(Stem) cells to treat type 1 diabetes

Prof. Robert Hilbrands
Diabetologist - Nephrologist
Diabeteskliniek UZBrussel

Universitair Ziekenhuis Brussel

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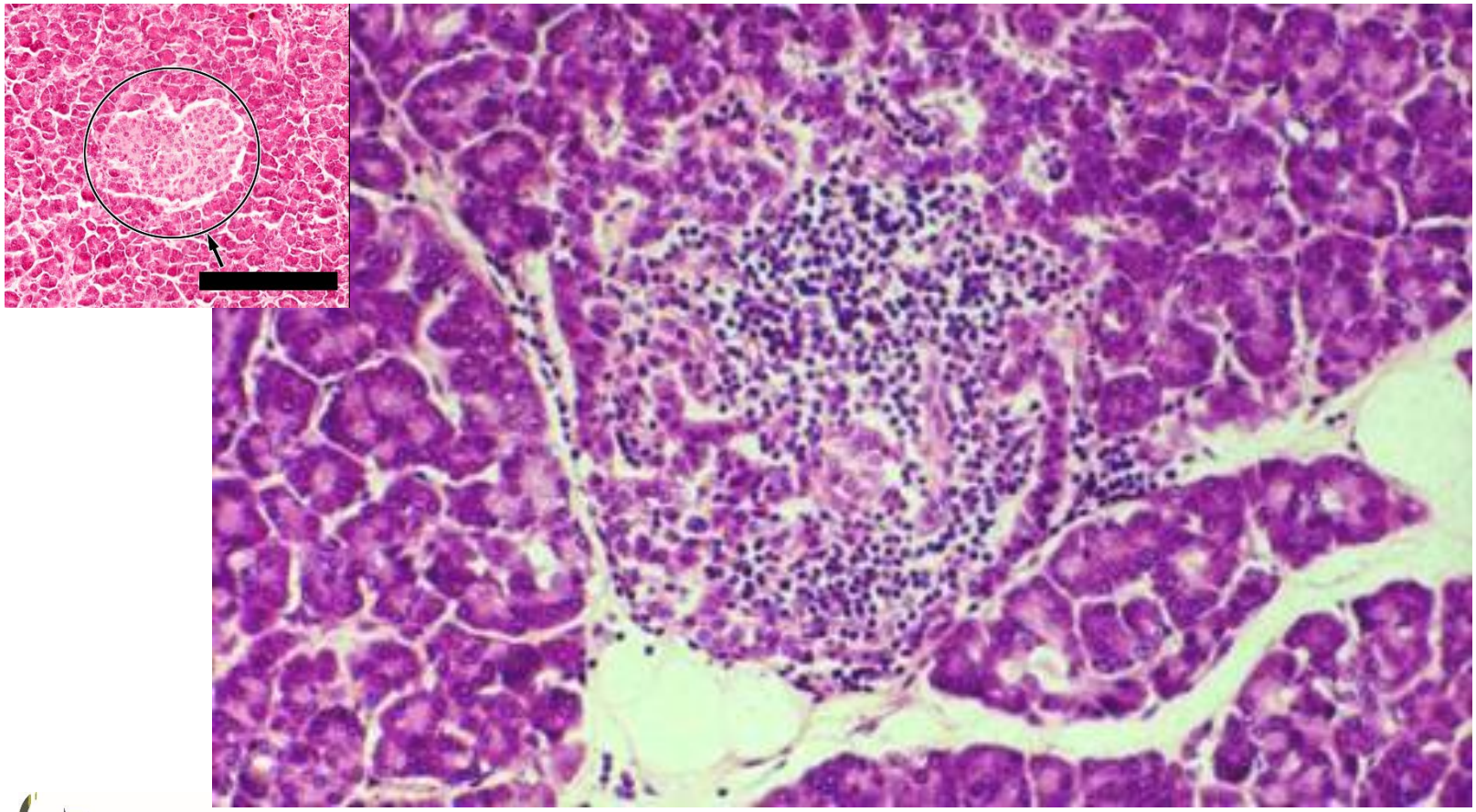
Type 1 diabetes

Insulitis = inflammatory infiltrate involving Ilsets of Langerhans



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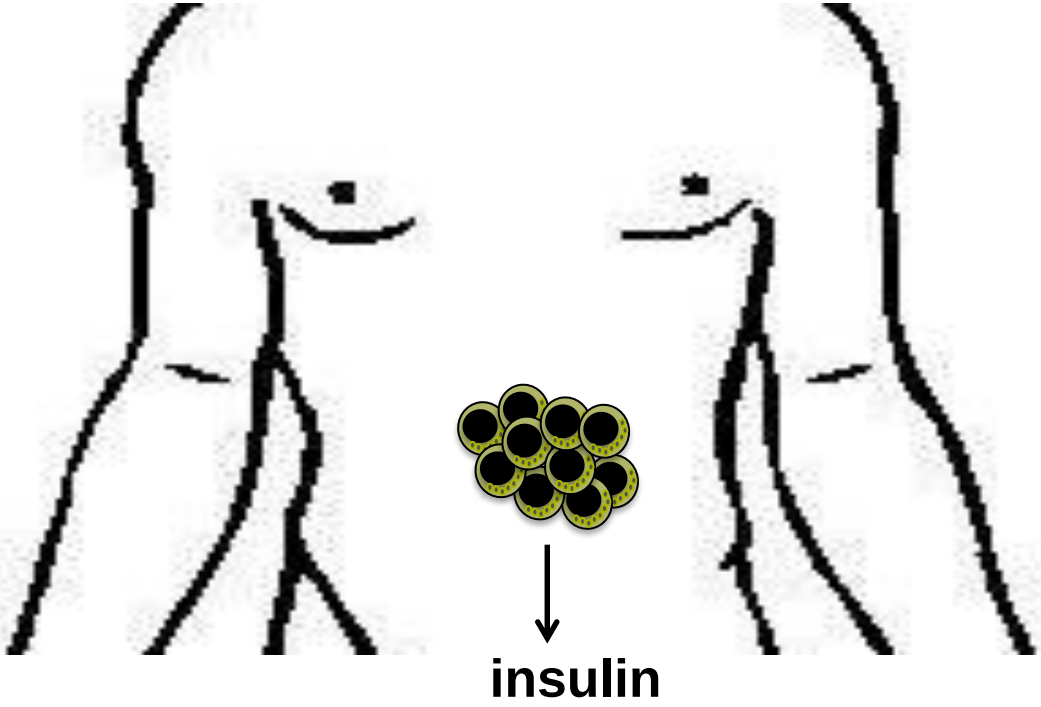
*Willy Gepts, Diabetes 1965

