From Stem Cell to Beta Cells?

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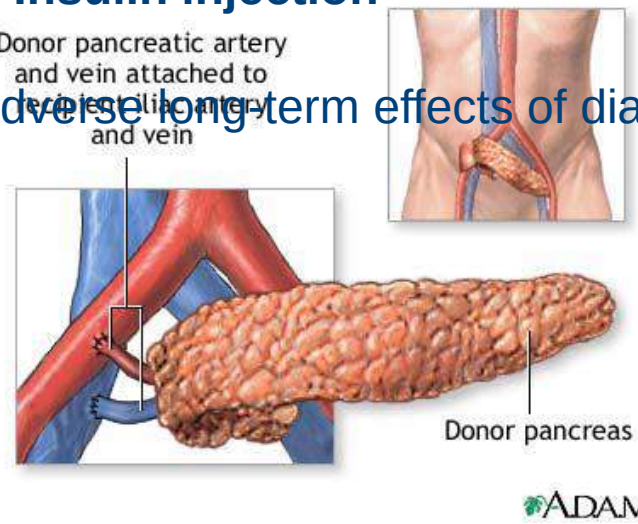
Epidemiology and Current therapy

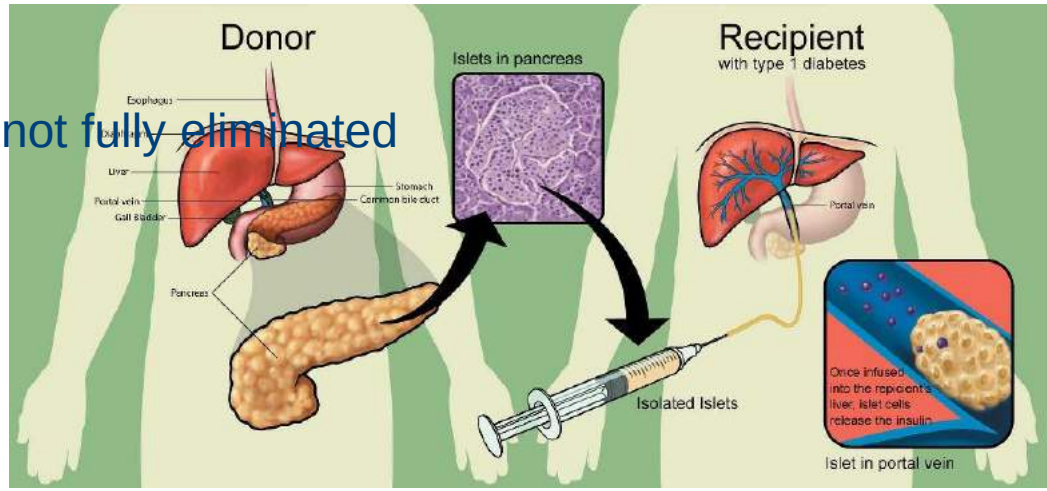
- Diabetes or diabetes mellitus is a clinical syndrome characterised by a chronic state of elevated levels of glucose in the blood (hyperglycaemia).
- There are currently 285 million diabetes patients worldwide and 55 million in Europe.

1) Insulin injection

2) Pancreas transplantation



3) Islet transplantation



Adverse long-term effects of diabetes not fully eliminated

Limitations:

1) Shortage of donors.
2) Immunosuppression.
3) Poor long-term graft survival.
4) Poor yield of islet material.

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Adapted from Harlan DM (2004) PLoS Medicine.

Can stem cells be used to treat diabetes?

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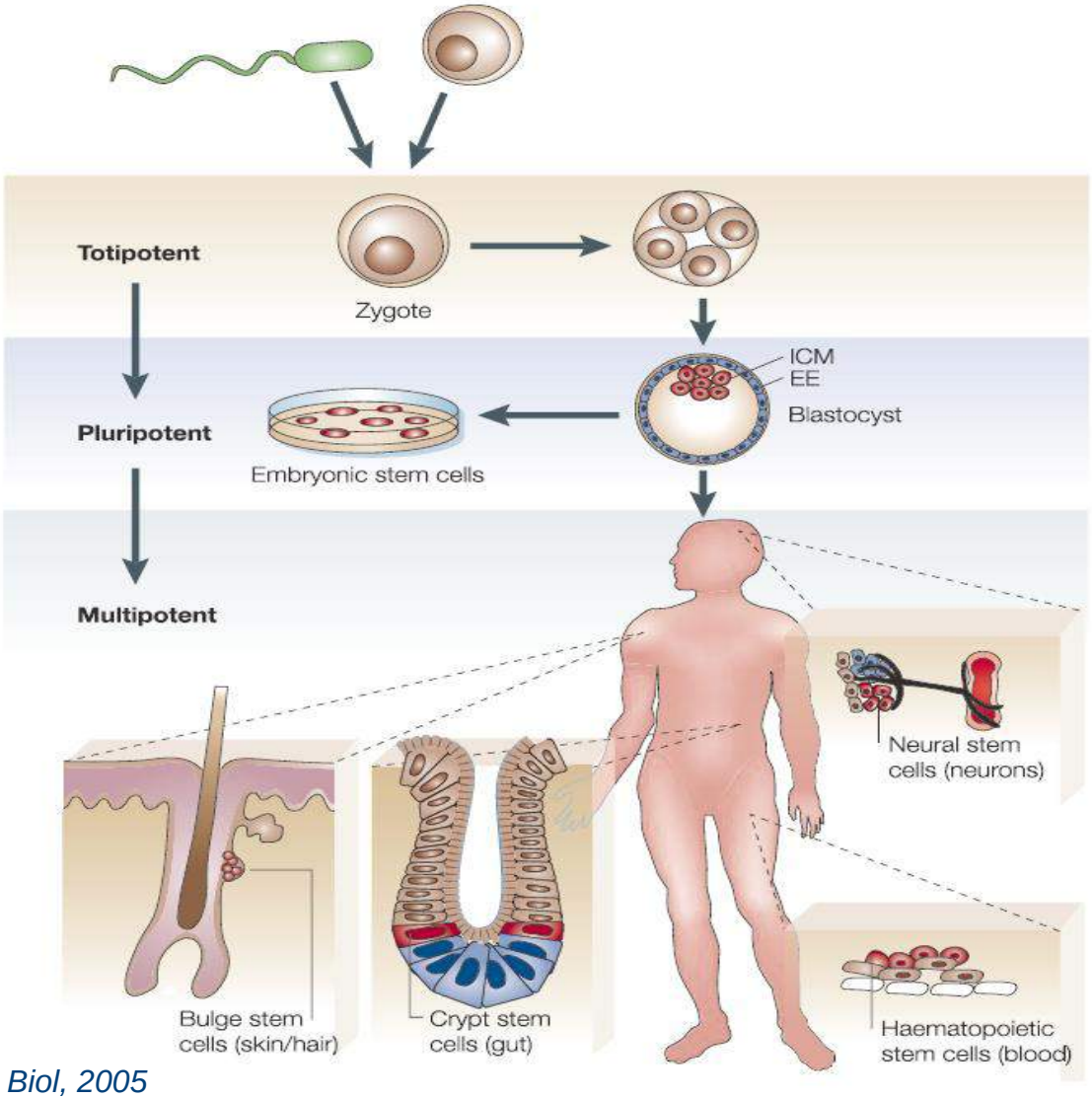
Stem cell: definition

- Stem cells self-renew
- Single stem cell differentiates into multiple, functional cell types
- Stem cells functionally reconstitute a given tissue *in vivo*.

