day	Day 0 (baseline)	Day 121-150	Day 241-270
Daily Insulin dose	34 units	2.6 units	0 units
Time in Range	40.1%	81.4%	99.9%
A1C	8.6%	6.7%	5.2%

Vertex Trial

FORWARD
Type 1 Diabetes Clinical Trial

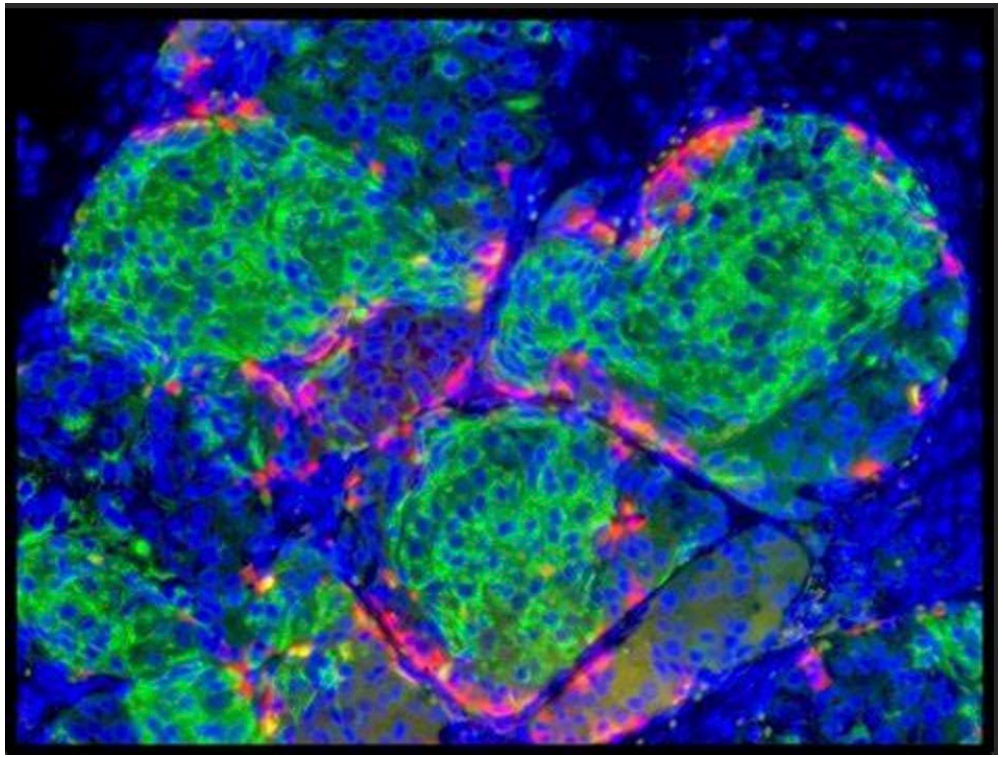
A Safety, Tolerability, and Efficacy Study of VX-880 (Zimislecel) in Participants with Type 1 Diabetes

Recruitment goal: 37 Subjects

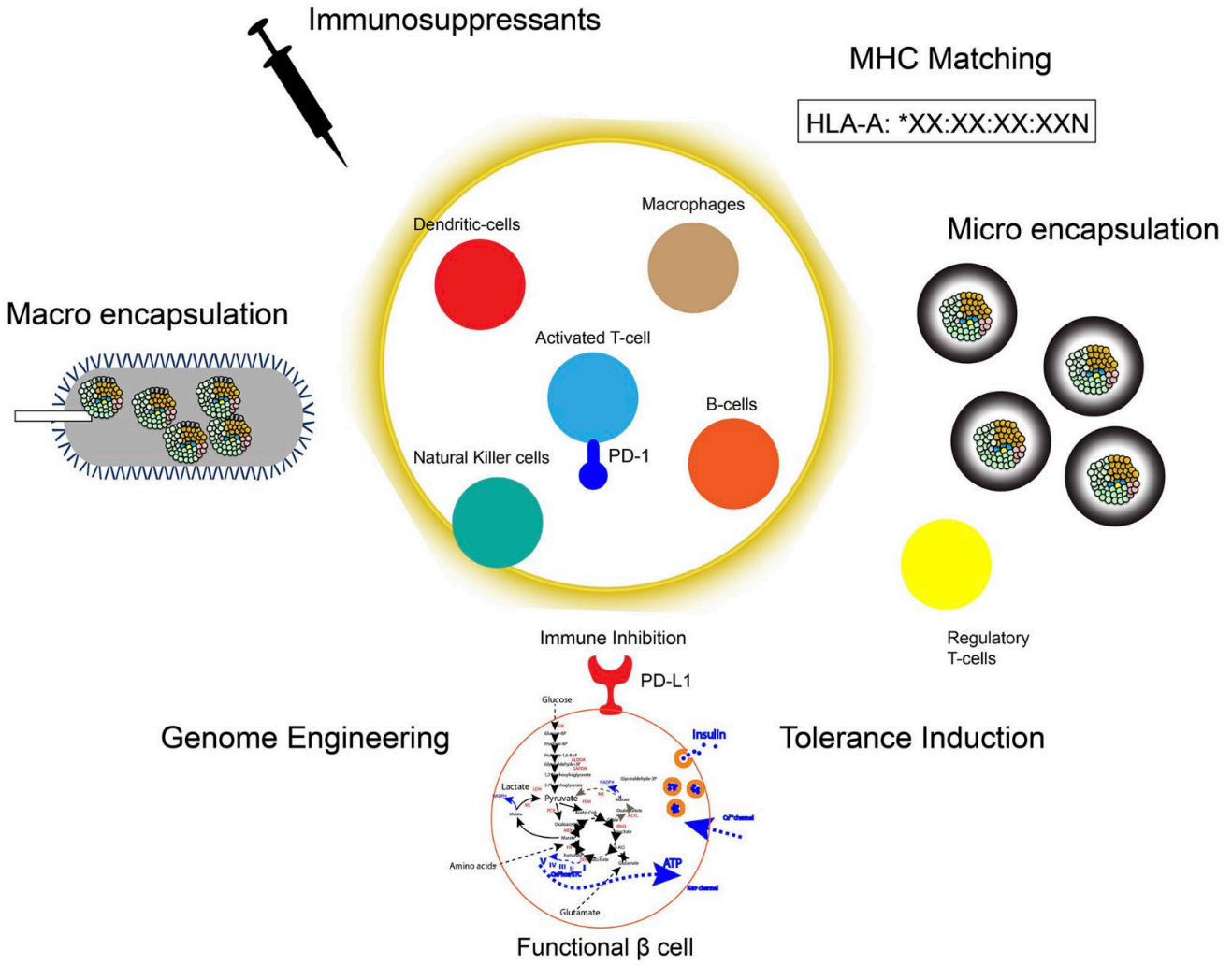


Summary

- Great progress in stem cell-derived beta cell research
- Ongoing clinical trials
- Viable future therapy
- Challenges remain
  - Directed differentiation
  - Variability between cell lines
  - Functional maturation
  - Graft survival
  - Immune protection



Immune protection of the beta cell



Tahbaz and Yoshihara, Frontiers in Endo 2021

Remaining Questions/Challenges

Is a functional cure possible without long-term immunosuppression?

Can the manufacturing process and quality control by more automated and scalable?

Cost?

What is the optimal transplantation site?

What is the optimal cell composition?

Future Roadmap of Stem Cell Therapies