Introduction



Introduction

Type 1 Diabetes

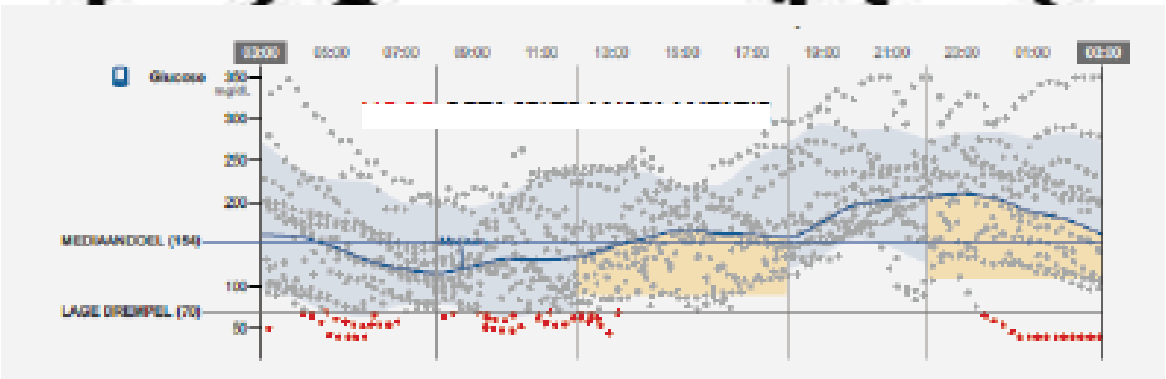
Auto-immunity

Insulin

↓

Glycaemic instability

Hypoglycaemia



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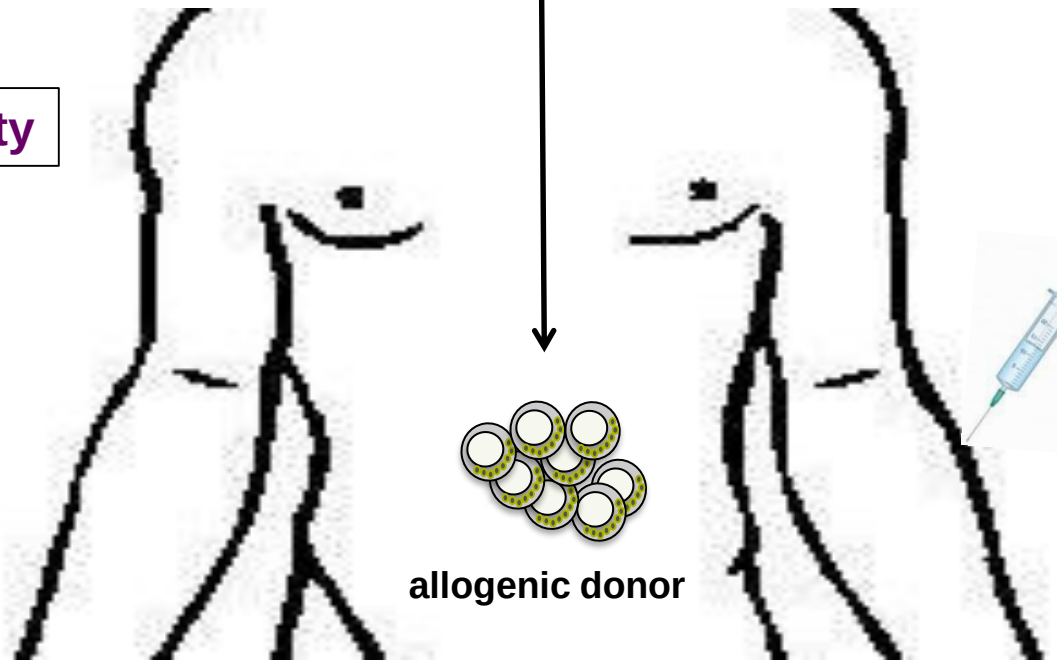
Introduction