Different types of stem cells



→ β-cell SC??

Eckfeldt, Nat Rev | Mol Cell Biol, 2005

Isolation of Embryonic Stem Cells

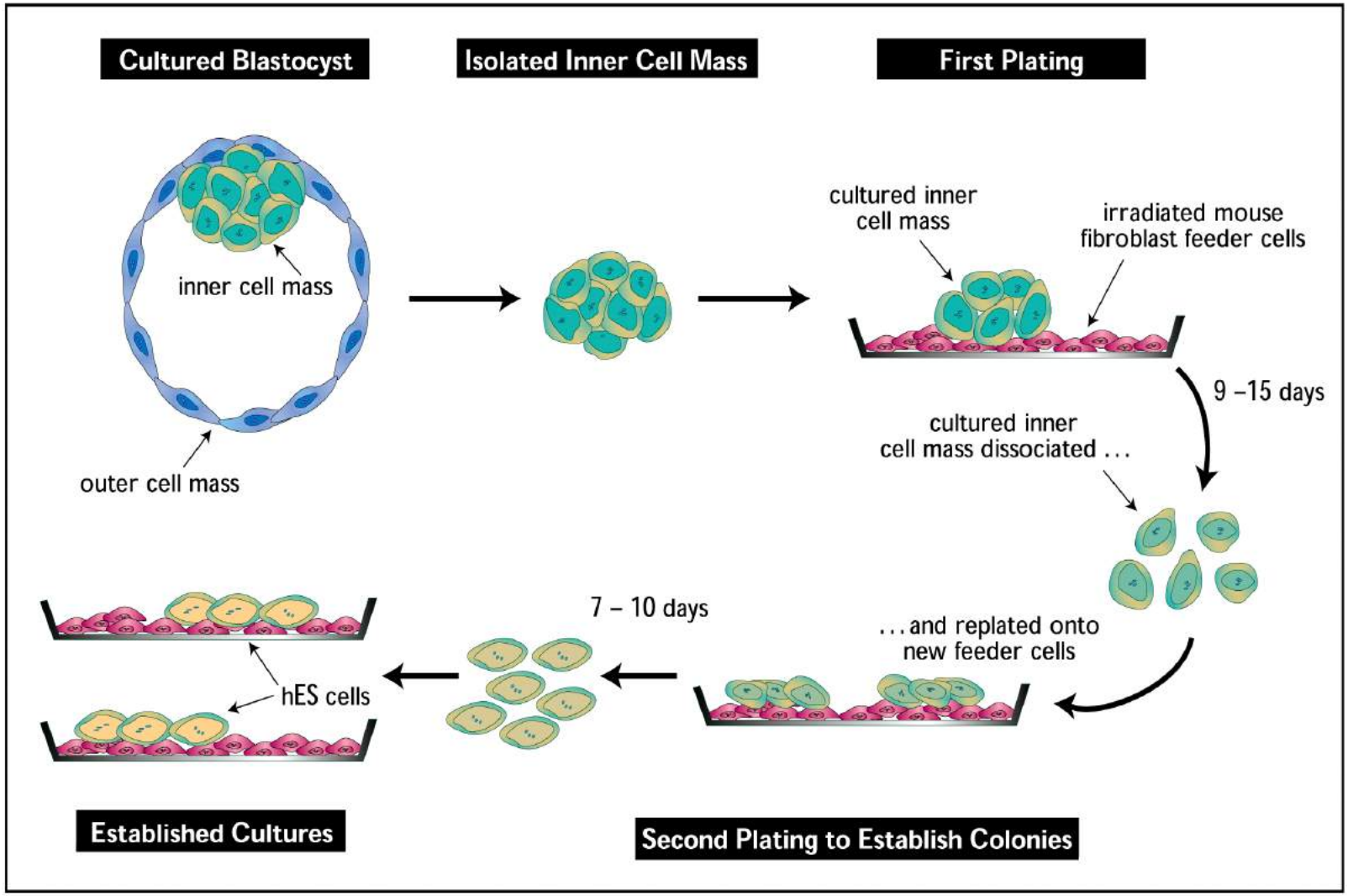


Figure 1: Derivation of hES Cells

Pluripotency of embryonic stem cells

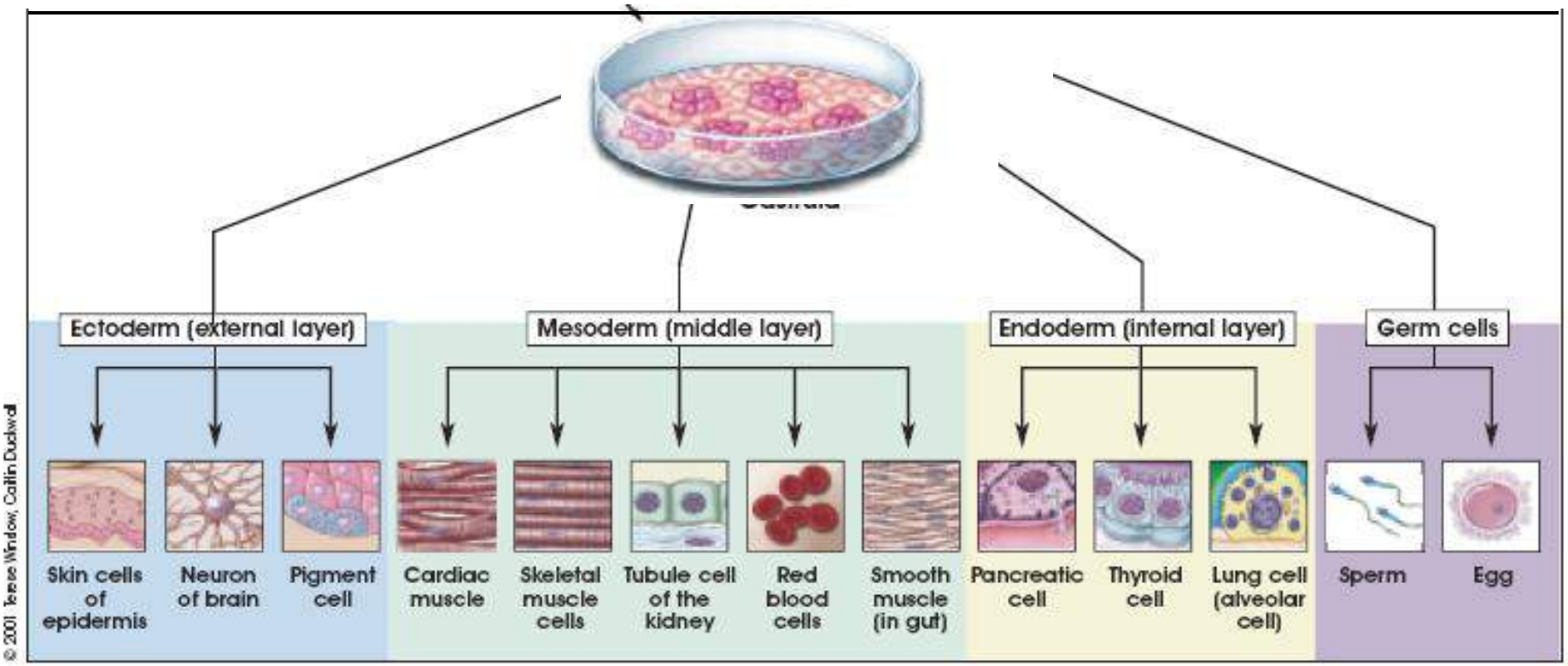


Figure 1.1. Differentiation of Human Tissues.

