

KEYNOTE ADDRESS

WORKING TOWARDS A CURE



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Sissel and Findlow Family Stem Cell Chair



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EPIC
DIABETES
CONFERENCE
MAY 21, 2022 | WEBINAR

EMPOWERING **P**ATIENTS
FOR
INDIVIDUALIZED **C**CARE



COI
NONE

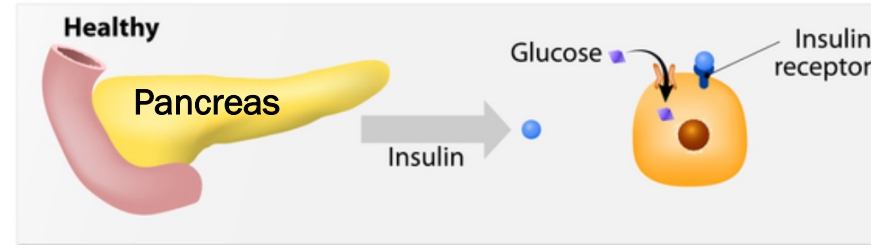


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TYPE 1 VS. TYPE 2 DIABETES

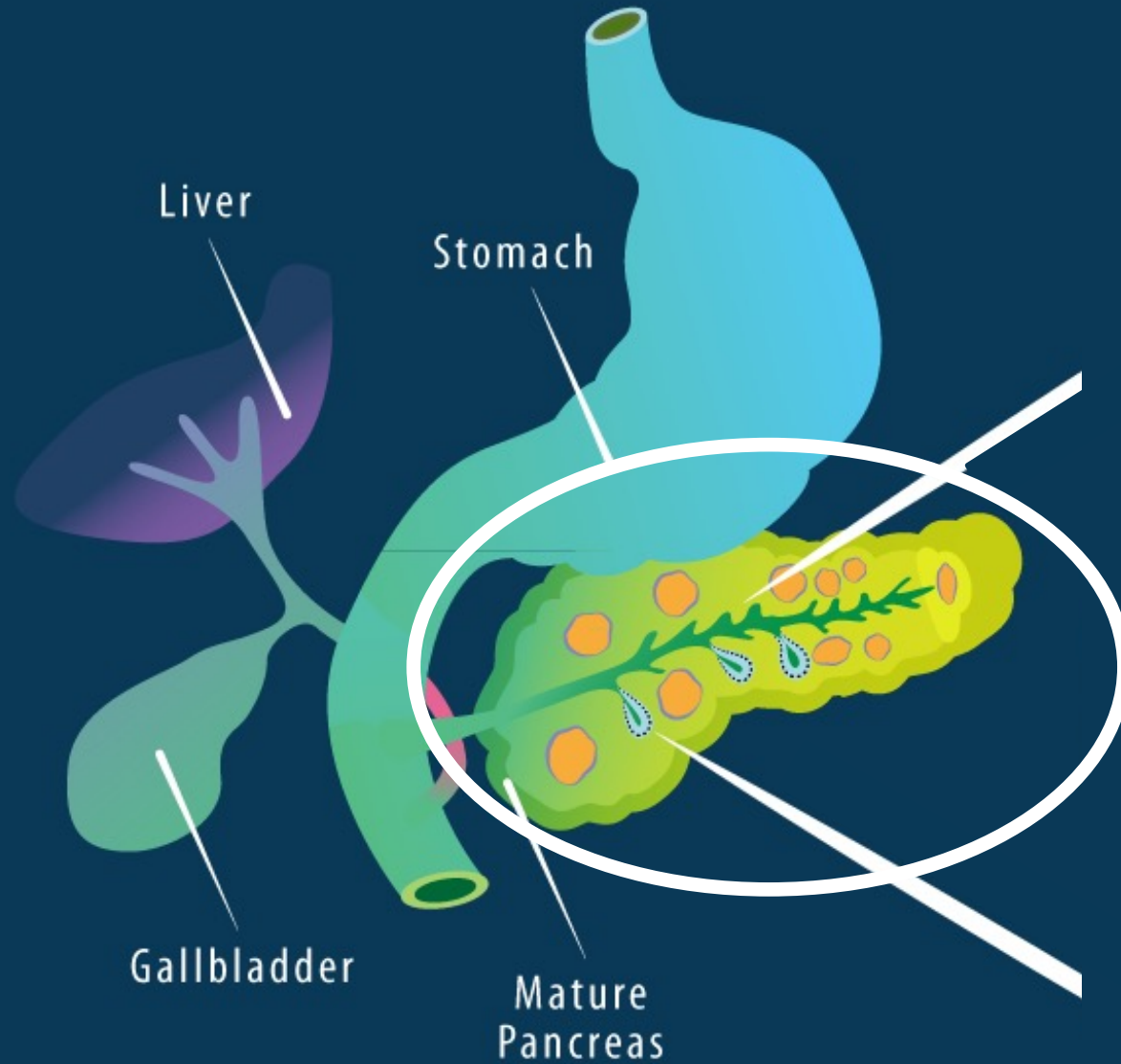


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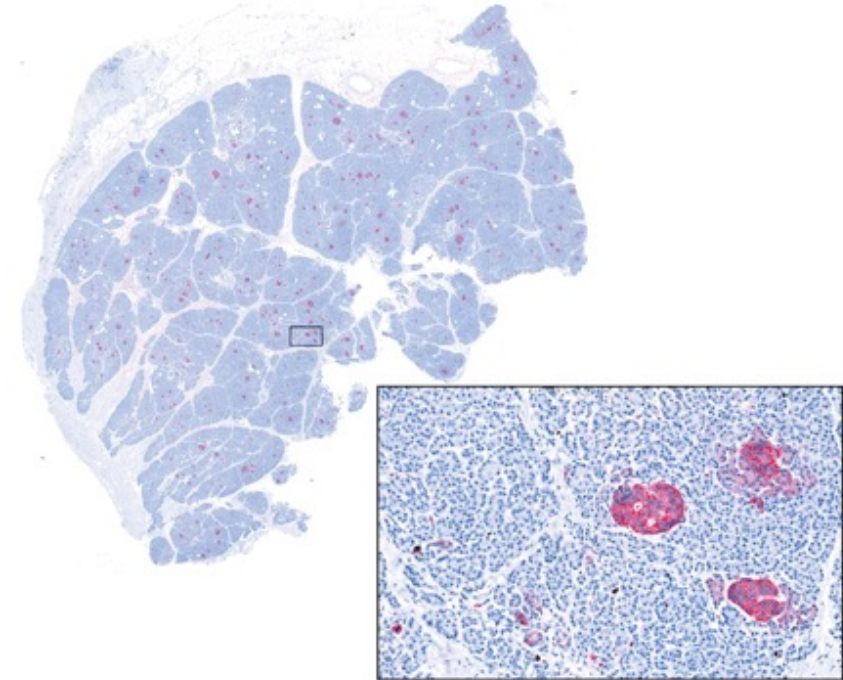
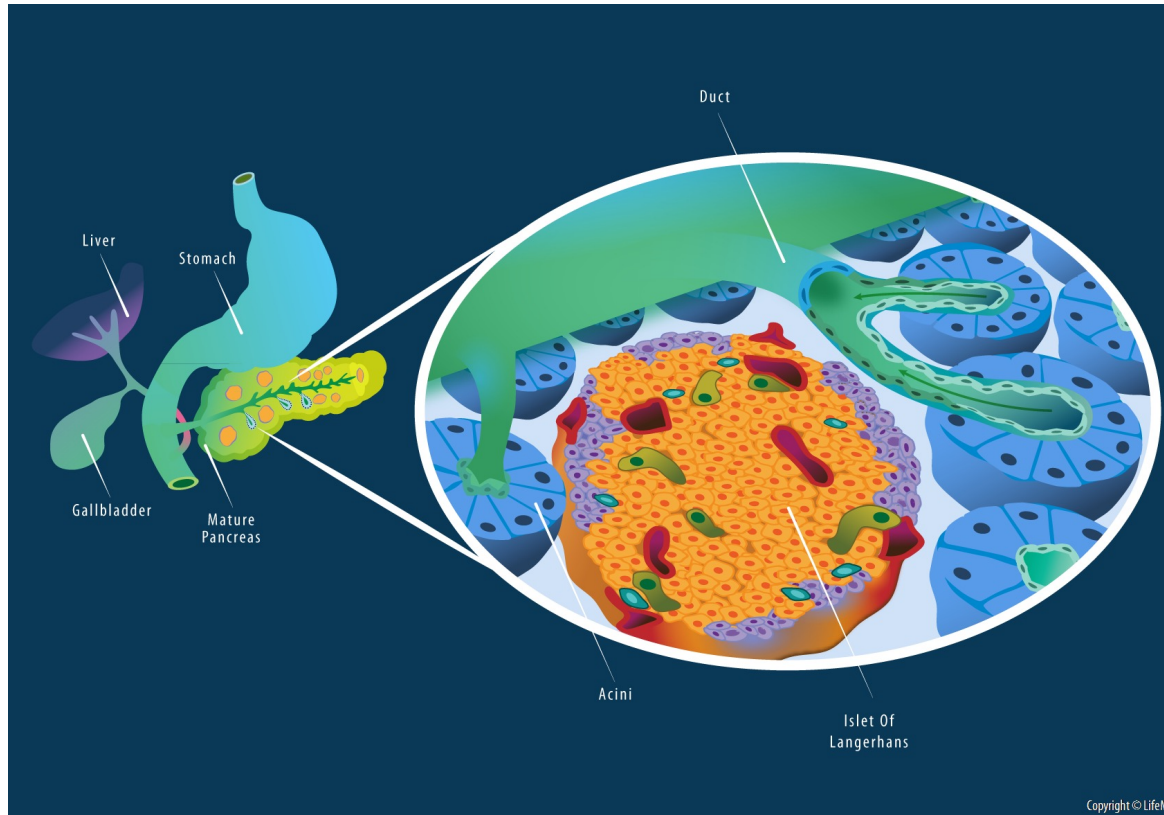
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INSULIN IS PRODUCED IN THE PANCREAS