Beta Cell Replacement Therapy

Auto-immunity



Insulin

Glycaemic instability

Hypoglycaemia

Potentially curative treatment

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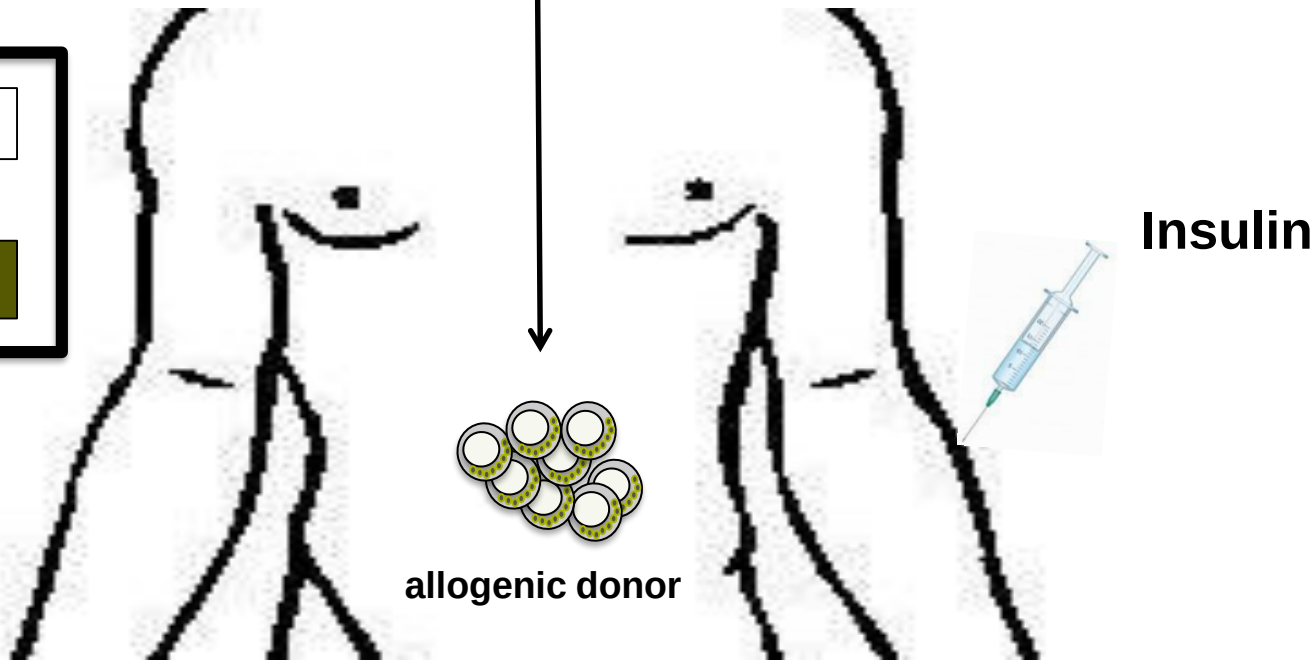
Introduction

Beta Cell Replacement Therapy

Auto-immunity

Allo-immunity



Insulin

Continuous Immunosuppression Required

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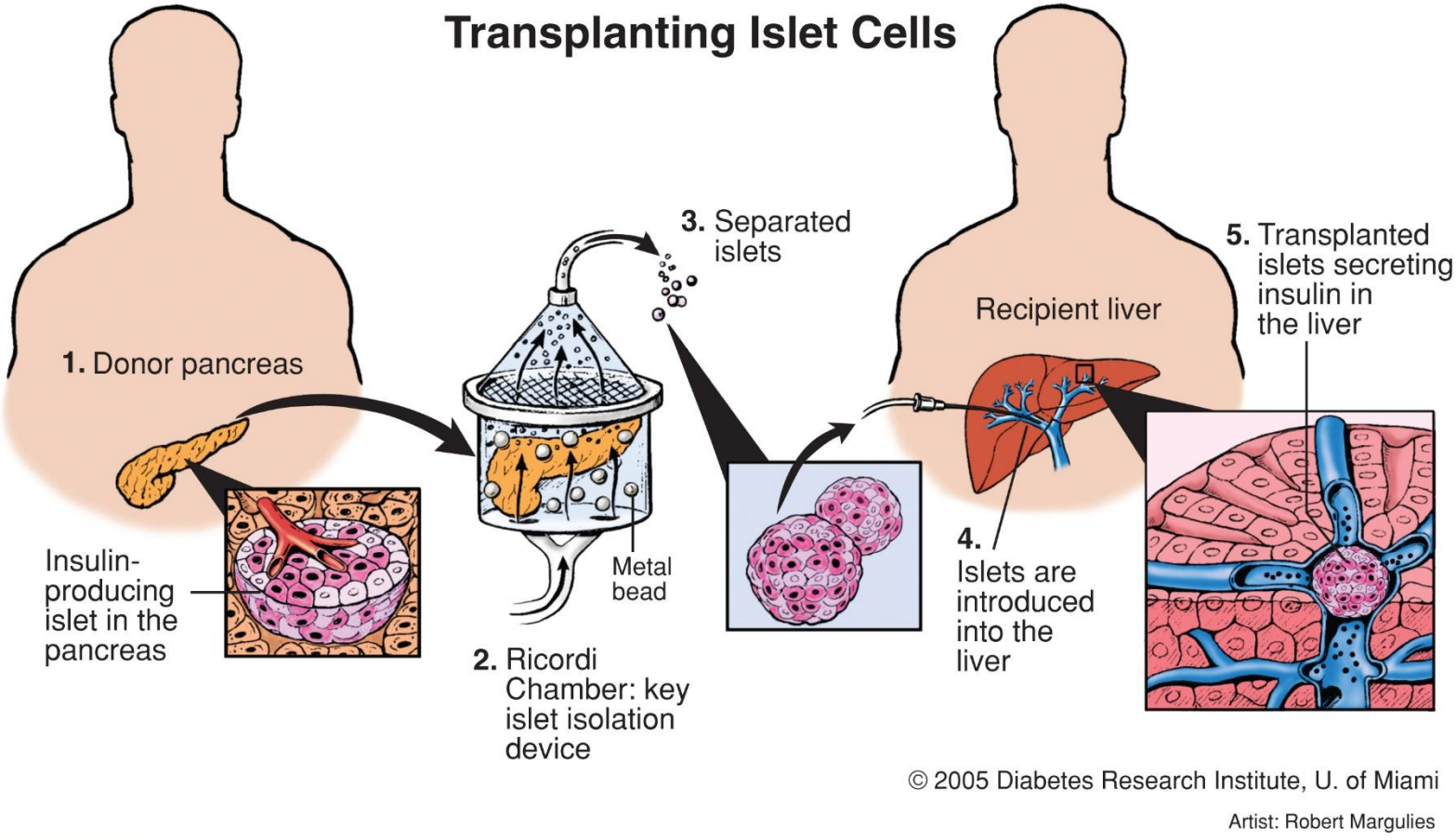