ADAPTED FROM NIH STEM CELL WEBSITE

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Enthusiasm surrounding embryonic stem cells

- **Does not age and can differentiate to all cell types**
- **Thus: embryonic stem cells can heal all diseases**
- **And, could provide all cell types needed to generate a tissue**
- **CAVEAT: but we can not yet differentiate the 220 cell types!**

But, scientific and ethical **questions** surrounding ES cells

- **Teratomas (non malignant tumor)**
- **Allogeneic (from other person)**
- **Need to destroy early embryos (rest embryos from IVF)**

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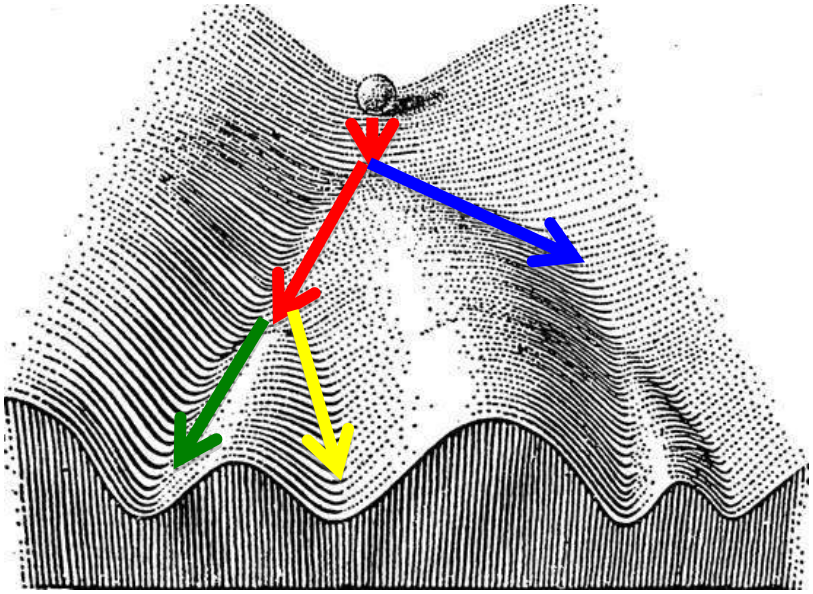
Differentiation one way street!

Waddingtons' epigenetic landscape (1957)

Development occurs through discrete changes in stem/progenitor cells



Irreversible cellular fate

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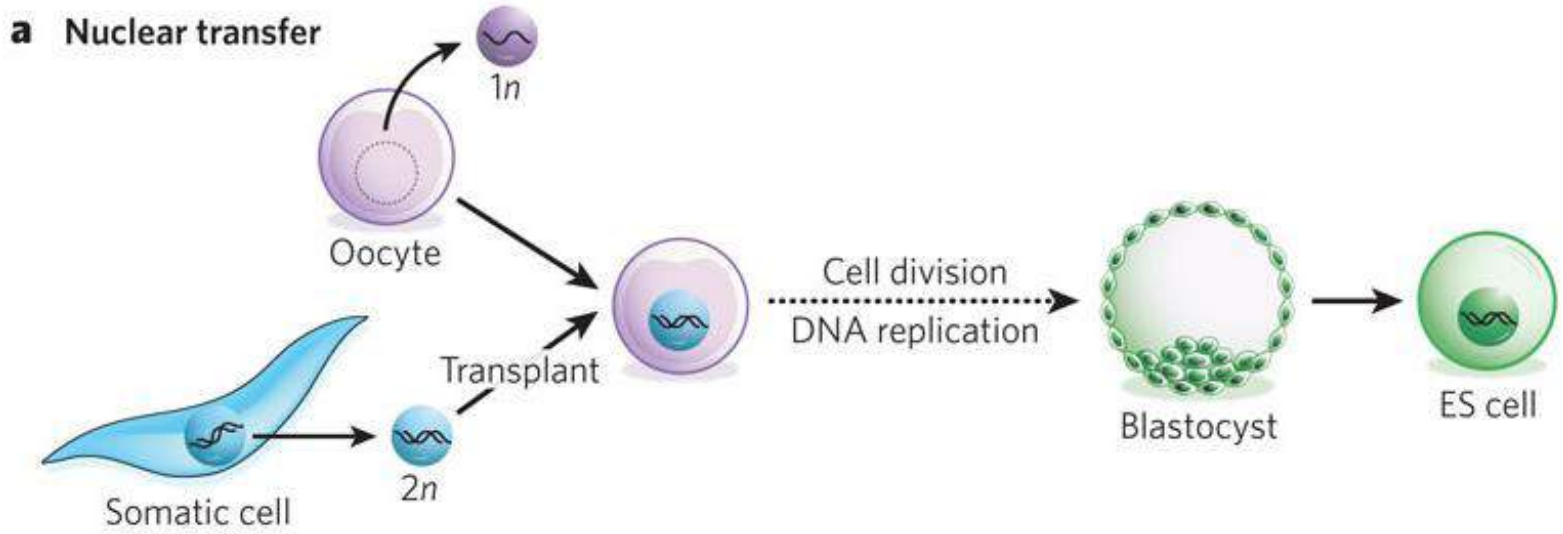
However, …



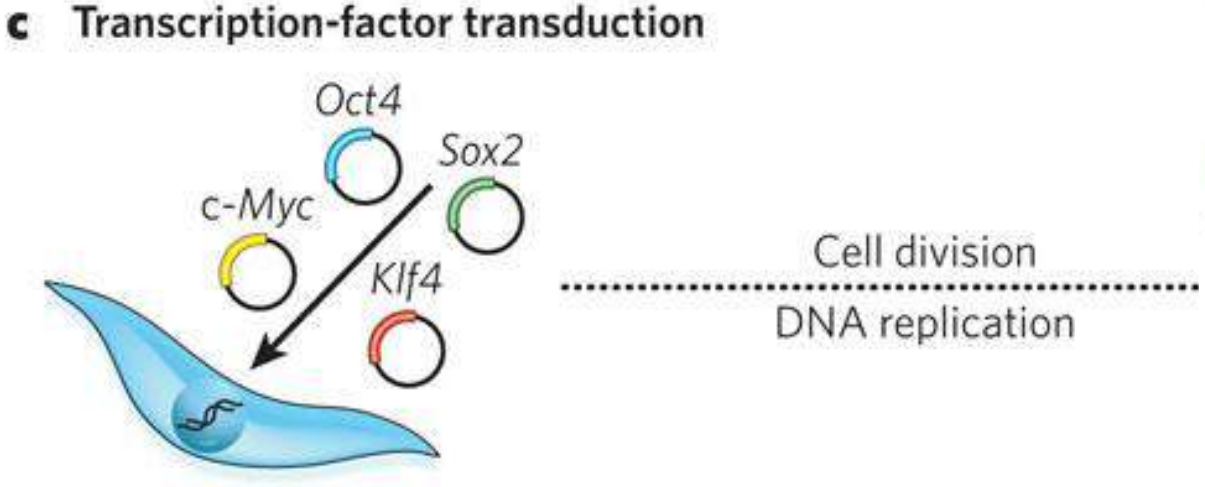
Gurdon *et al.* (Nature, 1957)

