Regenerative Medicine and Diabetes

Clinical Outlooks for Regenerative Medicine Metabolic Panel

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Why is diabetes such a problem?

Retinopathy – blindness

Nephropathy – renal failure

Neuropathy – amputation and more

Macrovascular disease – MI and stroke

The key is preventing hyperglycemia

The Diabetes Problem is Enormous and Growing

The cause is not enough insulin-producing cells - pancreatic beta cells. The resulting high blood glucose levels cause the complications.

In type 1 diabetes beta cells are almost entirely wiped out by autoimmunity.

In type 2 diabetes eventually beta cells are reduced to 40-60% of normal.

Replacement of beta cells with transplantation can reverse diabetes.

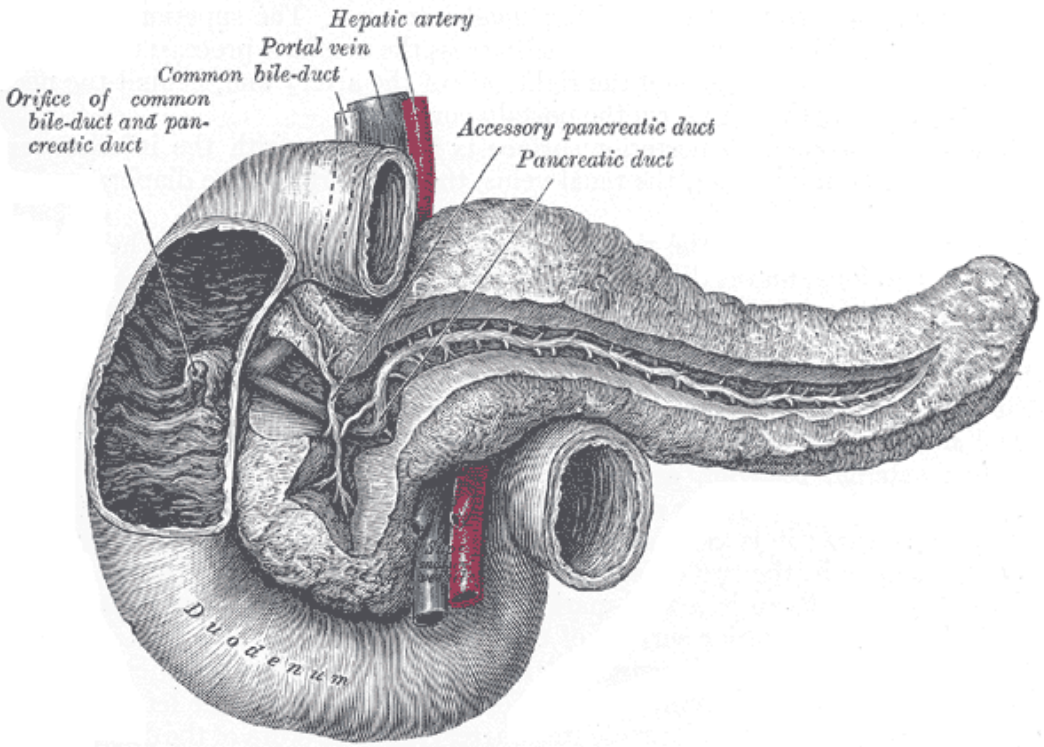
How might regenerative medicine help?