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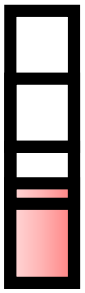
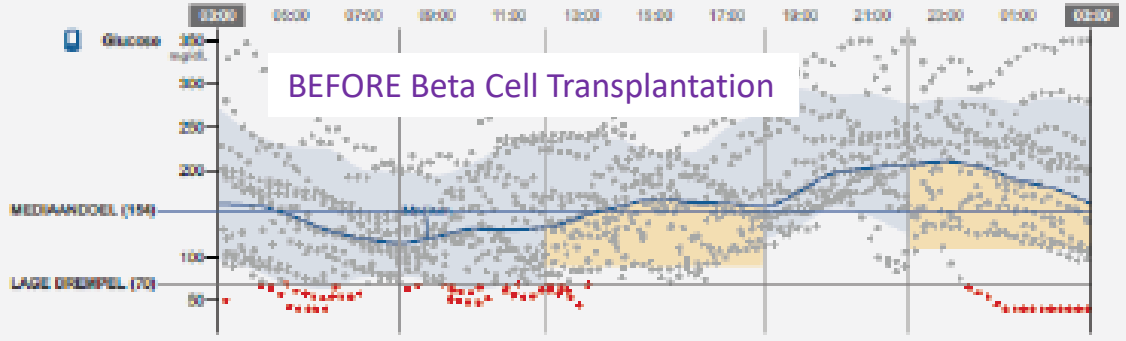
Minimal Functional β-Cell Mass in Intraportal Implants That Reduces Glycemic Variability in Type 1 Diabetic Recipients

Islet Beta-Cell Transplantation

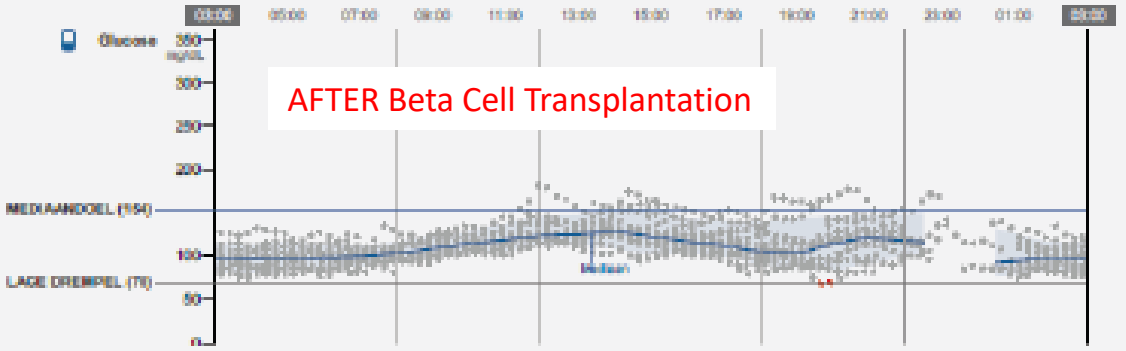


Basal C-peptide ≥0.5 ng/ml

FREESTYLE LIBRE



BEFORE Beta Cell Transplantation



AFTER Beta Cell Transplantation

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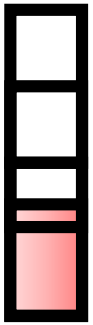
P. Gillard et al Diabetes Care. 2013

Islet Beta-Cell Transplantation

Age and long-term graft function



Age	Basal C-peptide > 0.5 ng/ml		
	Mean	IQR3	Longest
30- 39 yrs	3,3 yrs	5,0 yrs	8,7 yrs
40- 63 yrs	4,2 yrs	5,9 yrs	14,1 yrs

> 2 M Beta /kg; ATG MMF TAC

Diabetes Care Volume 38, June 2015

Evidence-Informed Clinical Practice Recommendations for Treatment of Type 1 Diabetes Complicated by Problematic Hypoglycemia

Pratik Choudhary,[1] Michael R. Rickels,[2] Peter A. Senior,[3] Marie-Christine Vantyghem,[4] Paola Maffi,[5] Thomas W. Kay,[6] Bart Keymeulen,[7] Nobuya Inagaki,[8] Frantisek Saudek,[9] Roger Lehmann,[10] and Bernhard J. Hering[11]