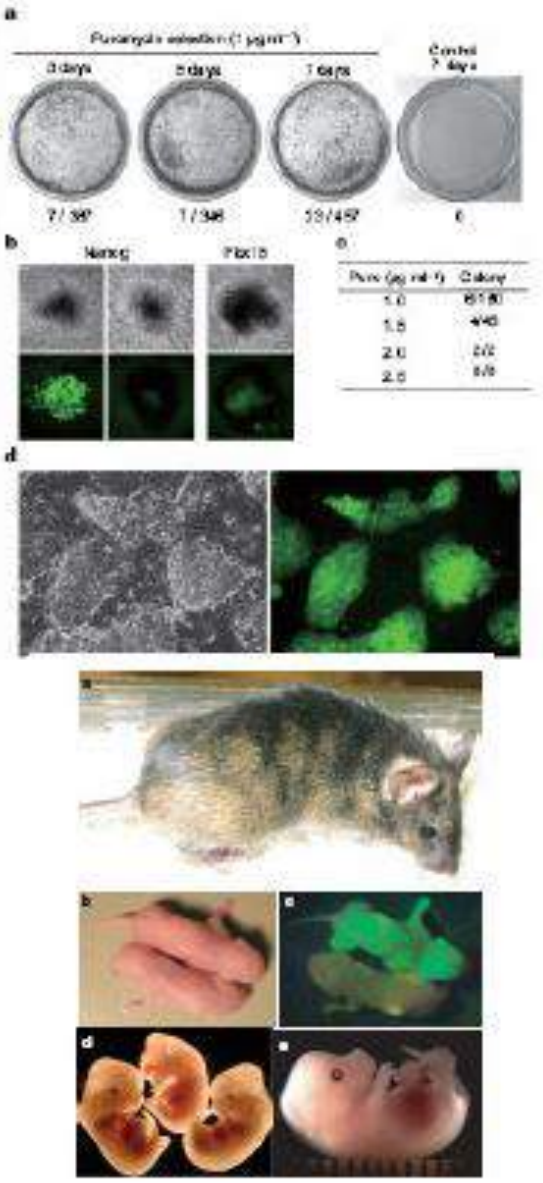
Wilmut *et al.* (Nature, 1997)

1957

1997

Is creation of greater potency possible?





Takahashi & Yamanaka (Cell 2006)
Takahashi *et al.* (Cell 2007)
Yu *et al.* (Nature 2007)

2006-2007

AFP/Getty Images

Gurdon, Yamanaka

The Nobel Prize in Physiology or Medicine

Affiliations: John B. Gurdon, born in 1933, is at the Gurdon Institute, part of Cambridge University. Shinya Yamanaka, born in 1962, is a professor at Kyoto University and is affiliated with the Gladstone Institutes in San Francisco.

In Their Research: Mr. Gurdon discovered in 1962 that the specialization of cells is reversible. More than 40 years later, Mr. Yamanaka discovered how intact mature cells in mice could be reprogrammed to become immature stem cells.

In the Real World: Without this discovery, known as cellular reprogramming, Dolly the sheep and later cloning experiments would not have been possible. It also allows scientists to create human embryonic stem cells without destroying human embryos, sidestepping an approach long been fraught with ethical controversies.

> ***My goal, all my life, is to bring this stem cell technology to the bedside, to patients, to clinics.***
>
> — Shinya Yamanaka

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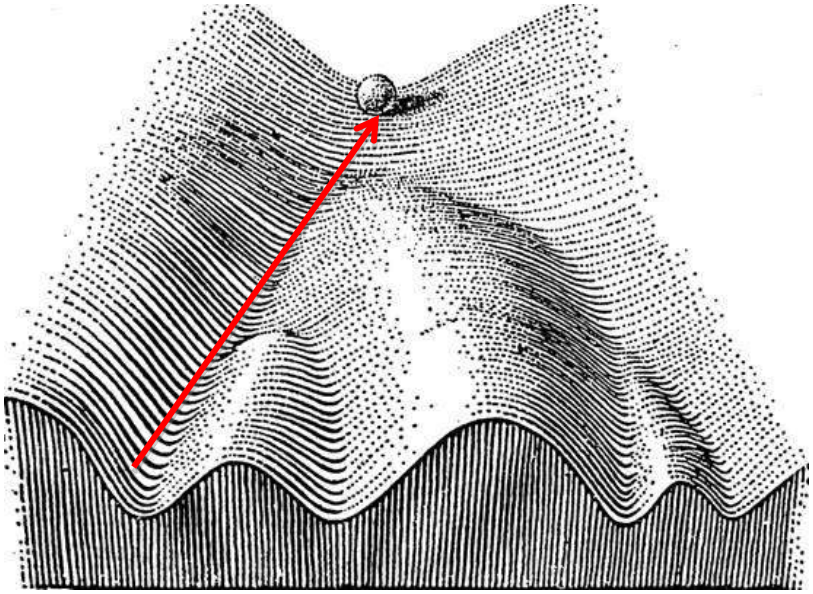
Scientific dogmas are there to be broken!

reversible cellular fate



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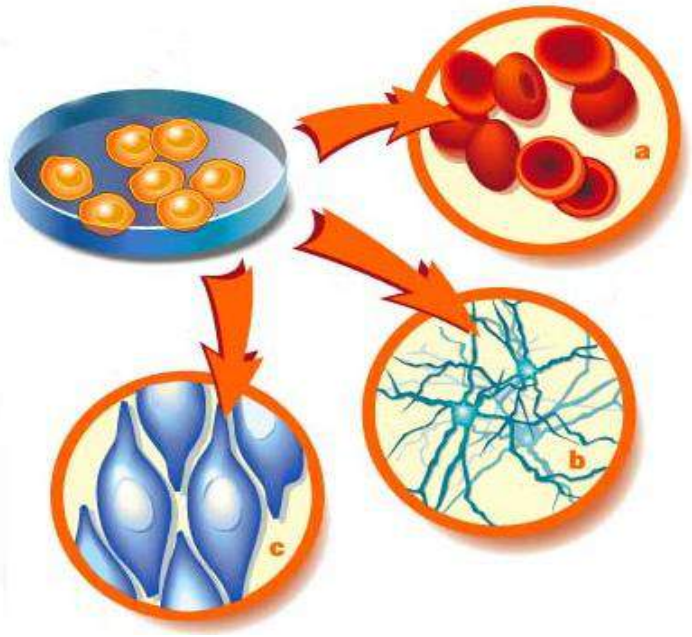
Waddington (1957)

Medical applications of reprogramming Type-1 Diabetes

- Insights in human development
- Drug toxicity
- Study human diseases
- Drug discovery