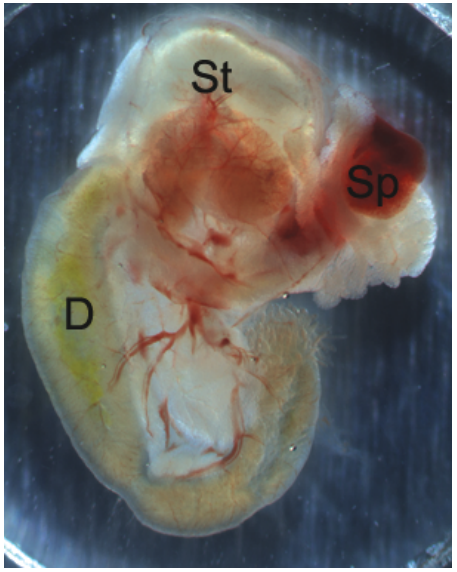
Replace the missing beta cells

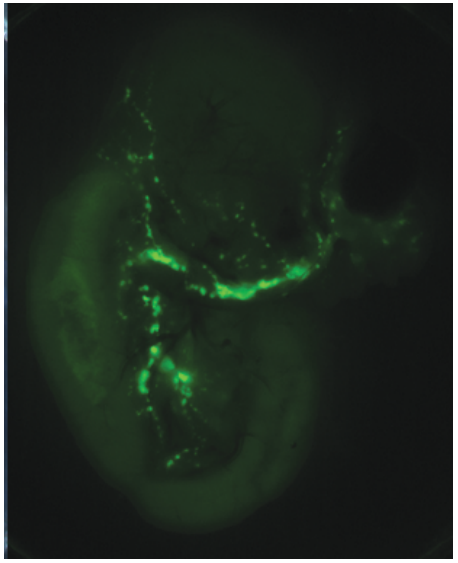
Shut off the autoimmunity that kills beta cells

Slow the progression of vascular disease

Serve as a disease model for both types 1 and 2 diabetes (induced pluripotent stem cells – iPS cells)