Diabetes Care 2015;38:1016–1029 | DOI: 10.2337/dc15-0090

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Problematic hypoglycemia

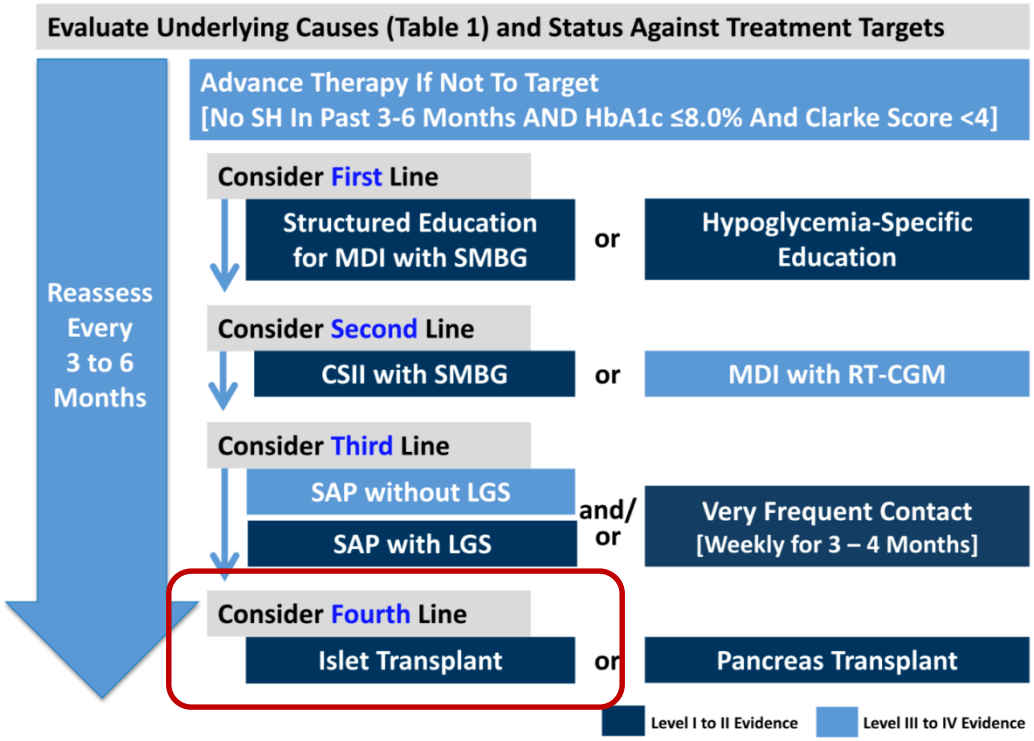
Definition:

Two or more episodes per year of severe hypoglycemia

or

One episode associated with impaired awareness of hypoglycemia, extreme glycemic lability or major fear and maladaptive behavior

Islet transplantation is an option!



Clinical routine

SAP: sensor augmented pump
LGS: low-glucose supsend

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Patients

Preclinical ▸Patient
1978- 1994-

Type 1 Diabetes

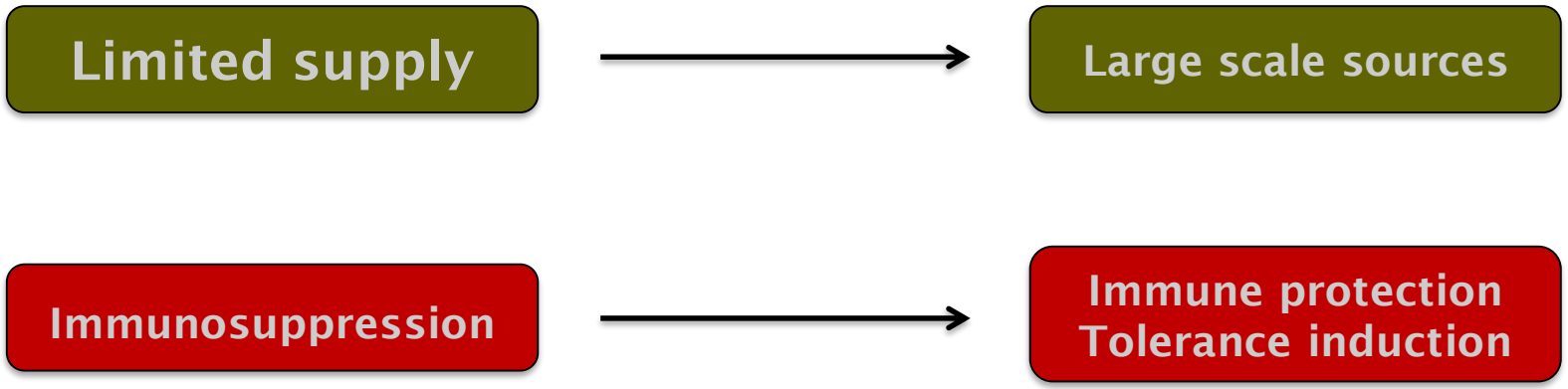
Donor cel Tx Allo

1st insulin independence: 2000

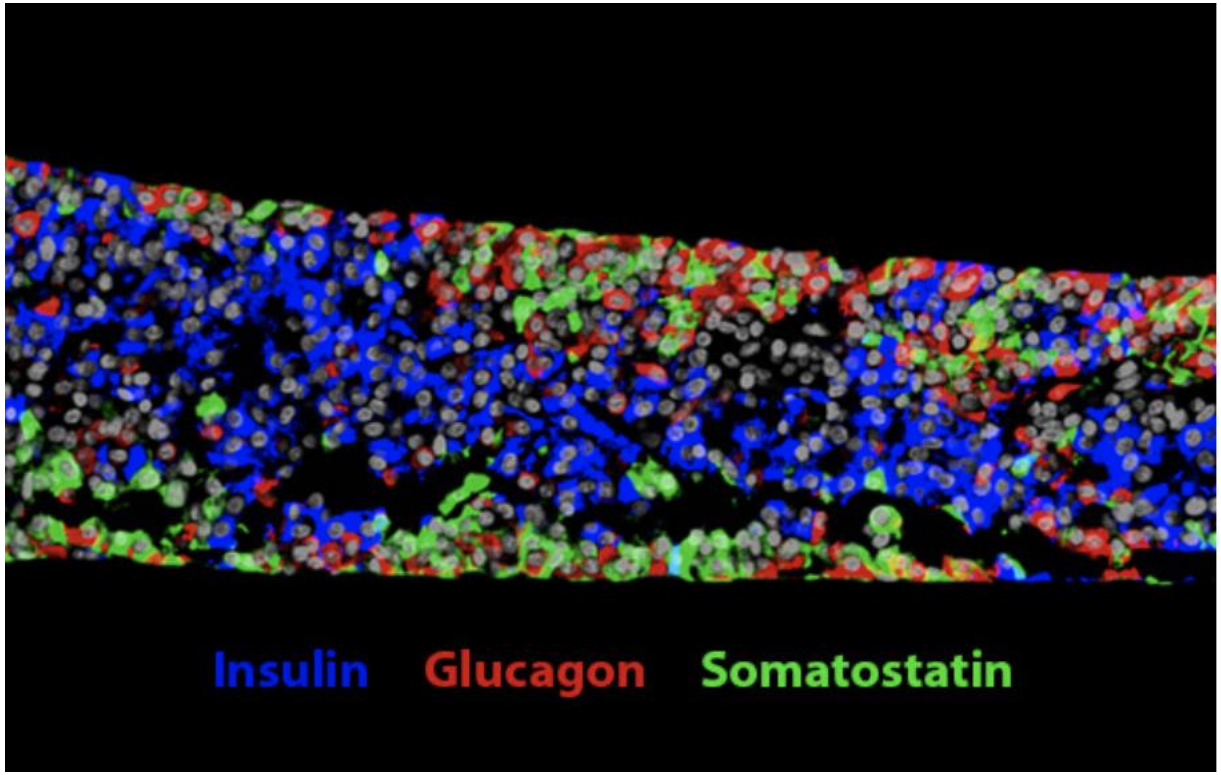
Preclinical = research in animal models Tx = Transplantation