- Cell therapy
- Tissue engineering

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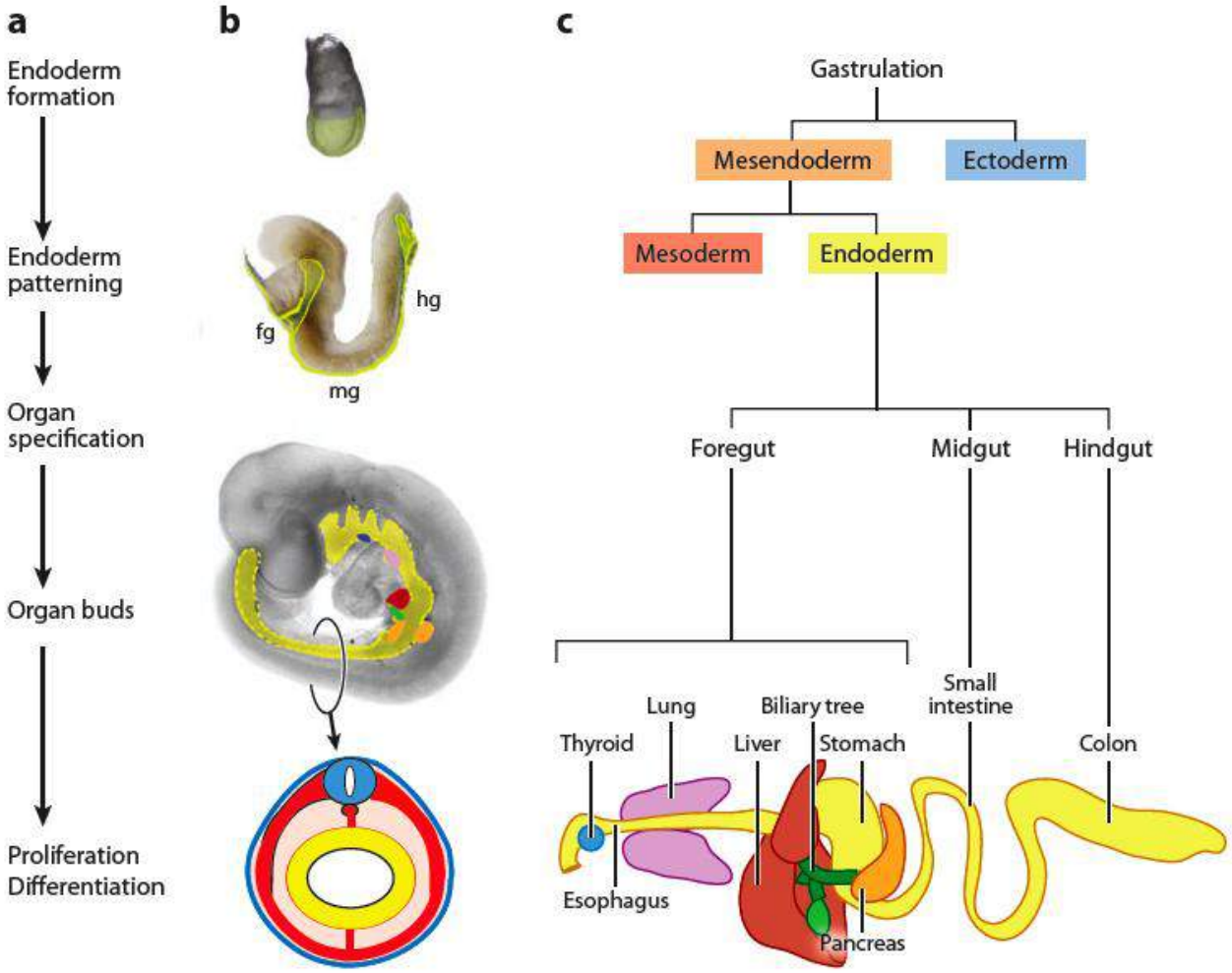
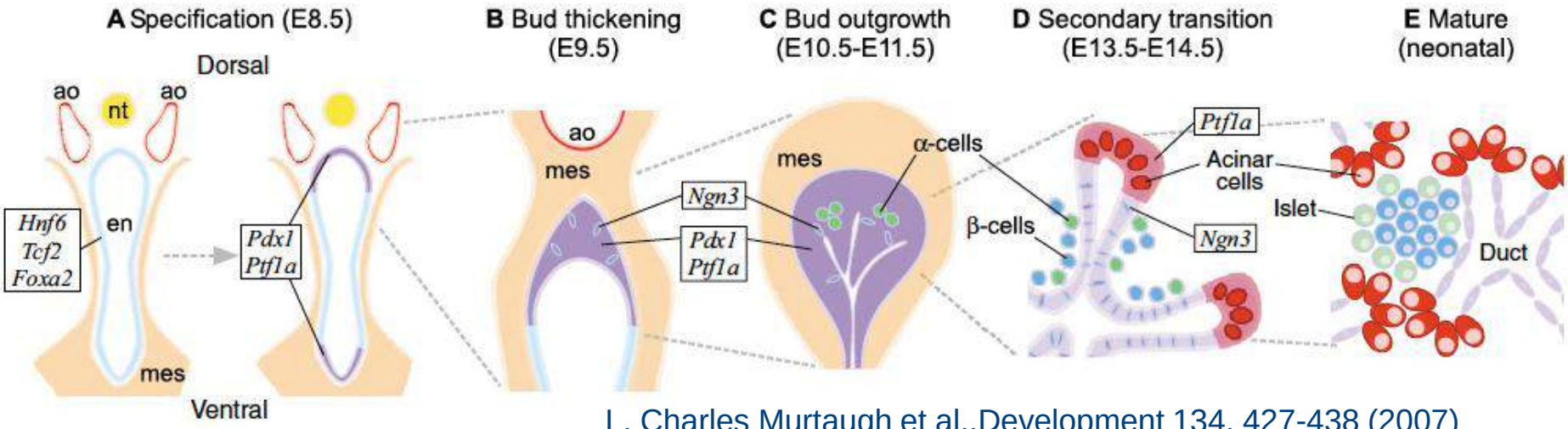
Endoderm organ formation from gastrulating embryo



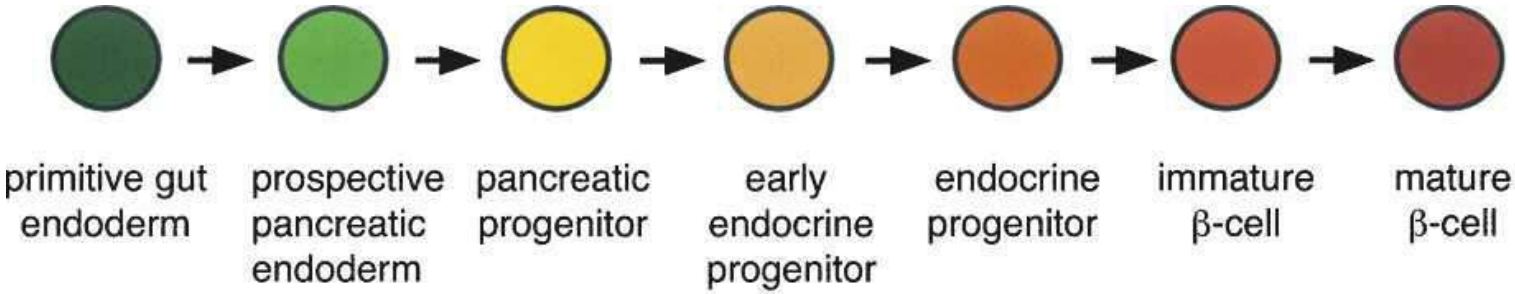
Aaron M. Zorn and James M.Wells, Annu. Rev. Cell Dev. Biol. 2009.25.