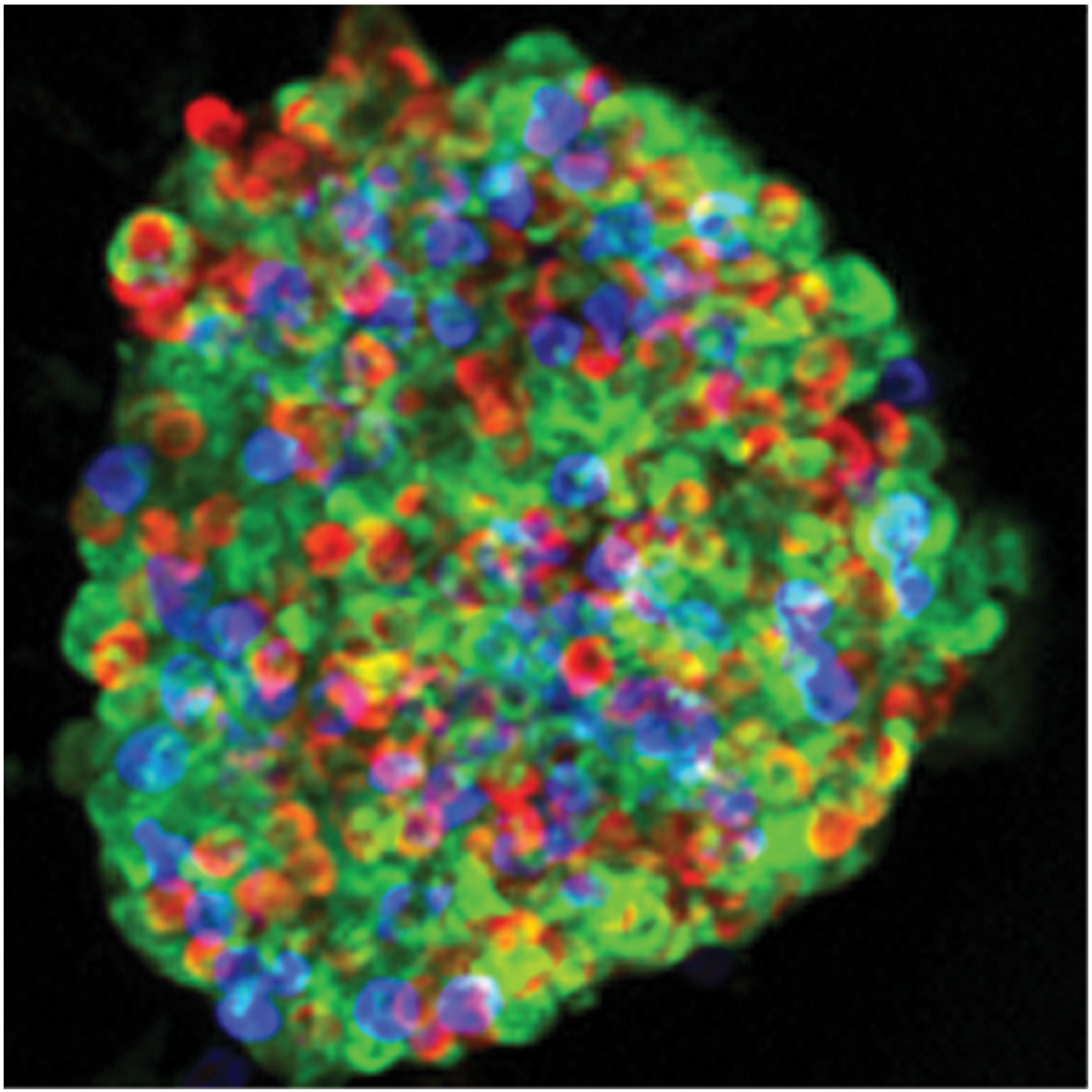


Human pancreas: 85 gm
Islet mass: 2%
About one million islets
About one billion beta cells