PANCREATIC ISLETS: SOURCE OF HORMONE PRODUCING CELLS

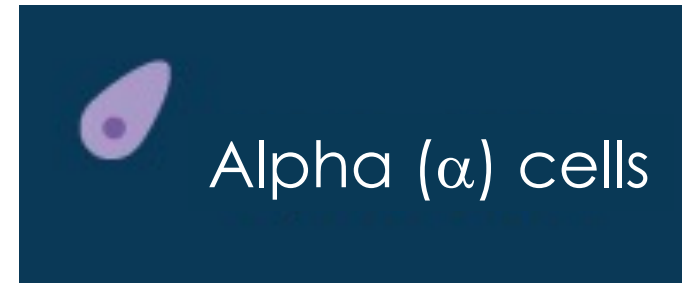
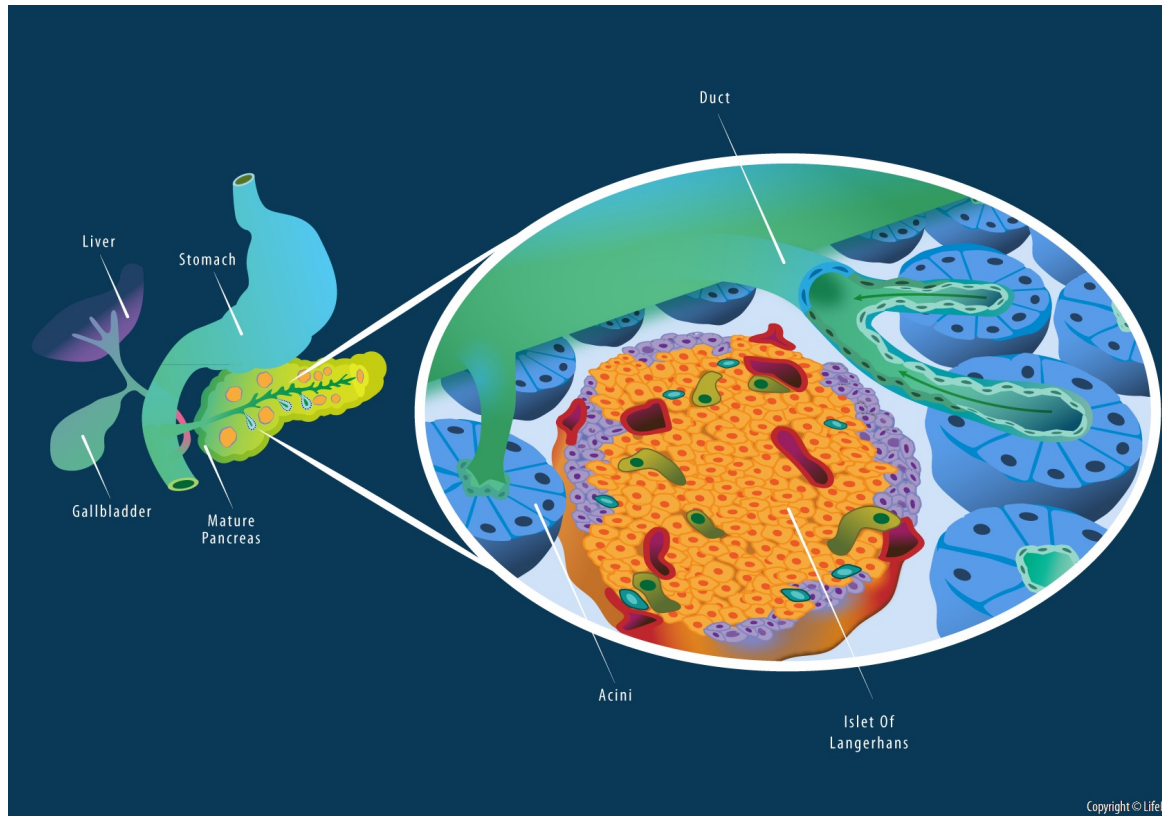


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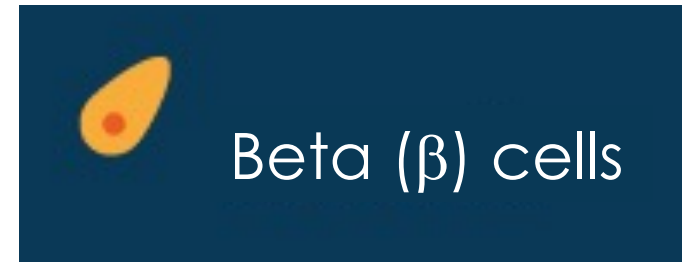
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PANCREATIC ISLETS: SOURCE OF HORMONE PRODUCING CELLS



Glucagon



Insulin



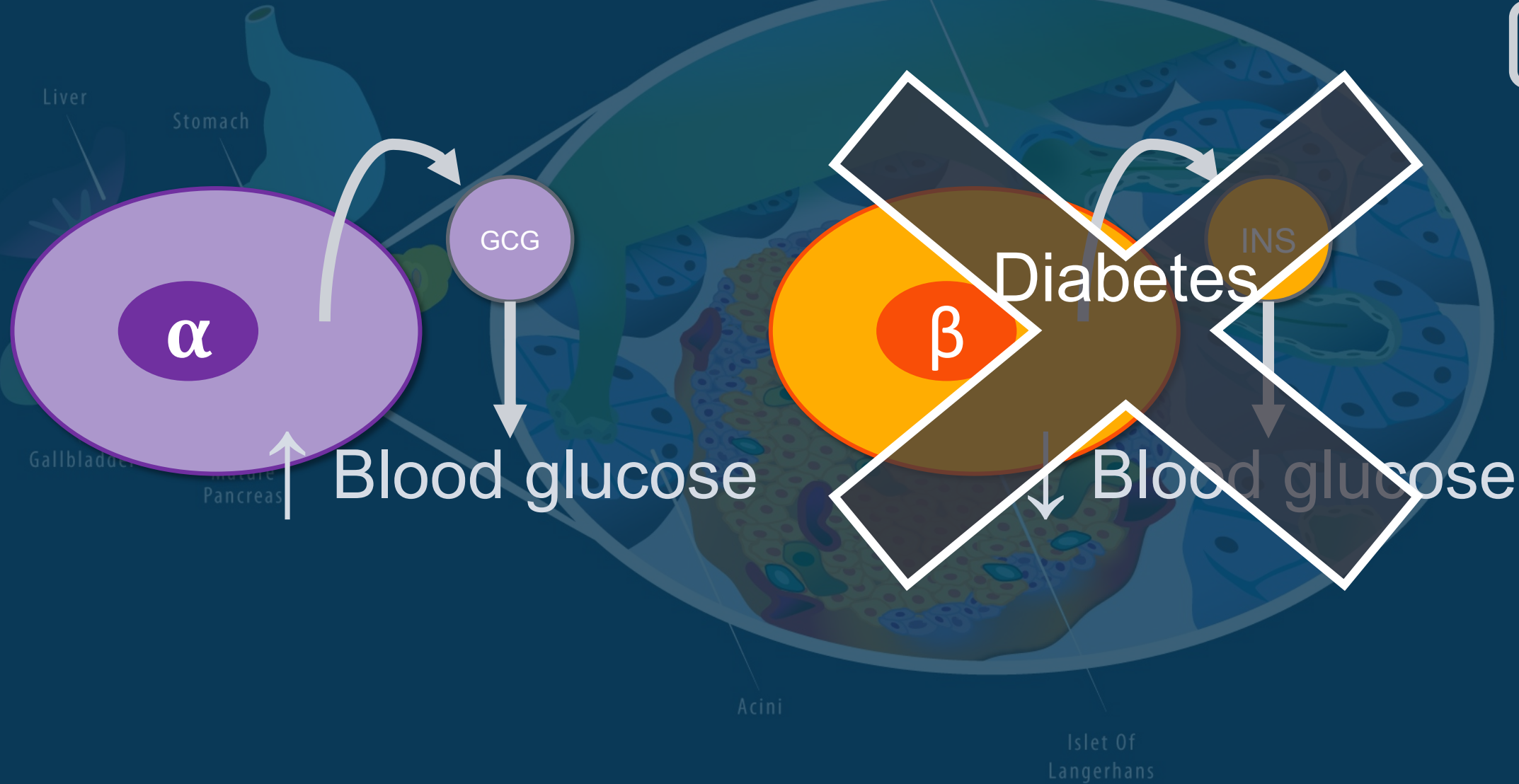
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FASTING