Development of pancreatic islet and beta cells



L. Charles Murtaugh et al.,Development 134, 427-438 (2007)

Beta cell formation from endodermal derivatives



Doris A. Stoffers et al., Genes and Development (2008)

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Science

AAAS

Differentiation of Embryonic Stem Cells to Insulin-Secreting Structures Similar to Pancreatic Islets

Nadya Lumelsky, *et al.*

Science **292**, 1389 (2001);

DOI: 10.1126/science.1058866

Diabetologia (2004) 47:1442–1451

In vitro directed differentiation of mouse embryonic stem cells into insulin-producing cells

T. León-Quinto[1] · J. Jones[1] · A. Skoudy[2] · M. Burcin[3] · B. Soria[1,4]

NATURE BIOTECHNOLOGY Received 31 August; accepted 3 October; published online 19 October 2006; doi: 10.1038/nbt1259

Production of pancreatic hormone–expressing endocrine cells from human embryonic stem cells

Kevin A D'Amour, Anne G Bang, Susan Eliazer, Olivia G Kelly, Alan D Agulnick, Nora G Smart, Mark A Moorman, Evert Kroon, Melissa K Carpenter & Emmanuel E Baetge

Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells *in vivo*

Evert Kroon, Laura A Martinson, Kuniko Kadoya, Anne G Bang, Olivia G Kelly, Susan Eliazer, Holly Young, Mike Richardson, Nora G Smart, Justine Cunningham, Alan D Agulnick, Kevin A D'Amour, Melissa K Carpenter, Emmanuel E Baetge

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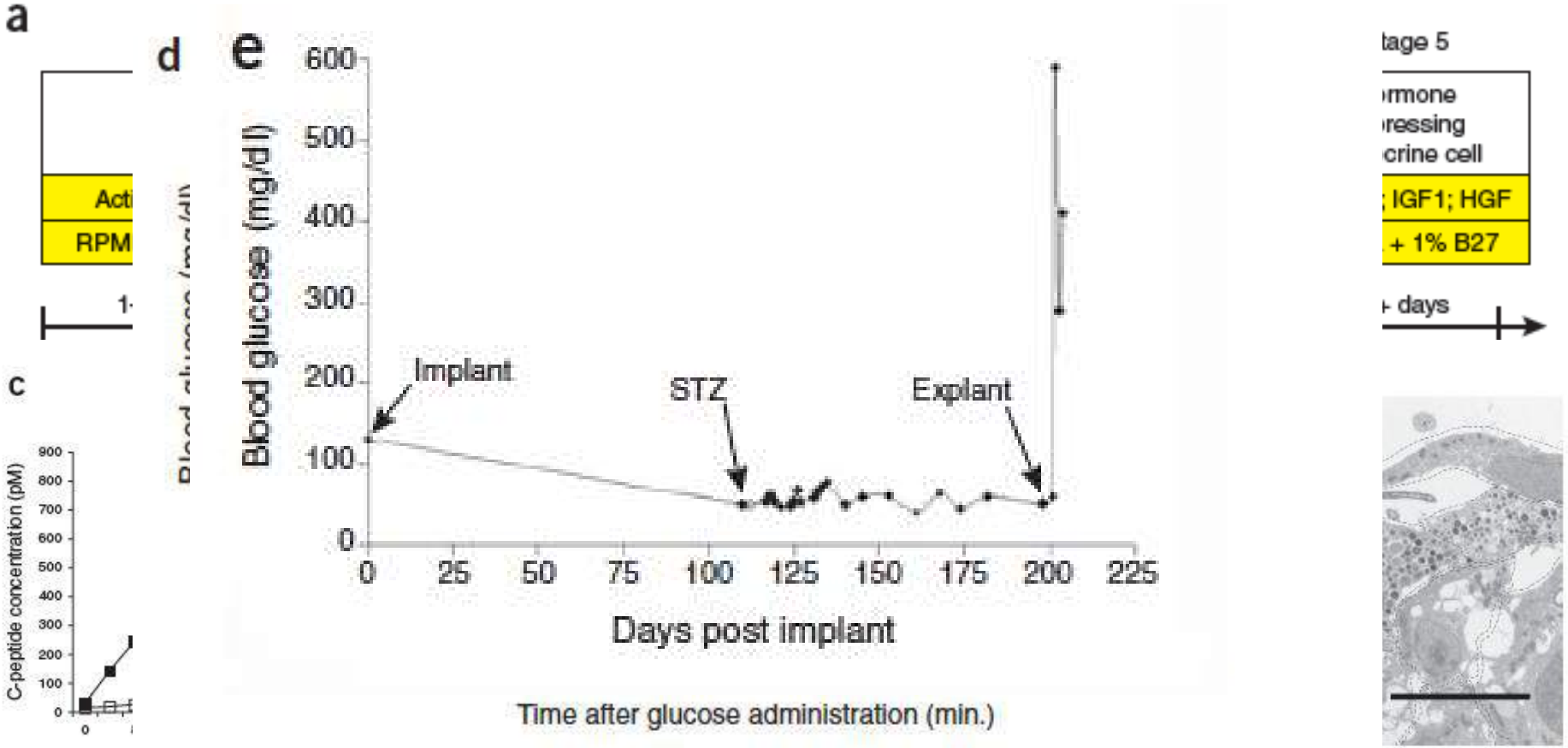
hESC can differentiate into pancreatic endoderm, and then beta cells in vivo