Courtesy Manami Hara

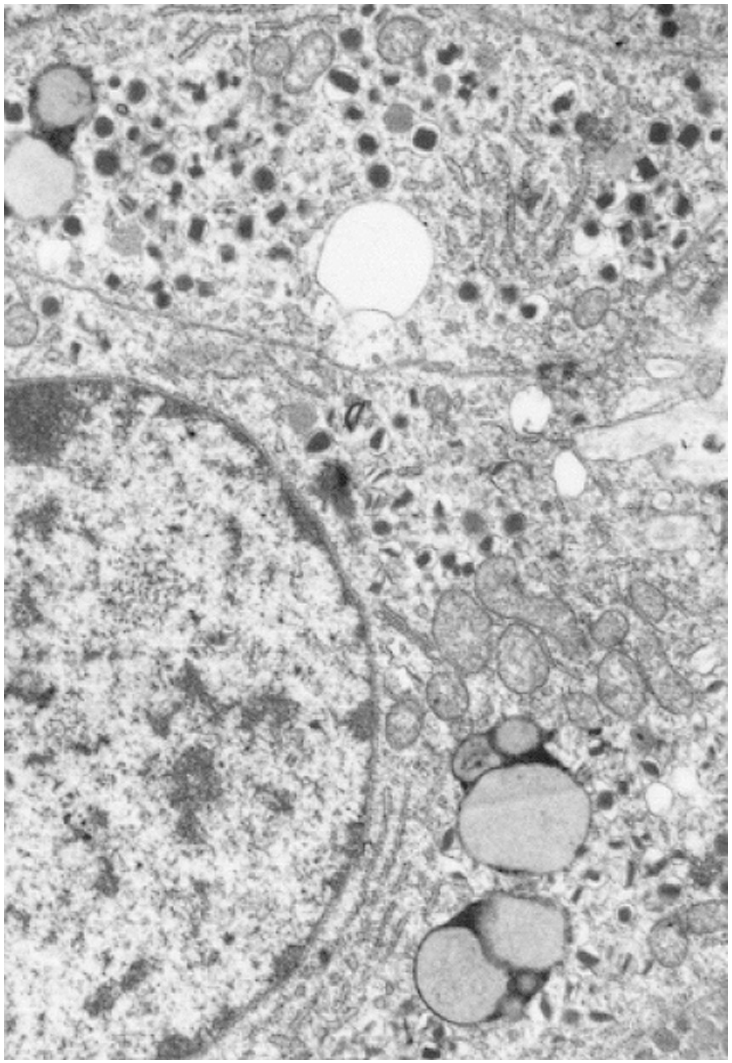
An Islet

Insulin
Glucagon
Somatostatin



Courtesy Alvin Powers

A Beta Cell



About 10,000 insulin granules

Courtesy Susan Bonner-Weir

Progress with Beta Cell Replacement

1960s: First pancreas transplants

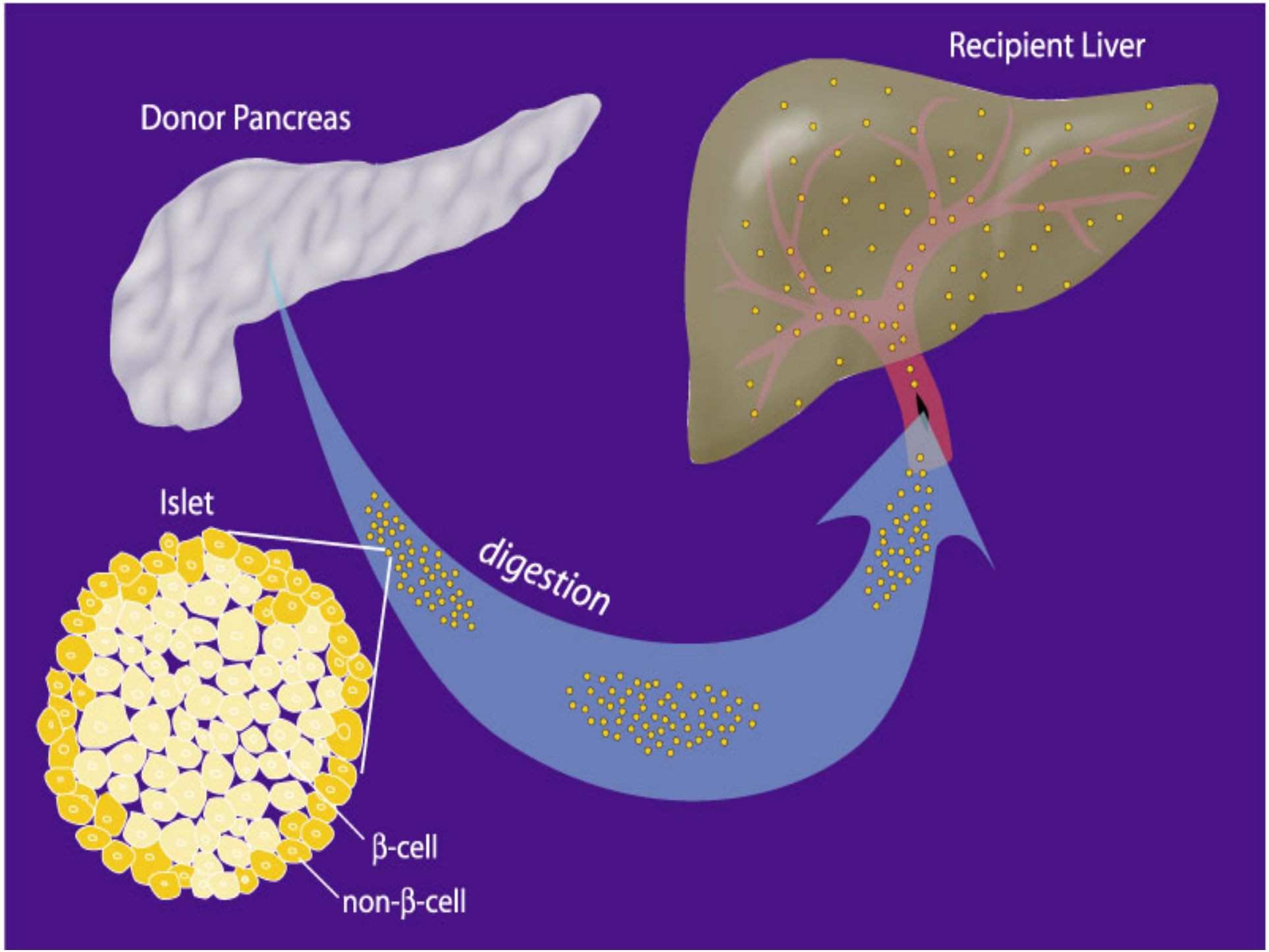
1972: Islet transplants in rats

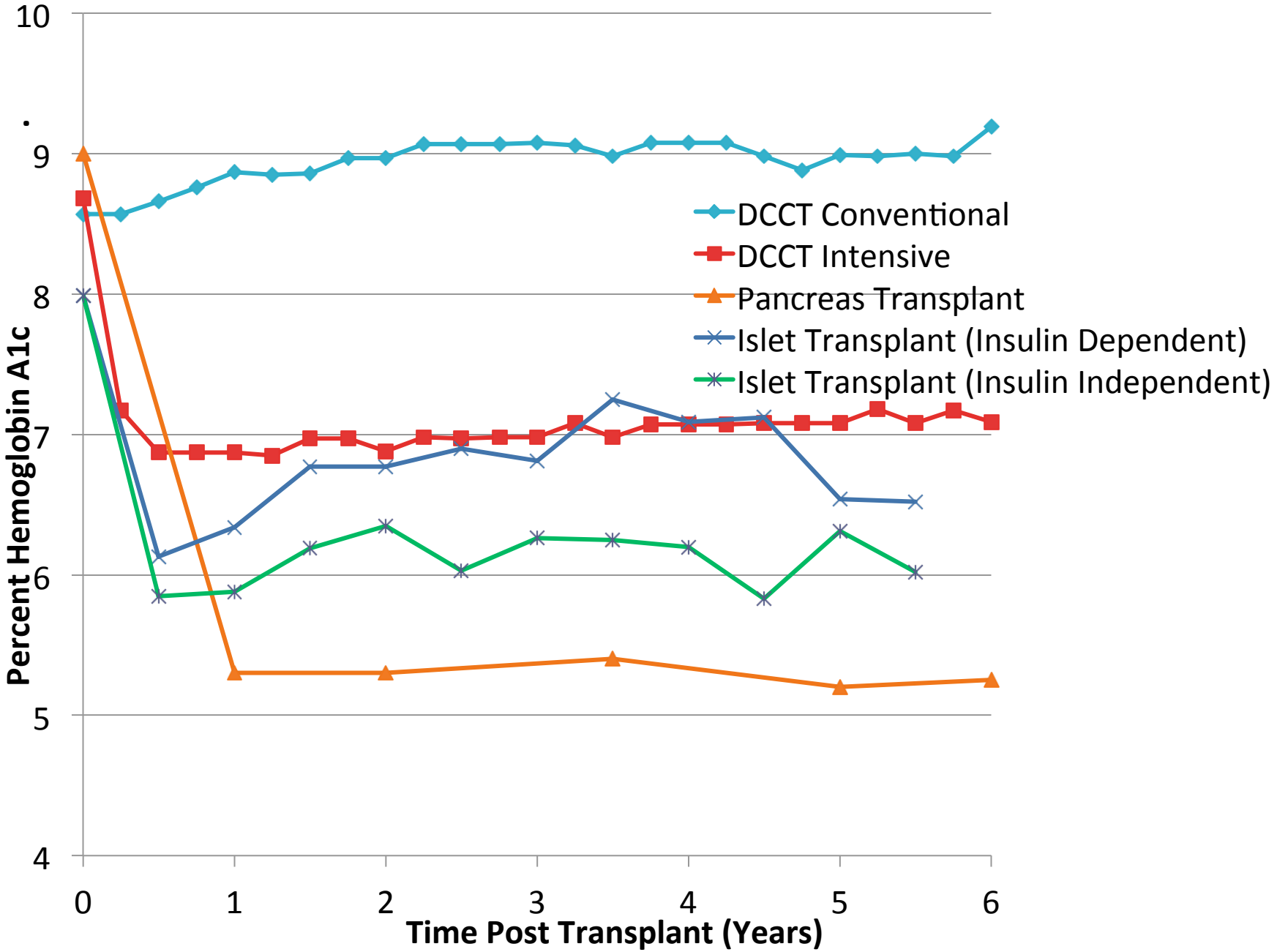
1980s: Pancreas transplants widespread

1980s: Large animal work with islets

1989: First serious human islet transplants - depressing results

2000: Edmonton Protocol


Recipient Liver
Donor Pancreas
Islet
digestion
β-cell
non-β-cell


10
9
8
7
6
5
4
Percent Hemoglobin A1c
0
1
2
3
4
5
6
Time Post Transplant (Years)
DCCT Conventional
DCCT Intensive
Pancreas Transplant
Islet Transplant (Insulin Dependent)
Islet Transplant (Insulin Independent)

Proof-of-Principle of Cell Transplantation is Established

- **Restores hypoglycemia awareness**
- **May have a protective effect on long-term diabetic complications**
- **Improved long-term health-related quality of life after islet transplantation**

Leitão et al. Diabetes Care 2008;31:2113-5.
Warnock et al. Transplantation 2008;86:1762-6.
Fiorina et al. Am J Transplant 2008;8:1990-7.
Tharavanij et al. Transplantation 2008;86:1161-7.

Where will we find enough beta cells?