FEEDING



Alpha Cells
(glucagon)

Beta Cells
(insulin)

Delta Cells
(somatostatin)

PP Cells

Acinar Cells

Centroacinar Cells

Endothelial Cells

TYPE 1 VS. TYPE 2 DIABETES



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TRADITIONAL THERAPIES FOR DIABETES

TYPE 2 (insulin resistance):

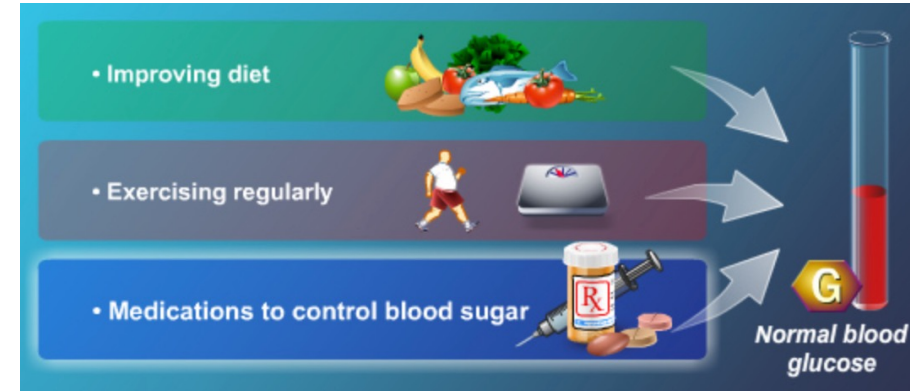
Stimulate insulin secretion

Decrease glucose release from liver/absorption from intestine

Improve insulin sensitivity (glucose uptake)

Decrease insulin resistance (muscle and fat)

Increase glucose excretion



TYPE 1 (autoimmune disease):

Exogenous insulin treatment

Immunotherapies

Beta cell replacement



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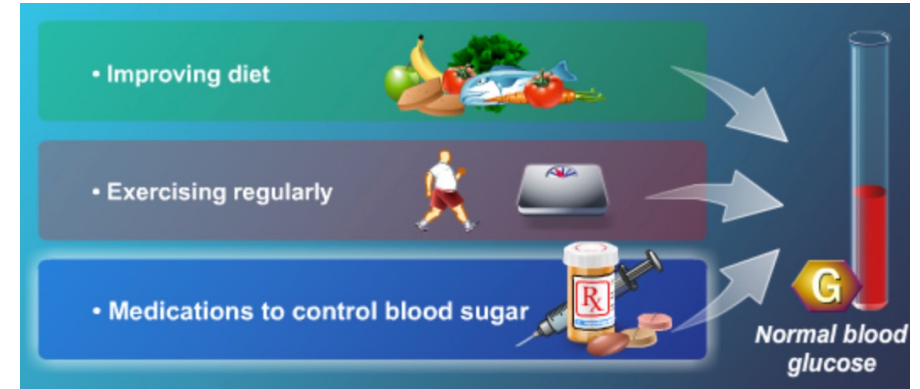
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TRADITIONAL THERAPIES FOR DIABETES

TYPE 2 (insulin resistance):

- Stimulate insulin secretion
- Decrease glucose release from liver/absorption from intestine
- Improve insulin sensitivity (glucose uptake)
- Decrease insulin resistance (muscle and fat)
- Increase glucose excretion



TYPE 1 (autoimmune disease):

- Exogenous insulin treatment
- Immunotherapies
- Beta cell replacement

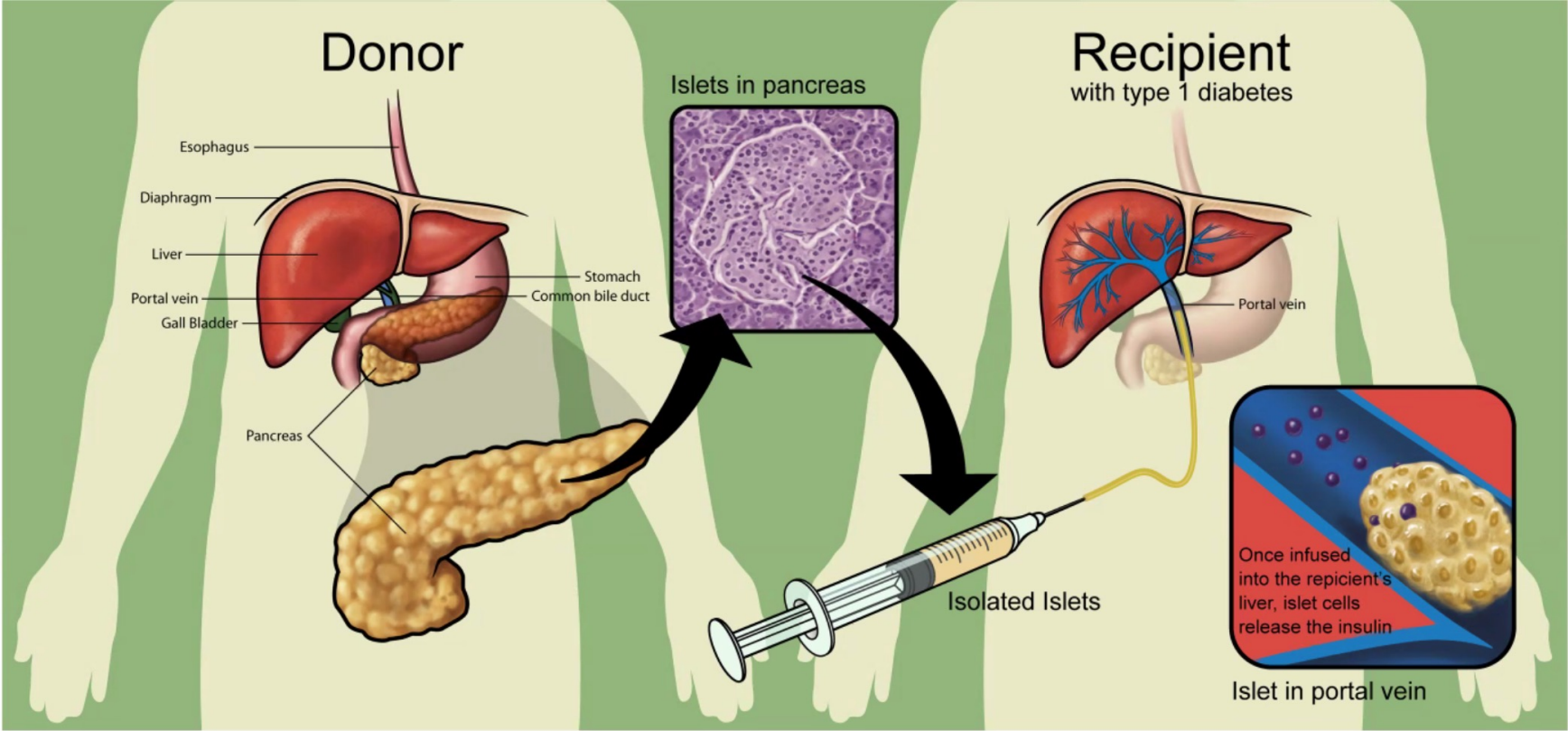


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ISLET TRANSPLANTATION AS A THERAPY



Naftanel et al., 2004



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ISLET TRANSPLANTATION AS A THERAPY

Recipients remain insulin independent for >5 years

- Reduced hypoglycemic episodes
- Improved quality of life

Challenges:

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

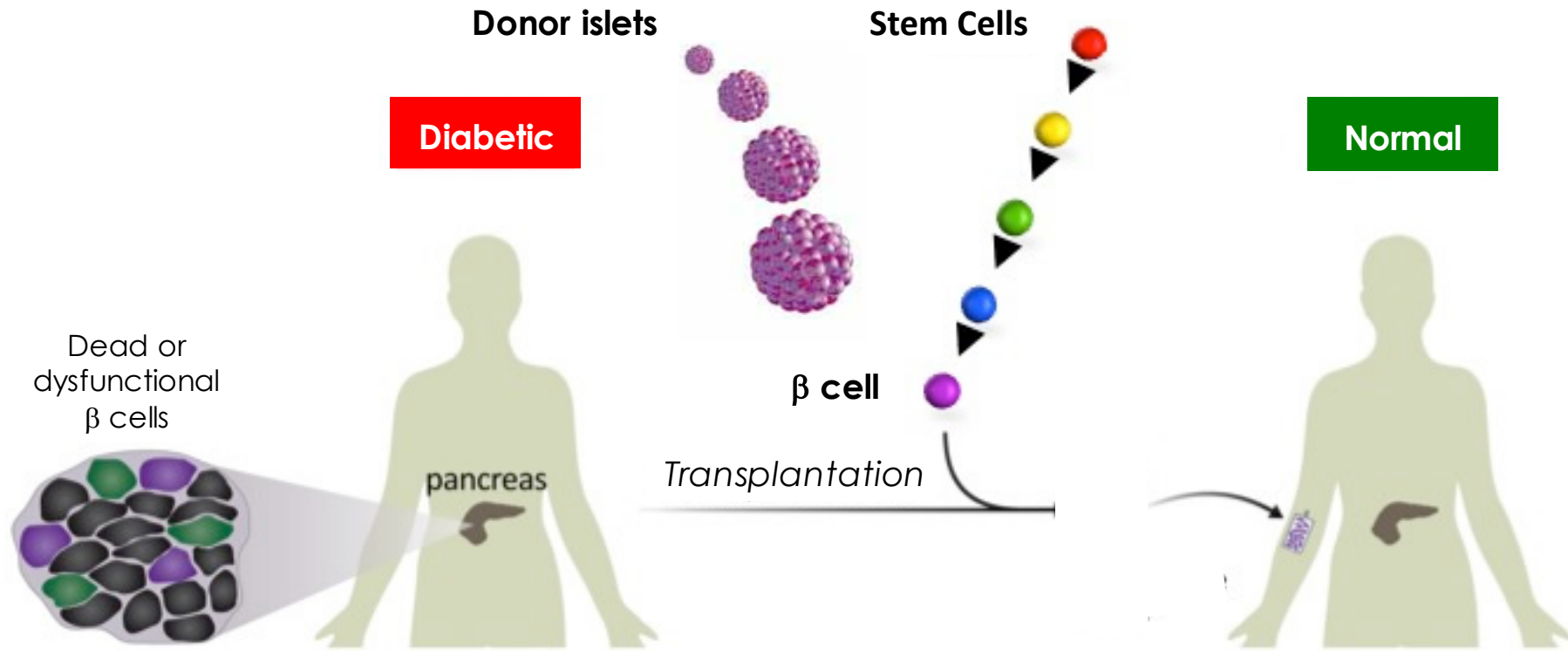


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CAN WE MAKE INSULIN-PRODUCING CELLS FROM STEM CELLS?



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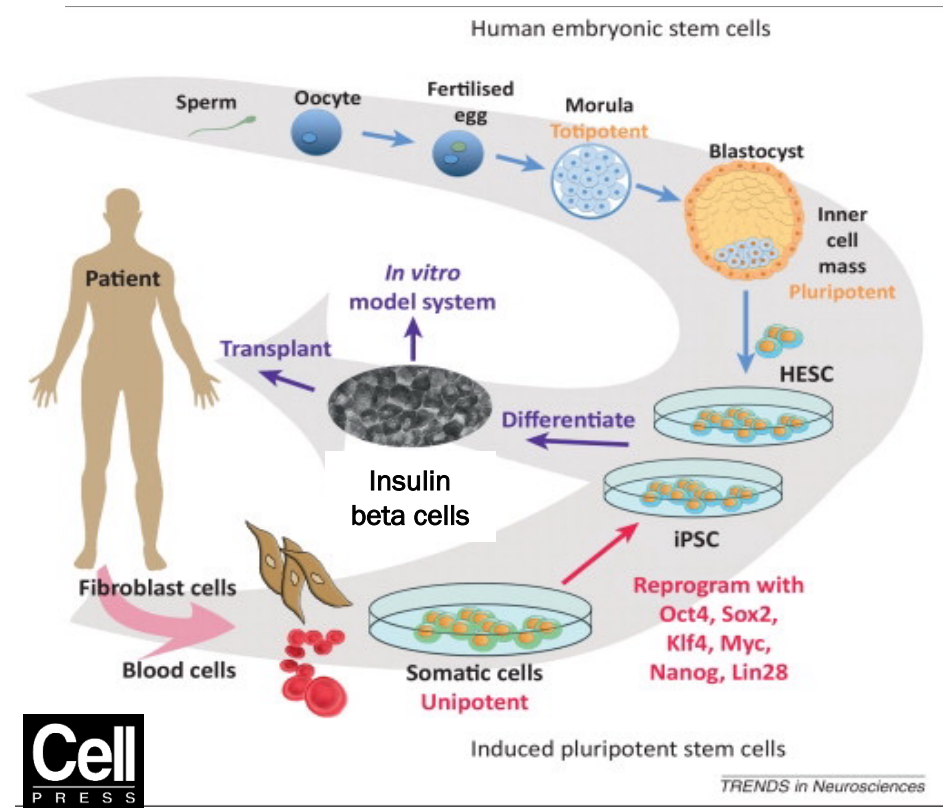
STEM CELLS (SHORT DIGRESSION)

Human Embryonic Stem (ES) Cell Lines

- Derived from early stage human embryo
- Line is established and frozen for future use
- Only handful of lines used today

Induced Pluripotent Stem Cells (IPS Cell lines)

- Derived from any tissue in the body (skin, blood, etc)
- Line is established and frozen for future use
- Reprogrammed to any cell in the body



Trends in Neurosciences 2013 36385-395DOI: (10.1016/j.tins.2013.03.006)



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GENERATION OF HUMAN ISLET BETA CELLS

~20 years ago

Stem Cells



Islet of Langerhans



Making pancreatic islet cells in complicated

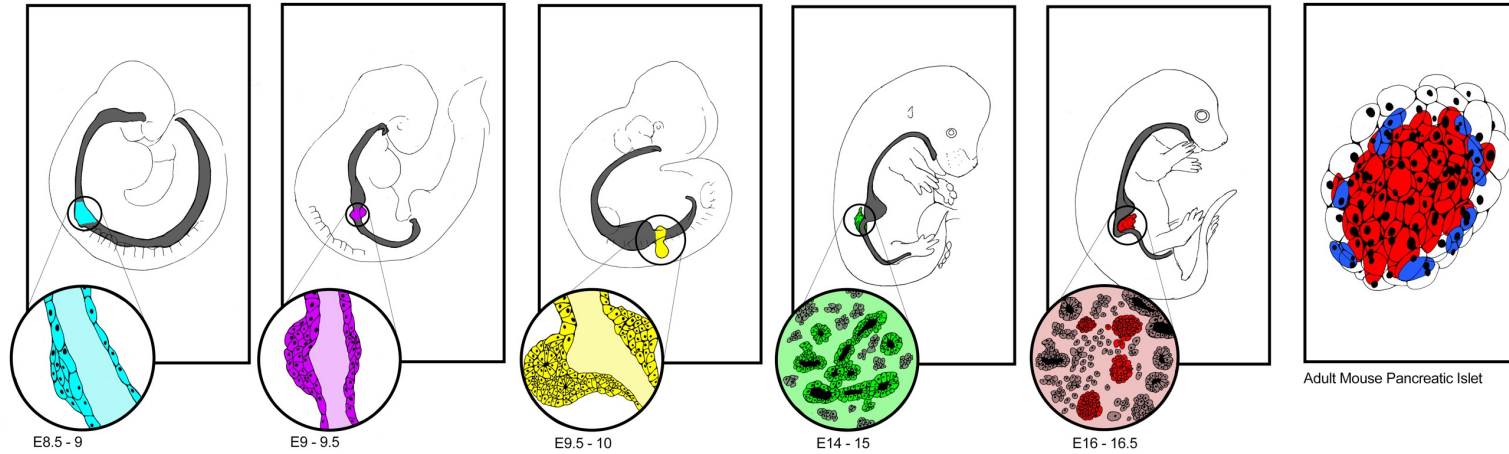


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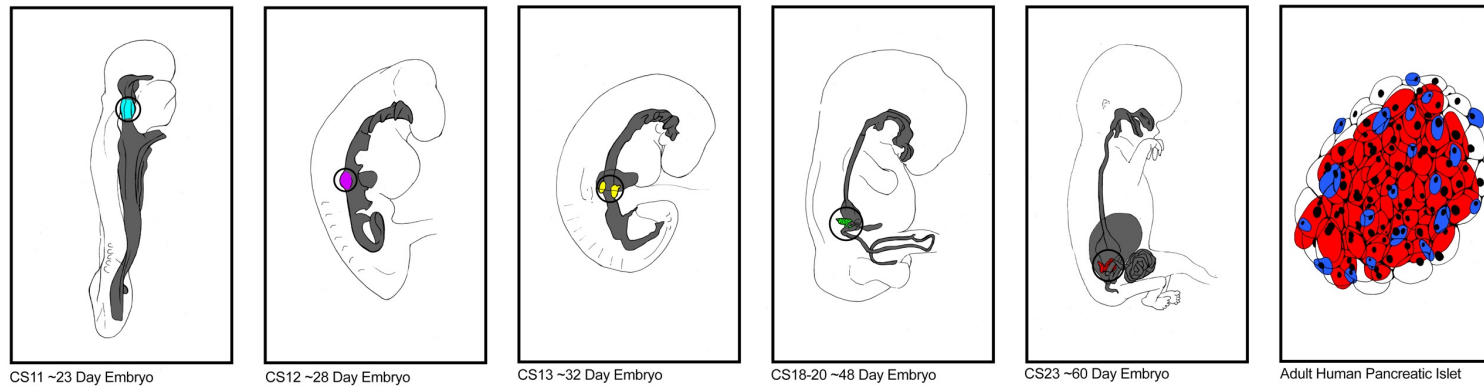
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CONSERVATION BETWEEN MICE AND MEN