Introduction

Potential cure for type 1 diabetes



Stem cells



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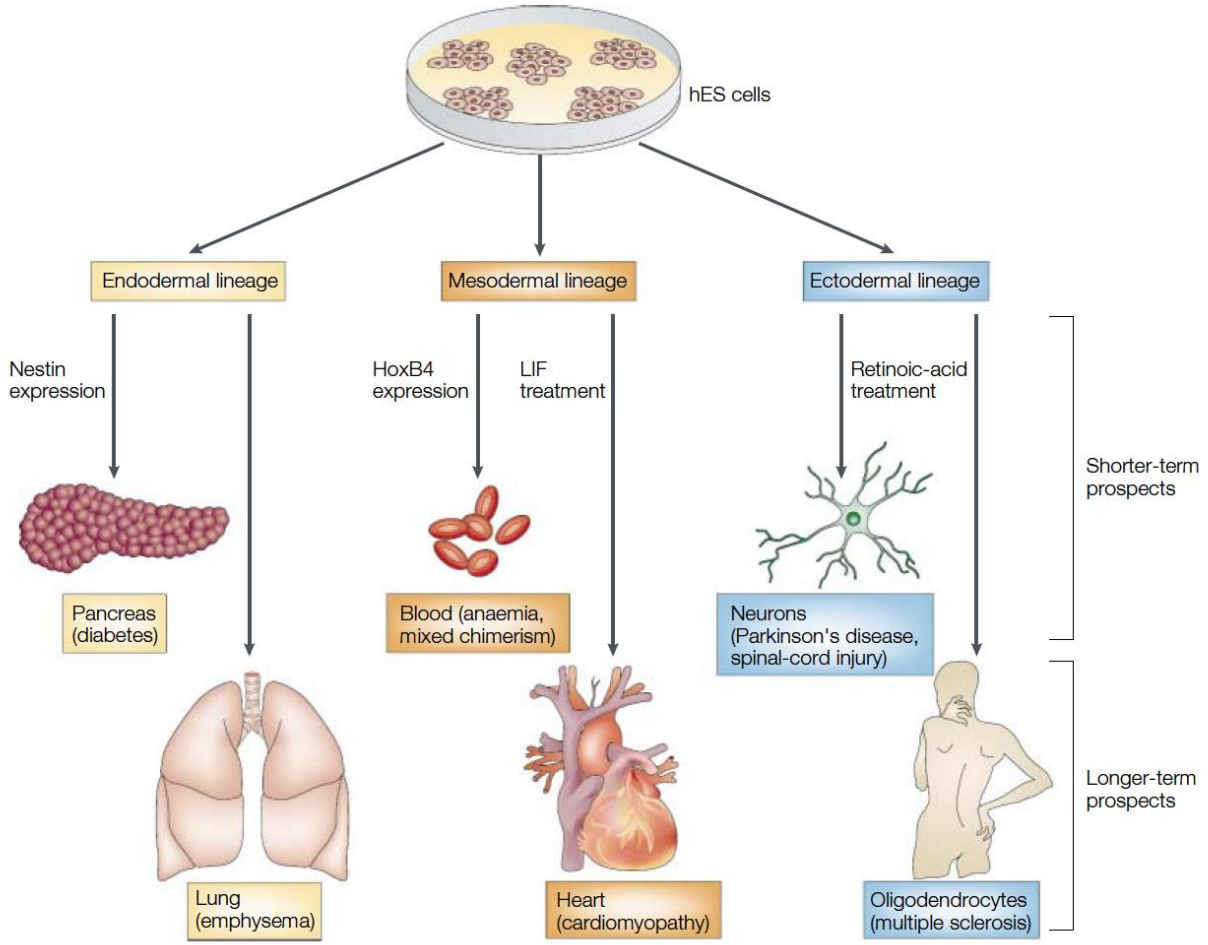
Embryonic stem cells