Embryonic stem cells

Adult stem/progenitor cells

Beta cell expansion

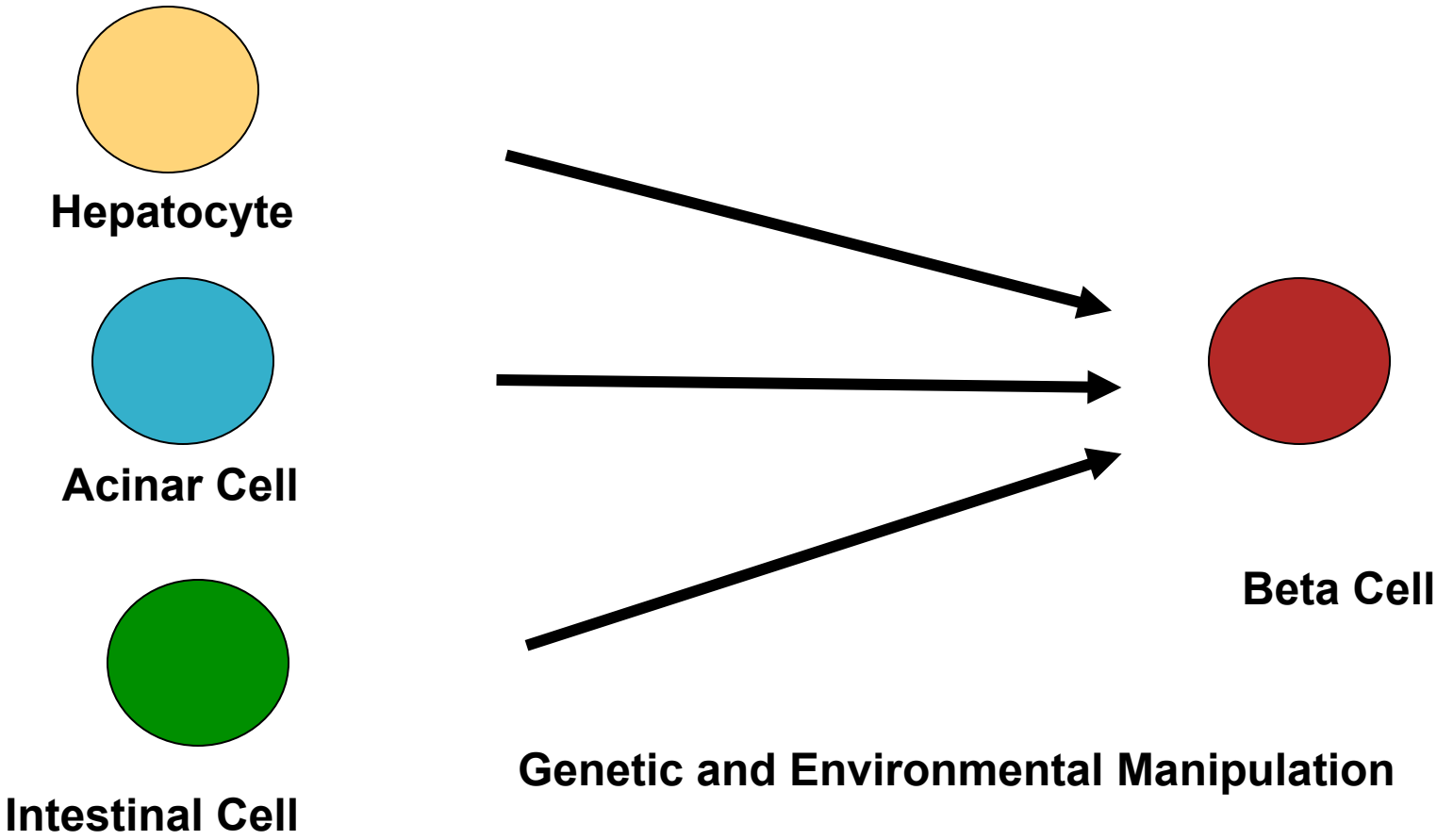
Genetic engineering

Transdifferentiation - liver, acinar, other

Regeneration

Xenotransplants

Transdifferentiation



Factors Contributing to Reprogramming Exocrine Pancreas