Mouse Pancreas Development



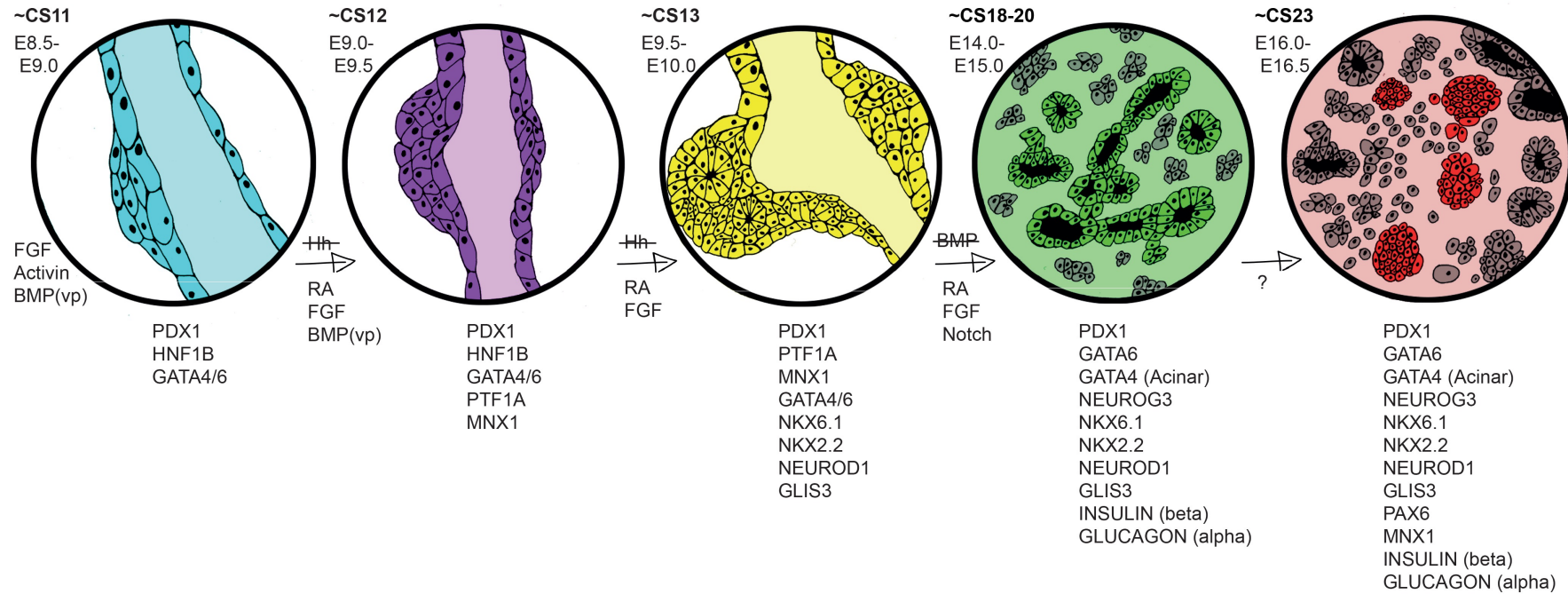
Human Pancreas Development

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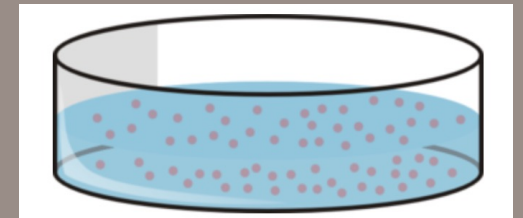
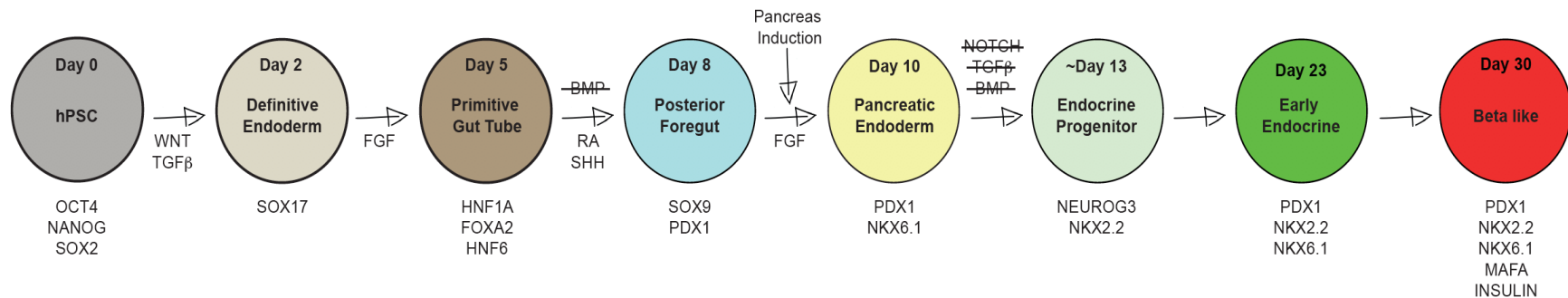
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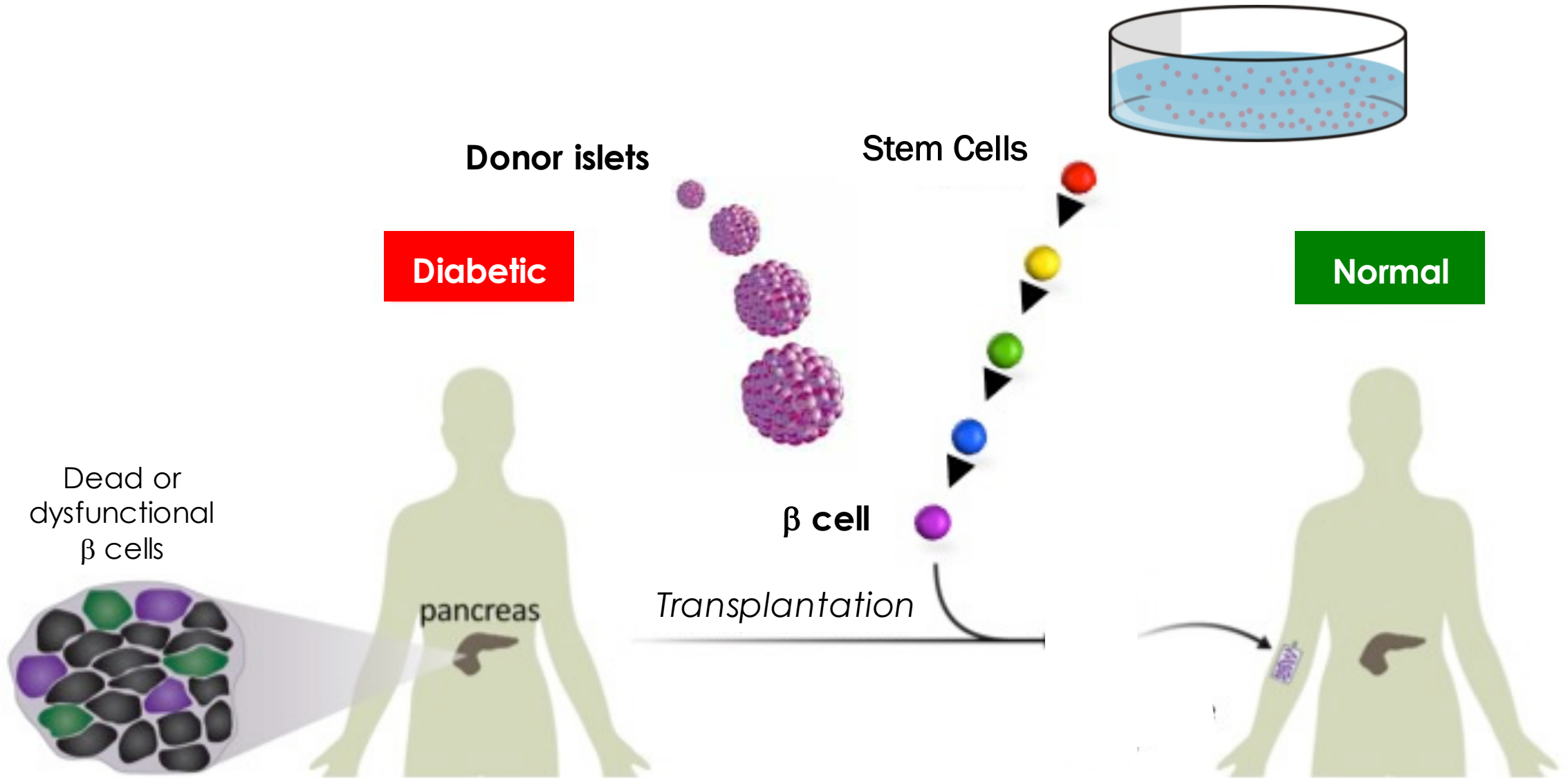
LEARNING FROM NORMAL FETAL DEVELOPMENT