D'Amour et al
Kroon et al

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Remaining Challenges

- Generation fully mature cells, prior to transplantation

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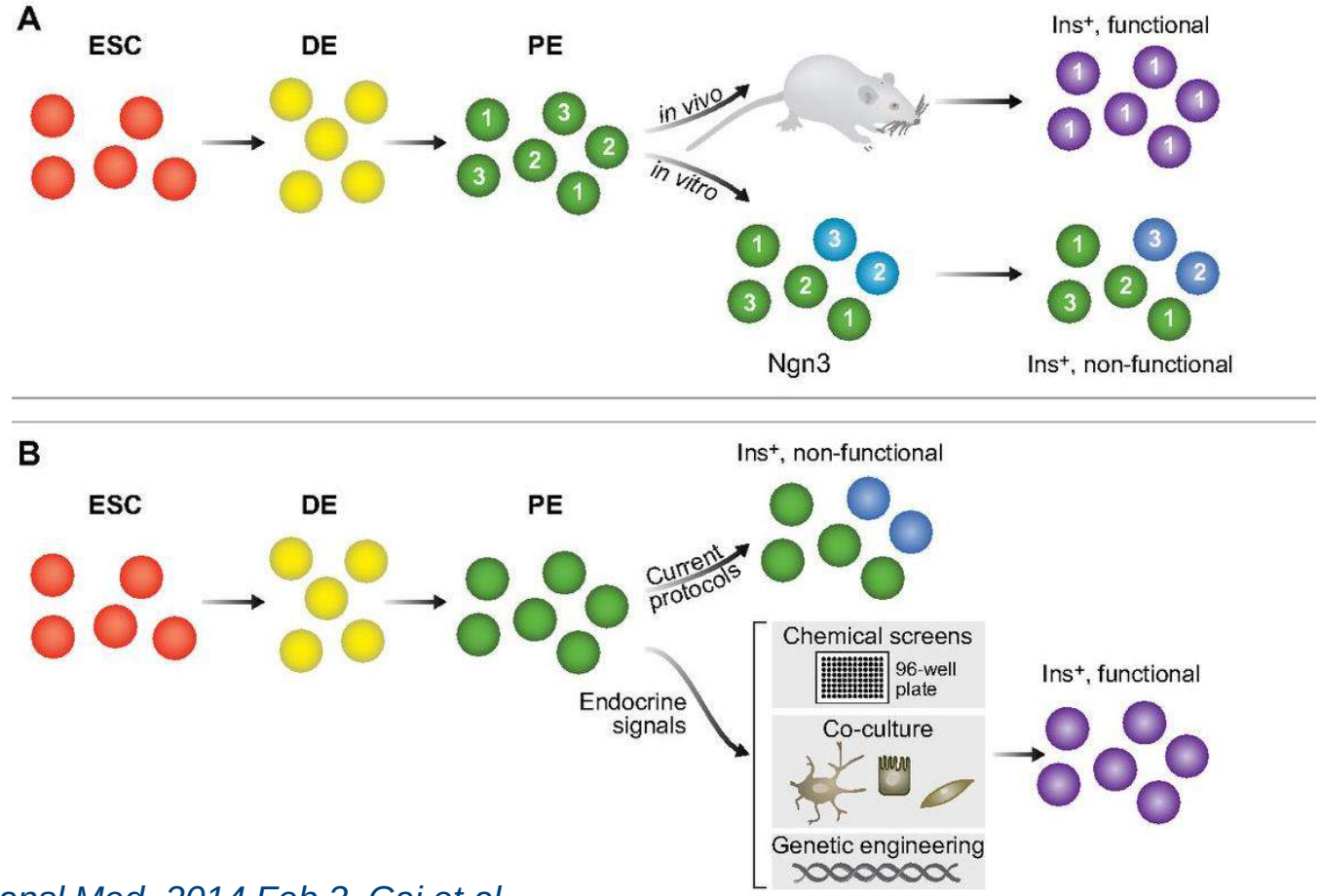
Use lineage tracing, chemical and genetic screens to improve maturation



Stem Cells Transl Med. 2014 Feb 3. Cai et al

Development 140, 2472-2483, 2013.

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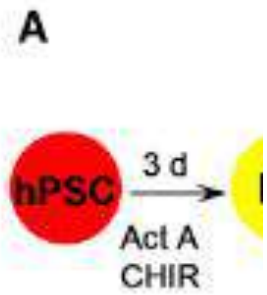
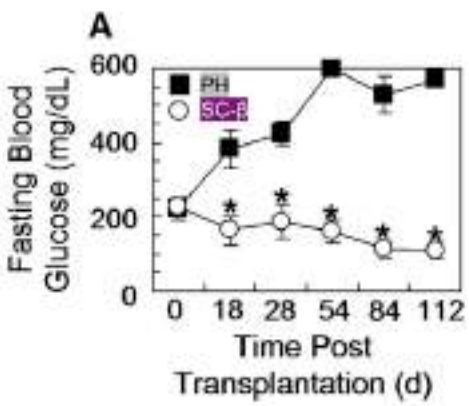
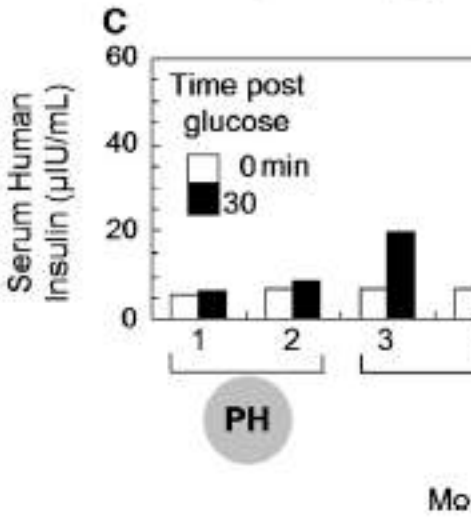
Cell

Resou







Alk5i

Control Differentiation

PH

New Differentiation

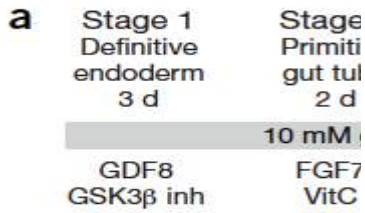
SC-β

5i

RL Supplemented

t al., 2014, Cell

nature biotechnology



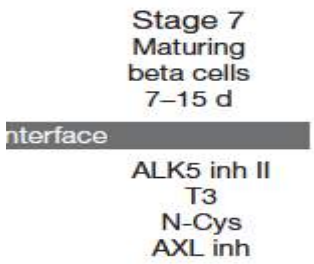


Figure 6. Transplanted SC-β Cells Rapidly Ameliorate Hyperglycemia in Diabetic Mice

Timothy j Kieffer et al., 2014, Nature Biotechnology

BetaLogics Venture, Janssen R&D LLC, Raritan, New Jersey, USA.

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Remaining Challenges

- Generation fully mature cells, prior to transplantation
- Create all xenogeneic free system (all defined molecules)

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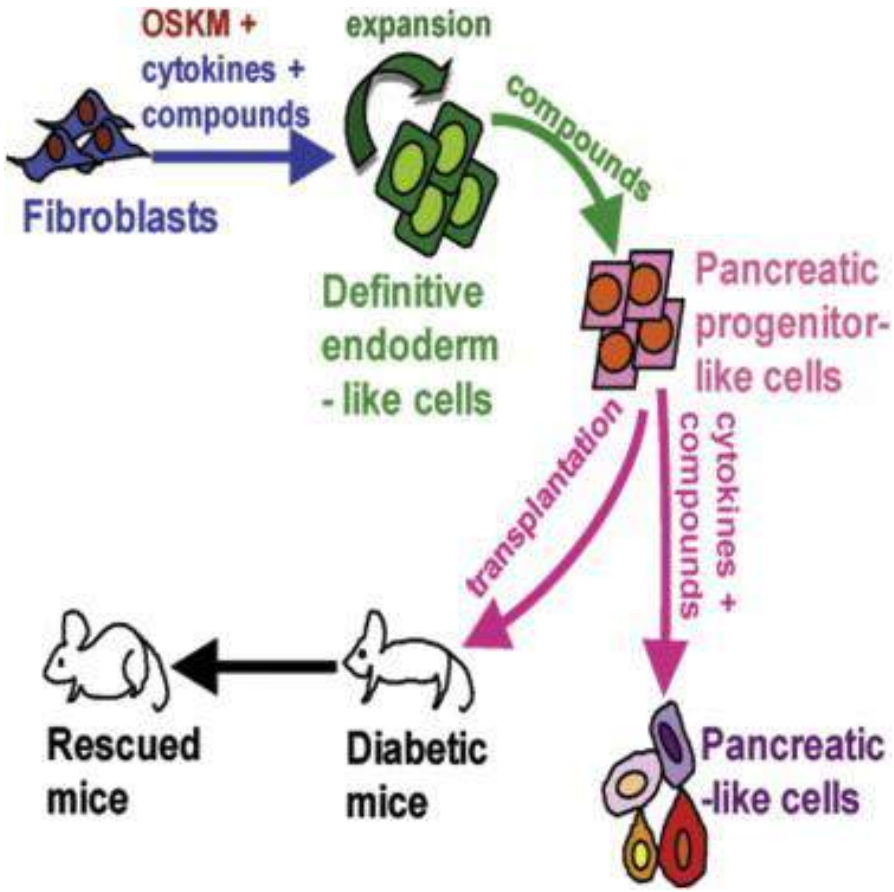
Small Molecules Facilitate the Reprogramming of Mouse Fibroblasts into Pancreatic Lineages