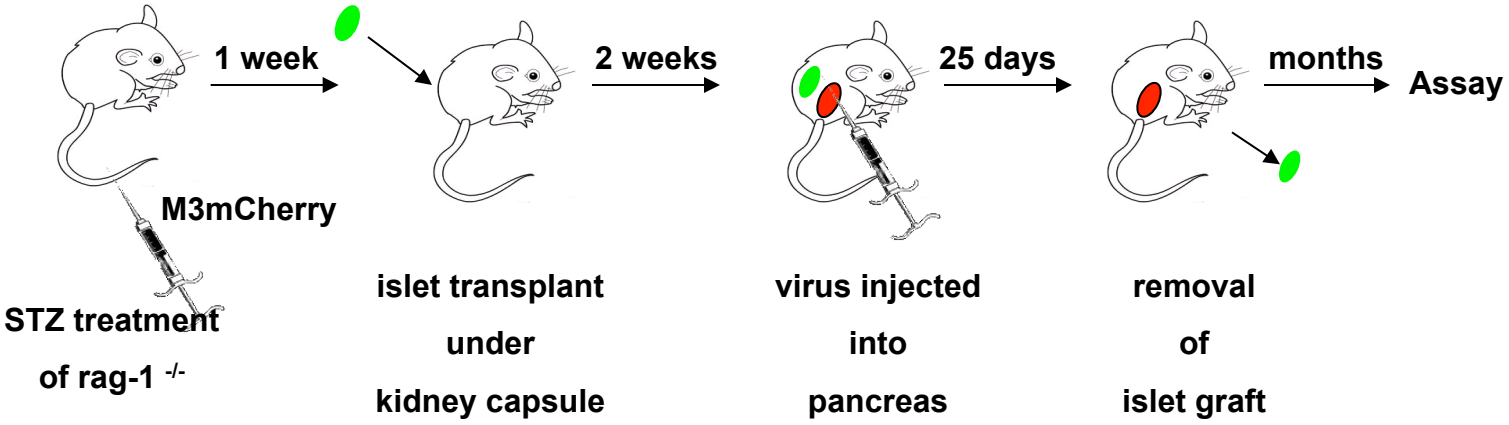
1. Islets and exocrine cells appear to originate from the same precursors during fetal development.

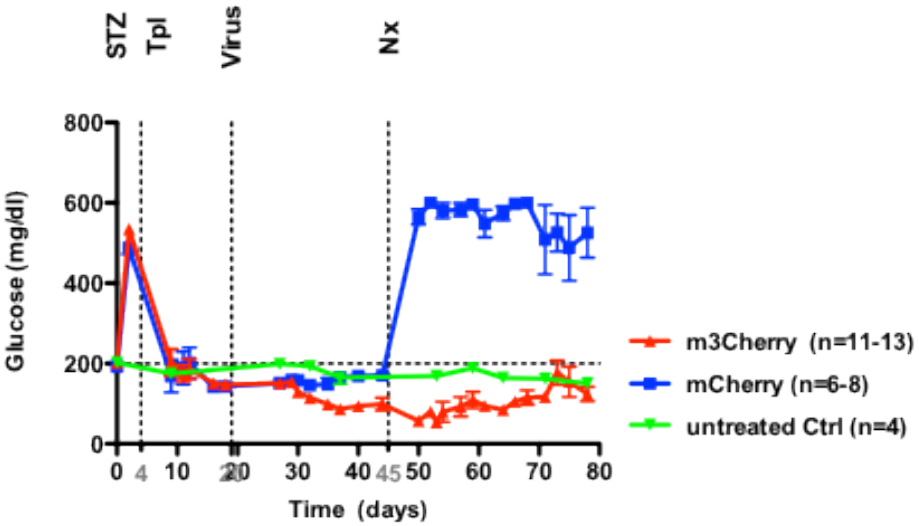
2. Pdx1 is needed for pancreas formation and to maintain normal beta cell differentiation.