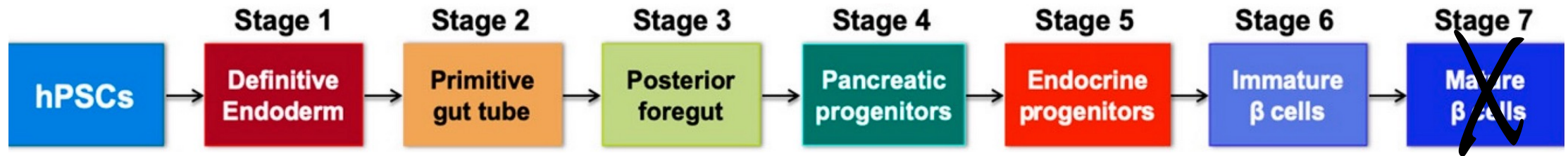
Human stem cell differentiation



CAN WE USE INSULIN CELLS MADE IN A DISH?



CAN WE USE INSULIN CELLS MADE IN A DISH?



> 20 years of research

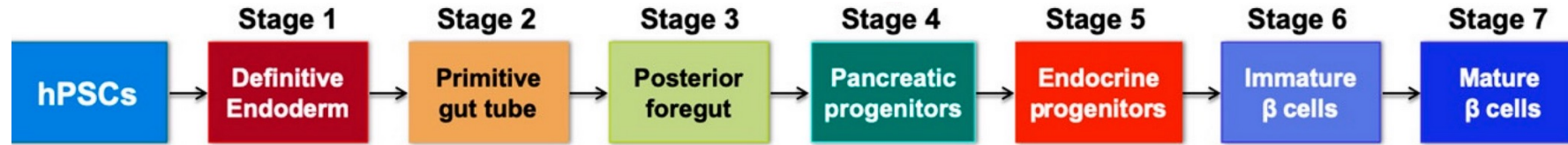


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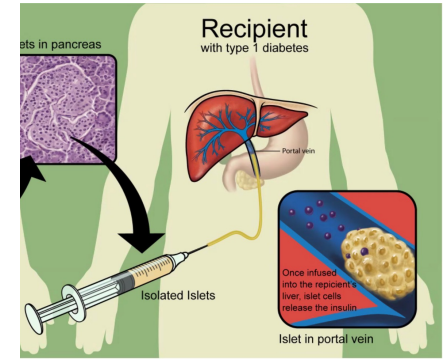
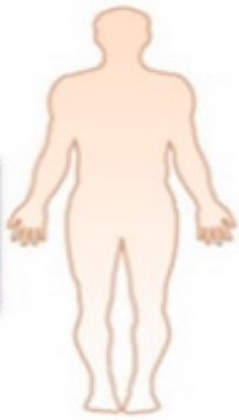
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VERTEX CLINICAL TRIAL



Phase 1/2
Clinical Trial



Naftanel et al., 2004

Immature β -cells:

- Polyhormonal
- Do not respond to glucose
- Do not express appropriate β -cell markers



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VERTEX CLINICAL TRIAL

The New York Times



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

Promising study, but with caveats:

- Only 1 Person
- 90 days
- Required immune suppression
- Status of implanted cells unknown
- Not peer-reviewed
- Expensive
- Not enough cells



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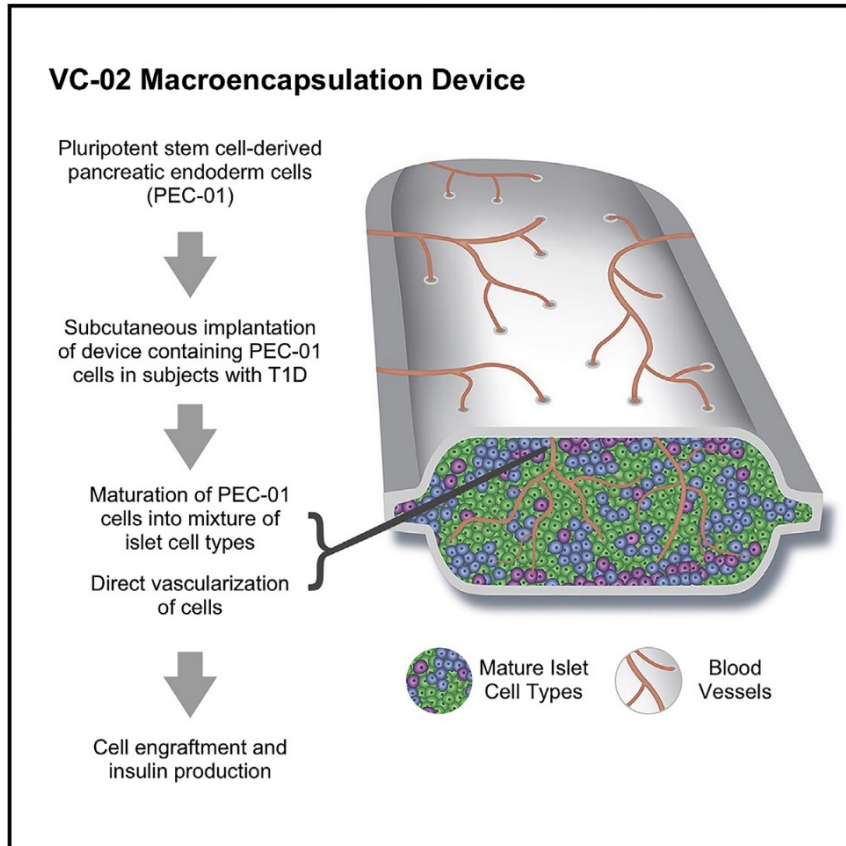
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Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes

Authors

Adam Ramzy, David M. Thompson, Kirsten A. Ward-Hartstonge, ..., Garth L. Warnock, Megan K. Levings, Timothy J. Kieffer



Cell Reports Medicine

Article

Insulin expression and C-peptide in type 1 diabetes subjects implanted with stem cell-derived pancreatic endoderm cells in an encapsulation device

Authors

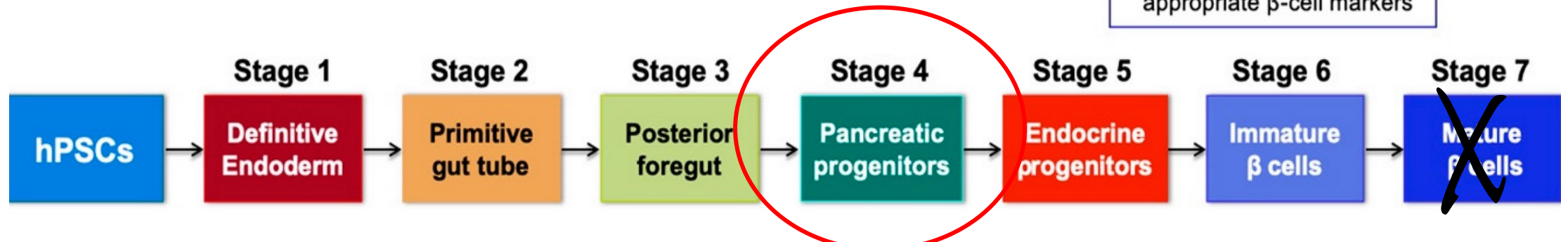
A.M. James Shapiro, David Thompson, Thomas W. Donner, ..., Evert J. Kroon, Kevin A. D'Amour, Howard L. Foyt

January/February 2022

VIACYTE CLINICAL TRIAL

Immature β -cells:

- Polyhormonal
- Do not respond to glucose
- Do not express appropriate β -cell markers