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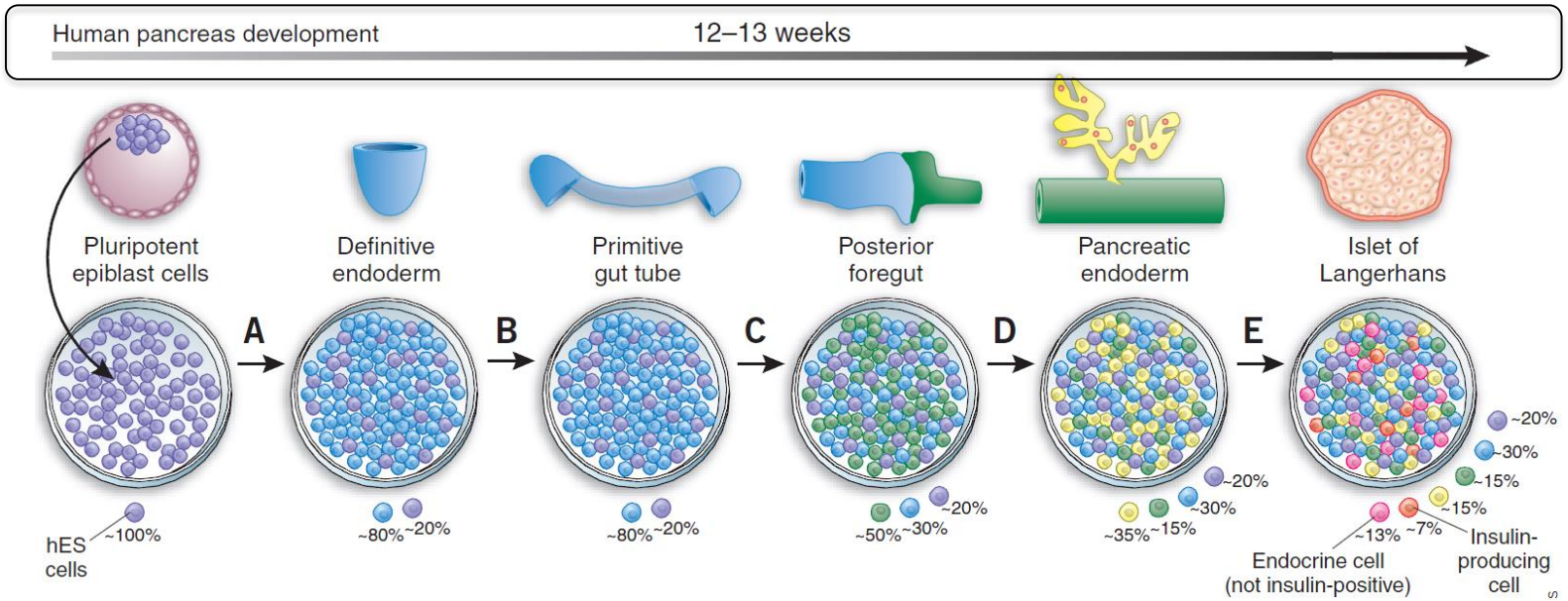
Human pancreas development
12–13 weeks
Pluripotent epiblast cells
Definitive endoderm
Primitive gut tube
Posterior foregut
Pancreatic endoderm
Islet of Langerhans
A
B
C
D
E
hES cells
~100%
~80%~20%
~80%~20%
~50%~30%~20%
~35%~15%~30%~20%
~13%~7%~15%~15%~30%~20%
Endocrine cell (not insulin-positive)
Insulin-producing cell
In vitro differentiation
~15–18 days

Lessons from mother nature

© 1997 Nature Publishing Group http://www.nature.com/naturegenetics

letter

MODY 4 (PDX-1)

Pancreatic agenesis attributable to a single nucleotide deletion in the human *IPF1* gene coding sequence

Doris A. Stoffers[1], Noah T. Zinkin[1], Violeta Stanojevic[1], William L. Clarke[2] & Joel F. Habener[1]

Hilbrands *et al. BMC Medical Genetics* (2017) 18:57
DOI 10.1186/s12881-017-0419-2

BMC Medical Genetics

CASE REPORT Open Access

Pancreas and gallbladder agenesis in a newborn with semilobar holoprosencephaly, a case report

Robert Hilbrands[1,6], Kathelijn Keymolen[2], Alex Michotte[3], Miriam Marichal[3], Filip Cools[4], Anieta Goossens[3], Peter In't Veld[1], Jean De Schepper[4], Andrew Hattersley[5] and Harry Heimberg[1*]

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nature biotechnology

2004-2005

Efficient differentiation of human embryonic stem cells to definitive endoderm

Kevin A D'Amour, Alan D Agulnick, Susan Eliazer, Olivia G Kelly, Evert Kroon & Emmanuel E Baetge

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

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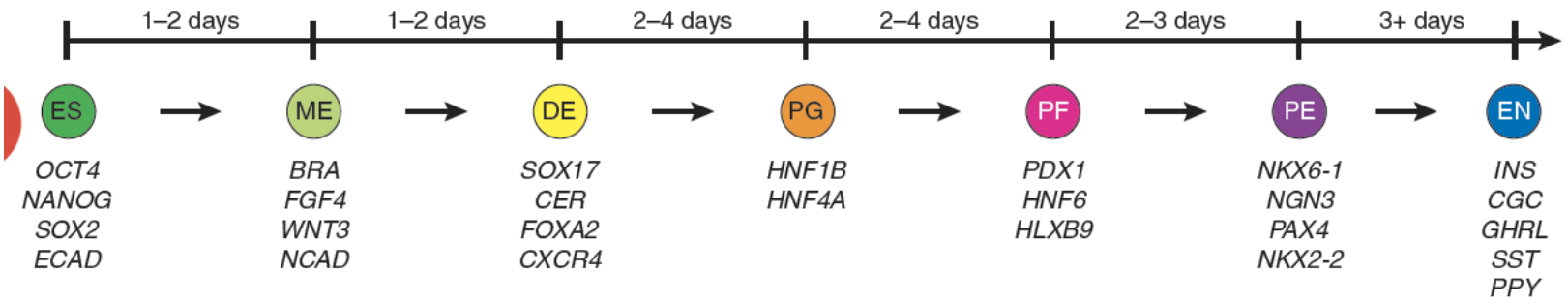
Nat. Biotech 2005 and 2006

How to make a beta cell from hESC

a

Stage 1		Stage 2	Stage 3	Stage 4	Stage 5
Definitive endoderm		Primitive gut tube	Posterior foregut	Pancreatic endoderm and endocrine precursor	Hormone expressing endocrine cell
Activin + Wnt	Activin	FGF10 + CYC	RA + CYC + FGF10	+/- DAPT; Ex4	+/- Ex4; IGF1; HGF
RPMI + 0% FBS	RPMI + 0.2% FBS	RPMI + 2% FBS	DMEM + 1% B27		CMRL + 1% B27