3. Ngn3 is required for the development of all islet cell types.

4. MafA is required for the latest stage of beta cell maturation (MafB to MafA transition).

Transdifferentiation Acinar to Beta Cells





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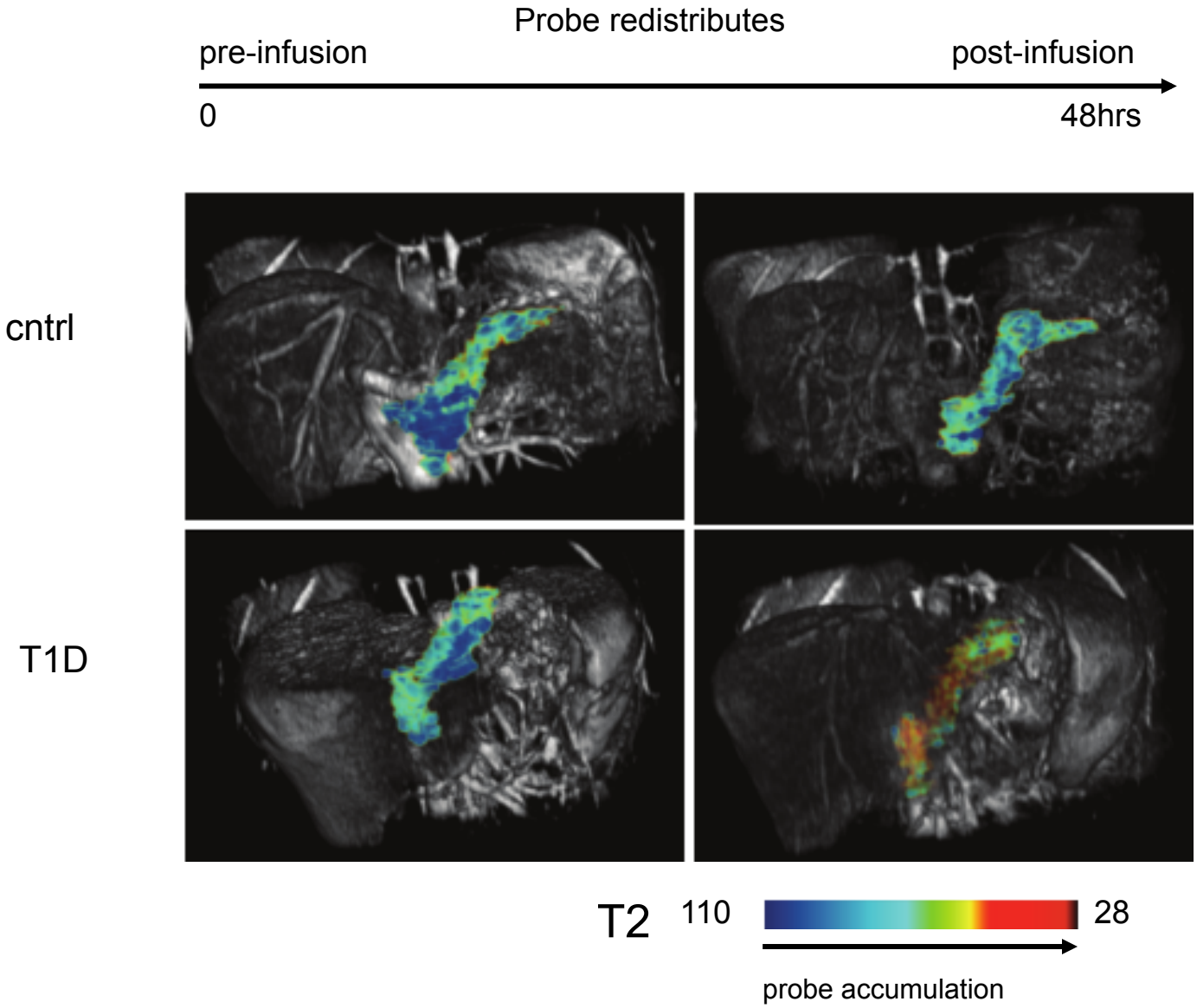
Courtesy Zhou, Weir, and Melton

Insulitis and Diabetes



Gaglia et al. J Clin Invest, 2011

Summary

- Diabetes is a major problem (morbidity, mortality, health care costs)
- The location and geography of the pancreas and the islets pose unique challenges
- Islet transplantation offers proof of principle of cell replacement therapy for diabetes
- Sources of islets
- Overcoming autoimmunity in type 1 diabetes