Cell Stem Cell 14, 228–236, 2014

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Remaining Challenges

- Generation fully mature cells, prior to transplantation, will likely require very prolonged culture ± epigenetic modifications
- Create all xenogeneic free system (all defined molecules)
- Remove all non-differentiated PSC to prevent teratomas and incorrect differentiated cells
  - Create fully mature cells
  - Encapsulate
  - Derive from non-pluripotent cell?

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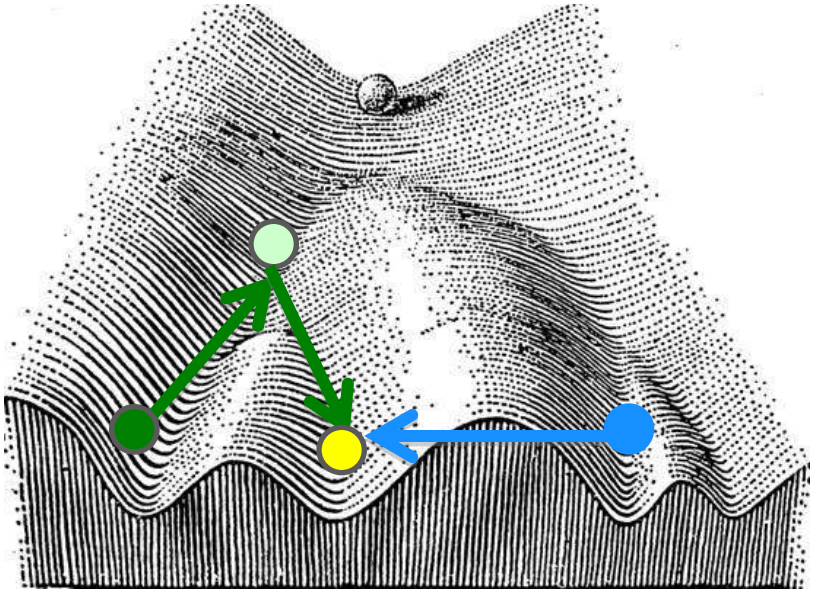
Scientific dogmas are there to be broken!

changeable cellular fate



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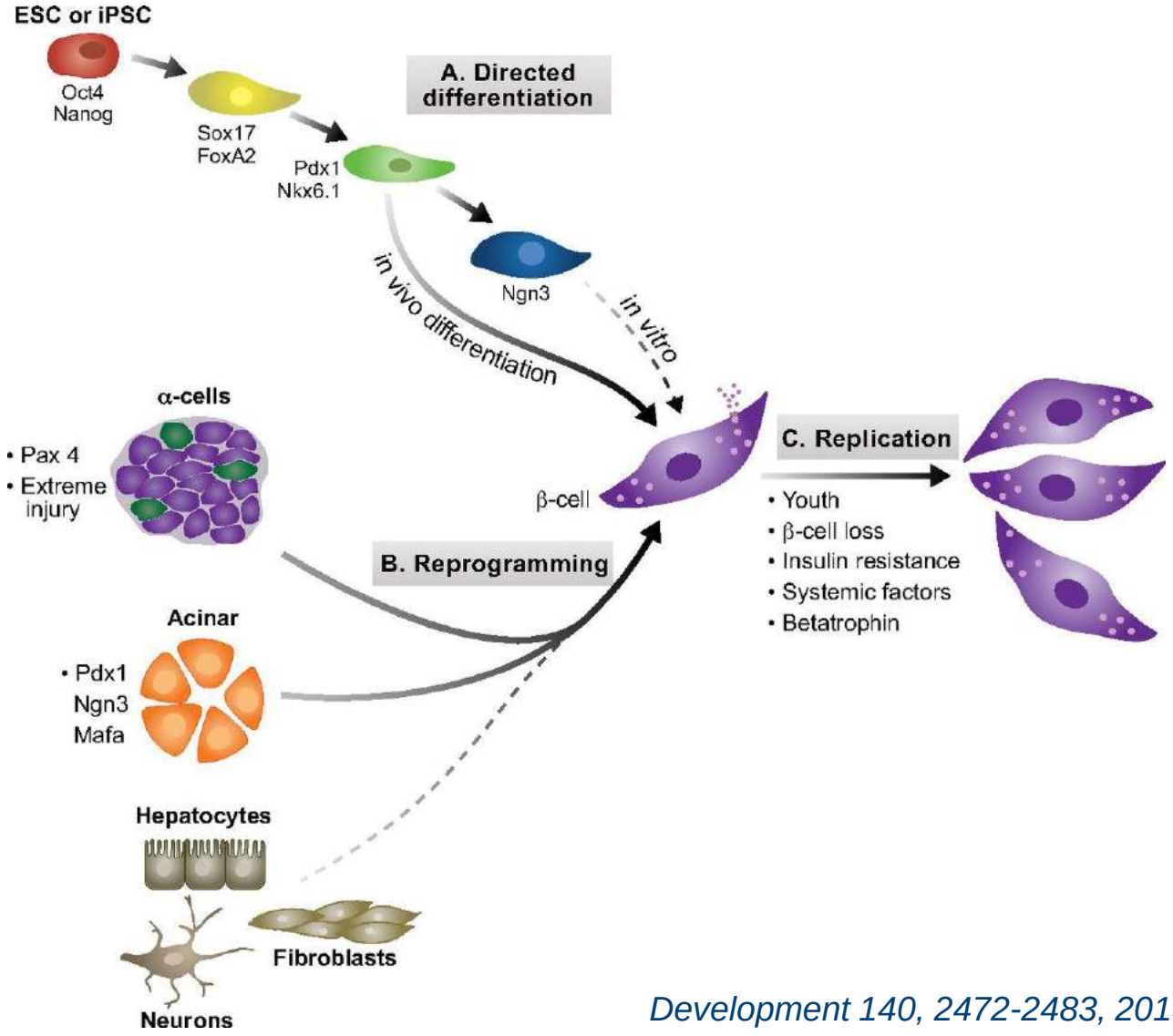
Transdifferentiation to generate β-cells?



Development 140, 2472-2483, 2013.

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Remaining Challenges

- Generation fully mature cells, prior to transplantation, will likely require very prolonged culture ± epigenetic modifications
- Create all xenogeneic free system (all defined molecules)
- Remove all non-differentiated PSC to prevent teratomas and incorrect differentiated cells
- Protect from immune system, in setting of allogeneic transplantation; but also for autologous iPSC derived cells
    - encapusulation?
    - immunomodulation as in islet transplantation?

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B-cell therapy from iPSC could possibly be tested clinically in the coming 5 years!

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Who did the work