Transplantation

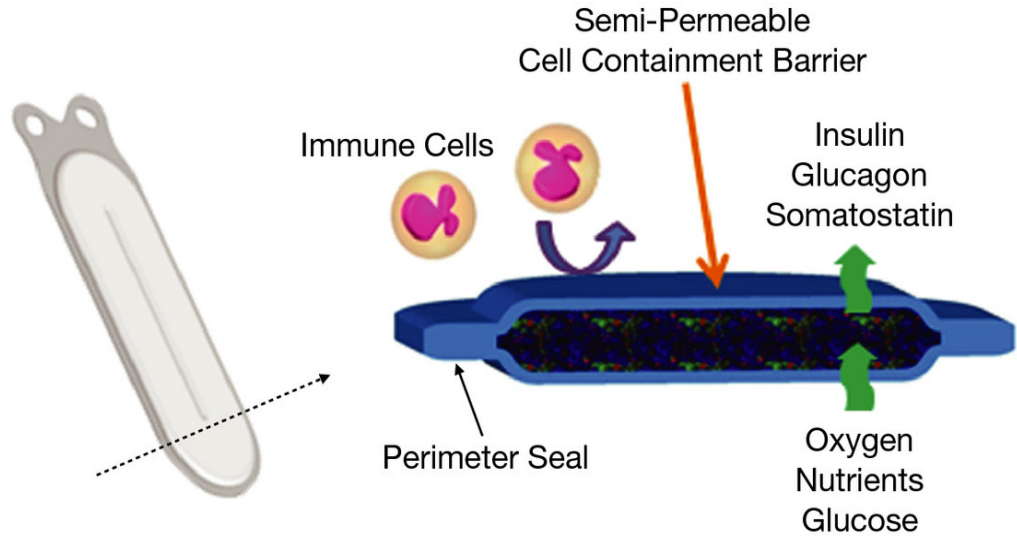


In vivo maturation

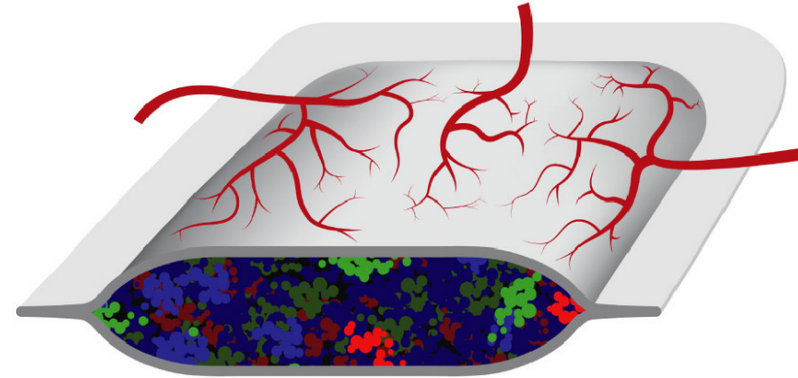
Mature β -cells:

- Monohormonal (INS)
- Respond to glucose
- Express appropriate β -cell markers

VIACYTE TRIAL: TRANSPLANT ISLET PROGENITOR CELLS

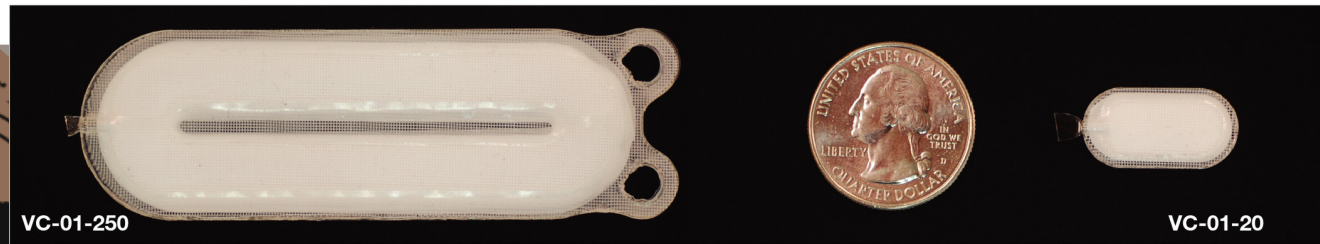


Encaptra is a cell-impermeable macro encapsulation device



Blood vessels grow along the device for gas and nutrient exchange

2-4 devices per patient



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VIACYTE MULTI-CENTER TRIAL

Transplanted pancreatic progenitor cells

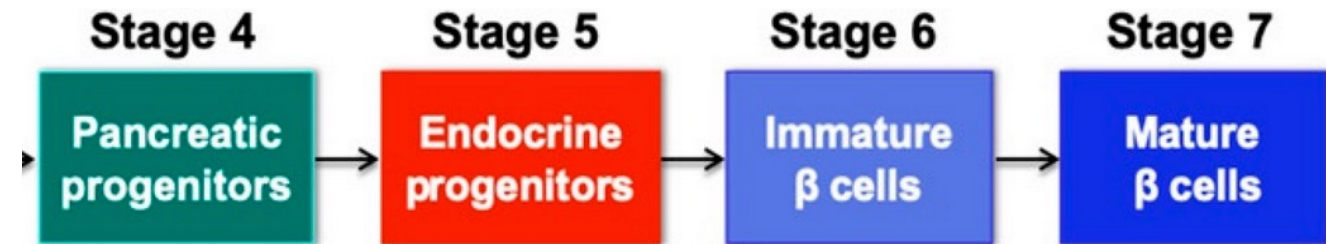
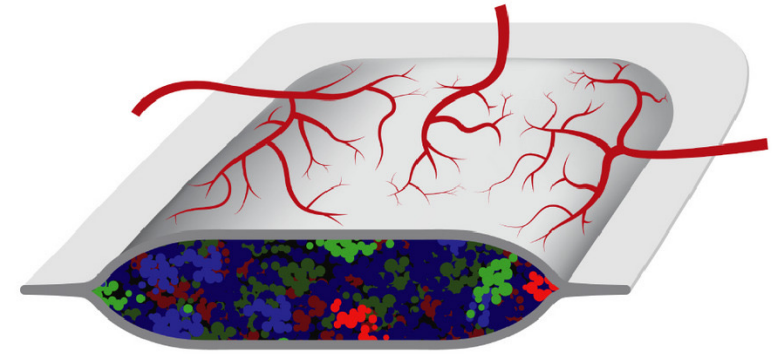
Immune suppression

Two trial sites (15 and 17 patients)

Two-thirds dropped out due to adverse reactions (surgery and immune suppression)

Good news:

- No tumor formation
- Meal responsive insulin secretion
- Good blood supply
- Relatively safe



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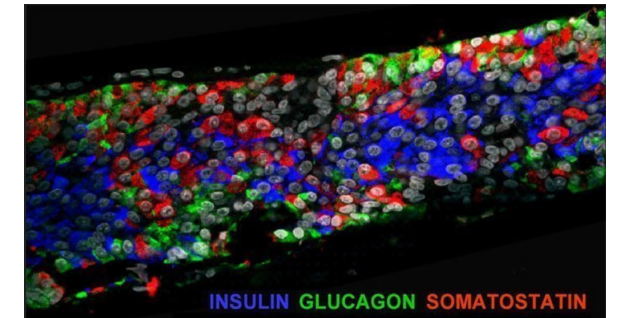
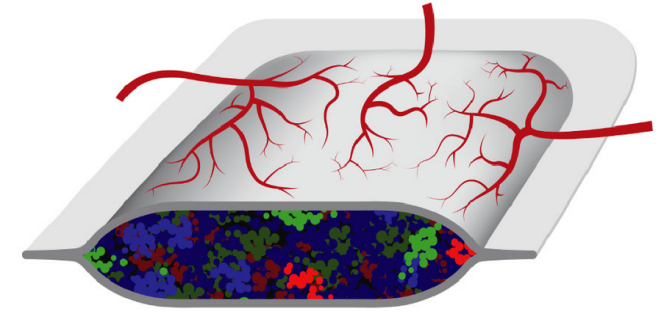
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VIACYTE MULTI-CENTER TRIAL

Not so good news:

- None of the patients lowered their insulin doses or achieved insulin independence
- Low circulating C-peptide (would need to increase 100X)
- Very few insulin-expressing cells; mostly glucagon
- Cell death

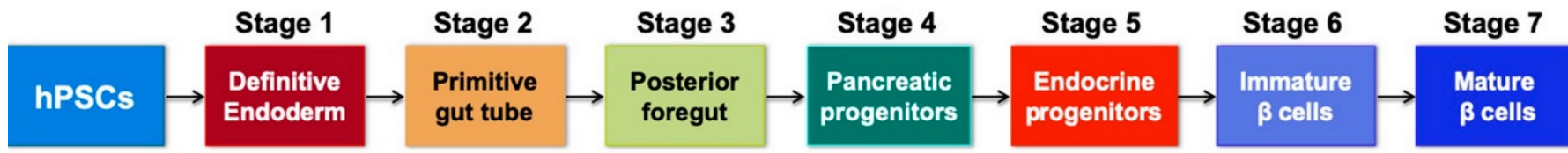


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COMPARING TRIALS

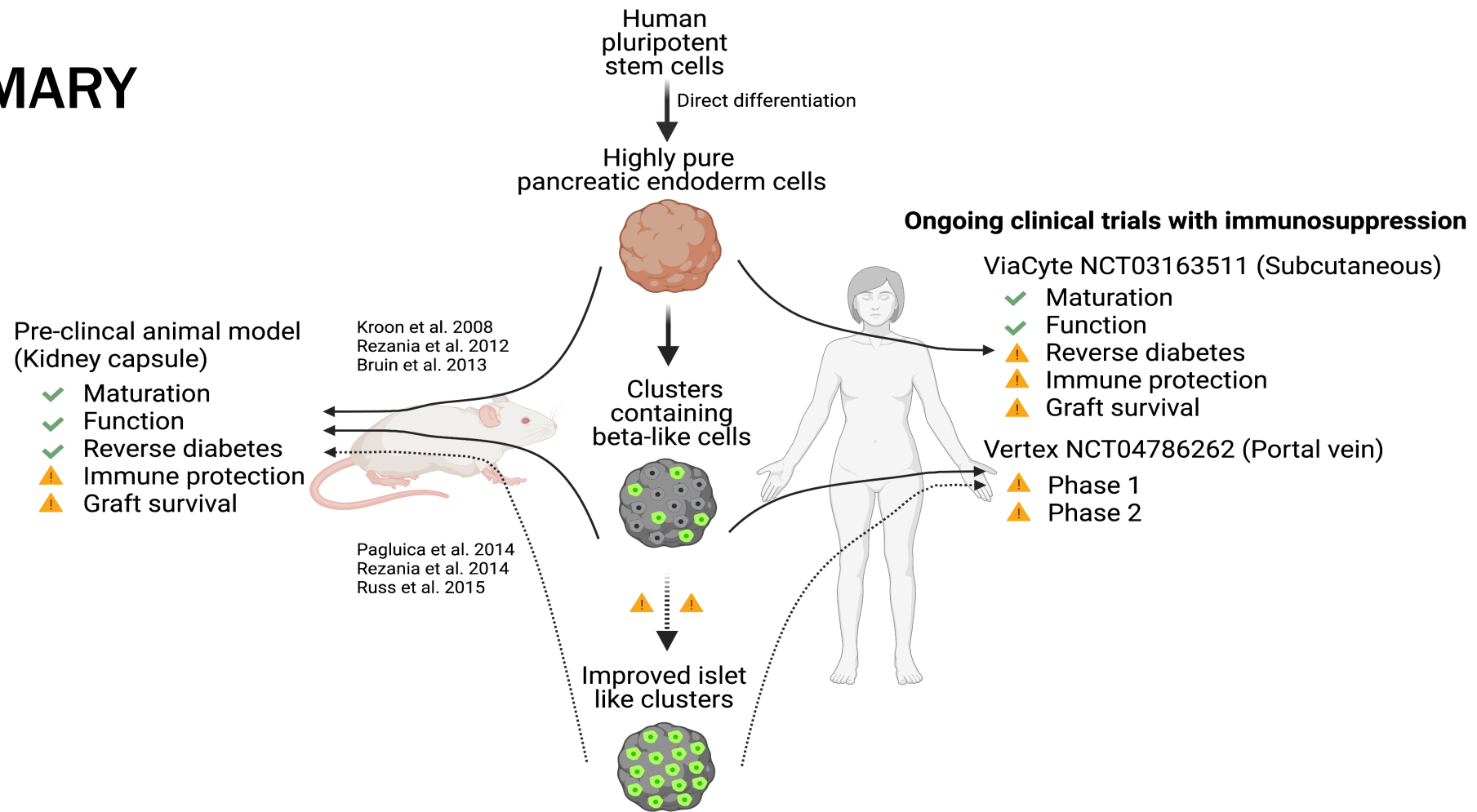


Highly efficient progenitor cell generation
Less time under GMP conditions
Less control of differentiation



Inefficient cell generation
More time under GMP conditions
More control of differentiation

SUMMARY



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BOTTOM LINE

Stem cell derived islet cell therapies are promising

Relatively Safe

But more research is required

- Better control of cell differentiation
- Move away from systemic immune suppression
- Increase cell survival post transplantation

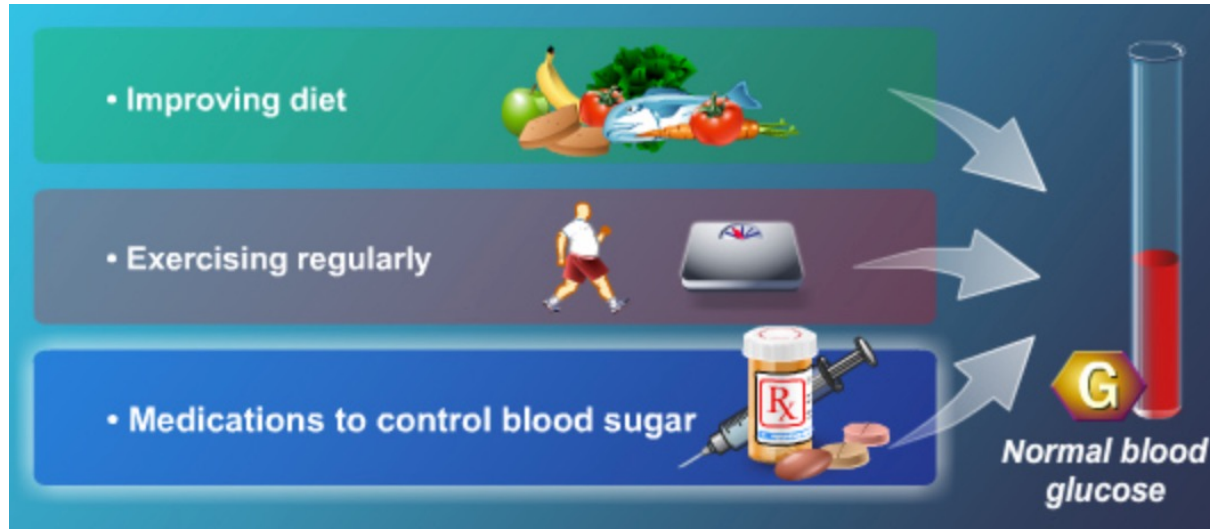


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BEST OPTIONS TODAY



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FUTURE OPTIONS: BDC RESEARCH DIVISION

- Improve generation of islet clusters in a dish (Sussel and Russ)
- Engineer "immuno-protected beta cells" (Russ, Nakayama, Michels)
- Improve beta cell graft survival post-transplant (Russ and Sussel)

Complimentary Studies:

Predict autoimmune destruction: Nakayama, Davidson, Smith, Yu

Block the immune response: Nakayama, Friedman, Jacobelli, Michels

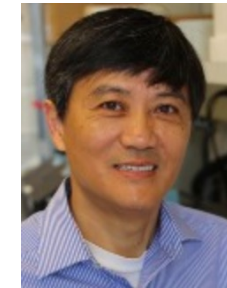
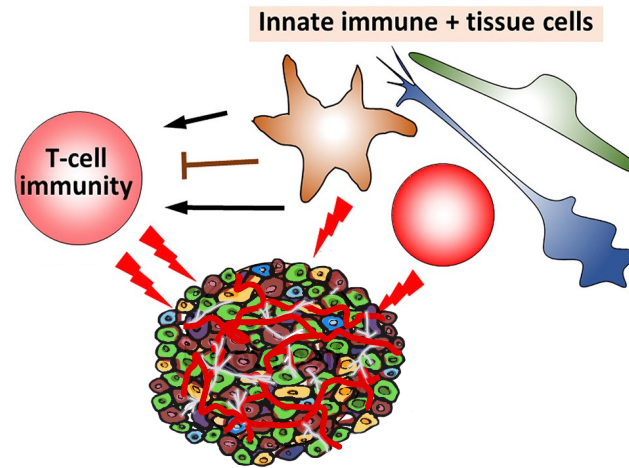
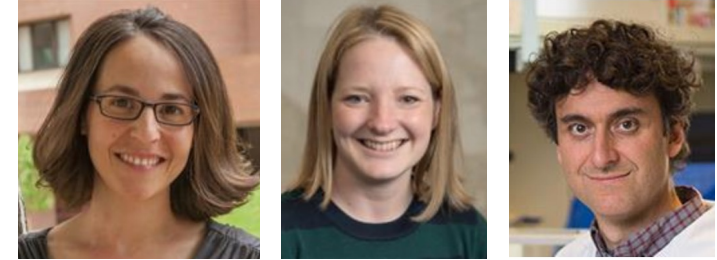
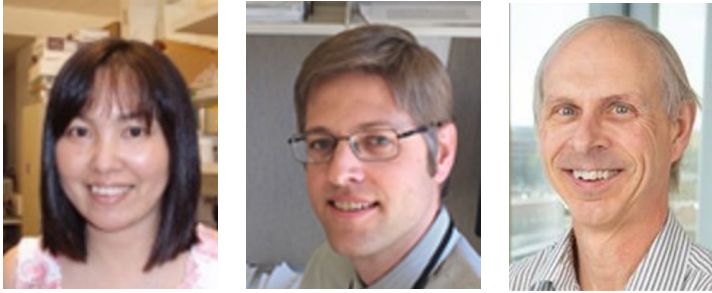


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FUTURE OPTIONS: BDC RESEARCH DIVISION



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THANK YOU!

Comments?
Questions?



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