D'Amour et al.Nat. Biotech 2006

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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

2008

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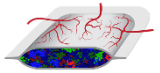
Nat. Biotech 2008

huESC-derived stage 4- pancr. endoderm (ViaCyte-Inc) 4.10^6 cells encapsulated in ViaCyte's Encaptra Device^{vc}

Macroencapsulation

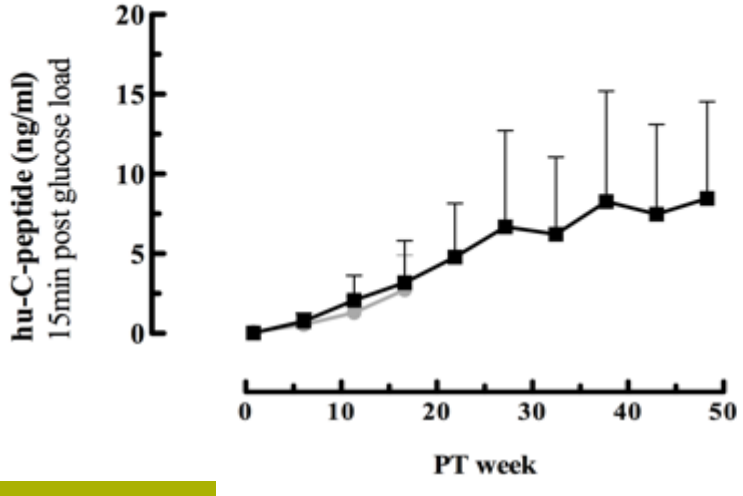
SC implant in NSG mice



Markers Functional Beta Cell Mass

In vivo 50 weeks : - basal glycemia of human

- hu-C peptide, glucose responsiveness



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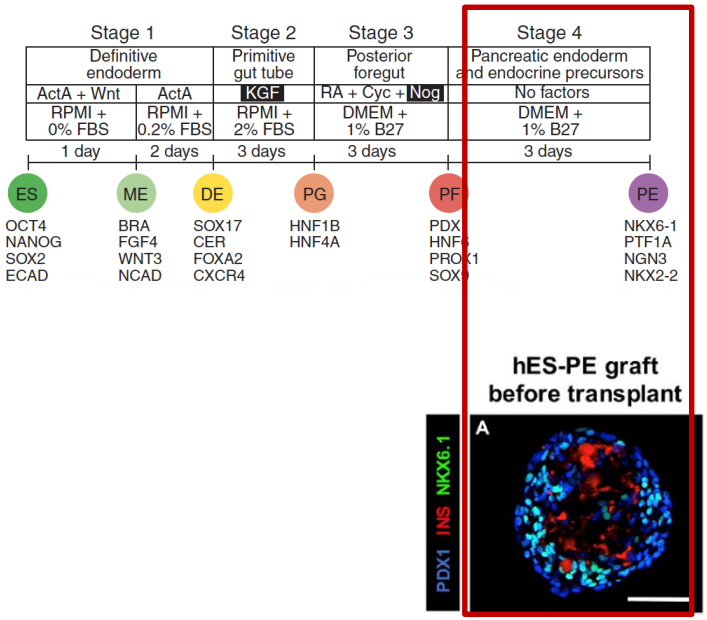
T. Robert et al, Stem Cell Reports, 2018

Preclinical studies

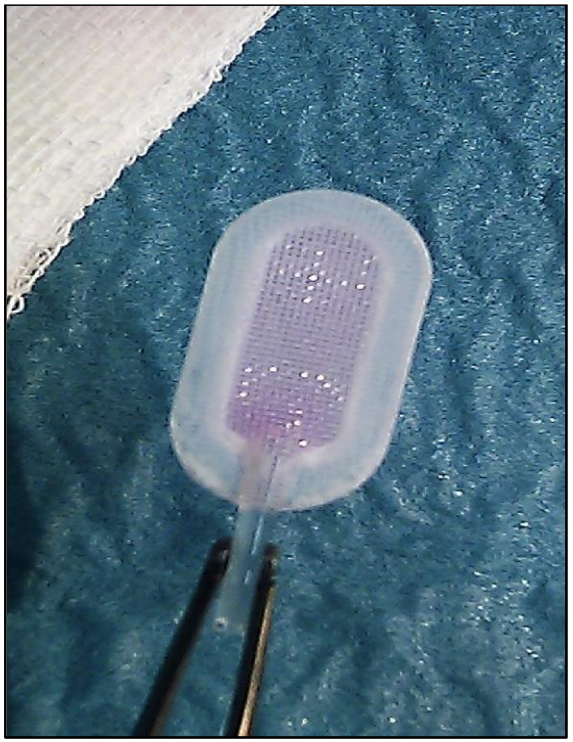


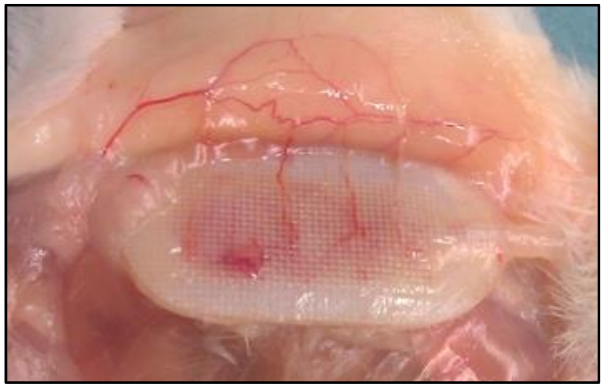
In vitro

In vivo

T. Robert et al, Stem Cell Reports, 2018

Preclinical studies



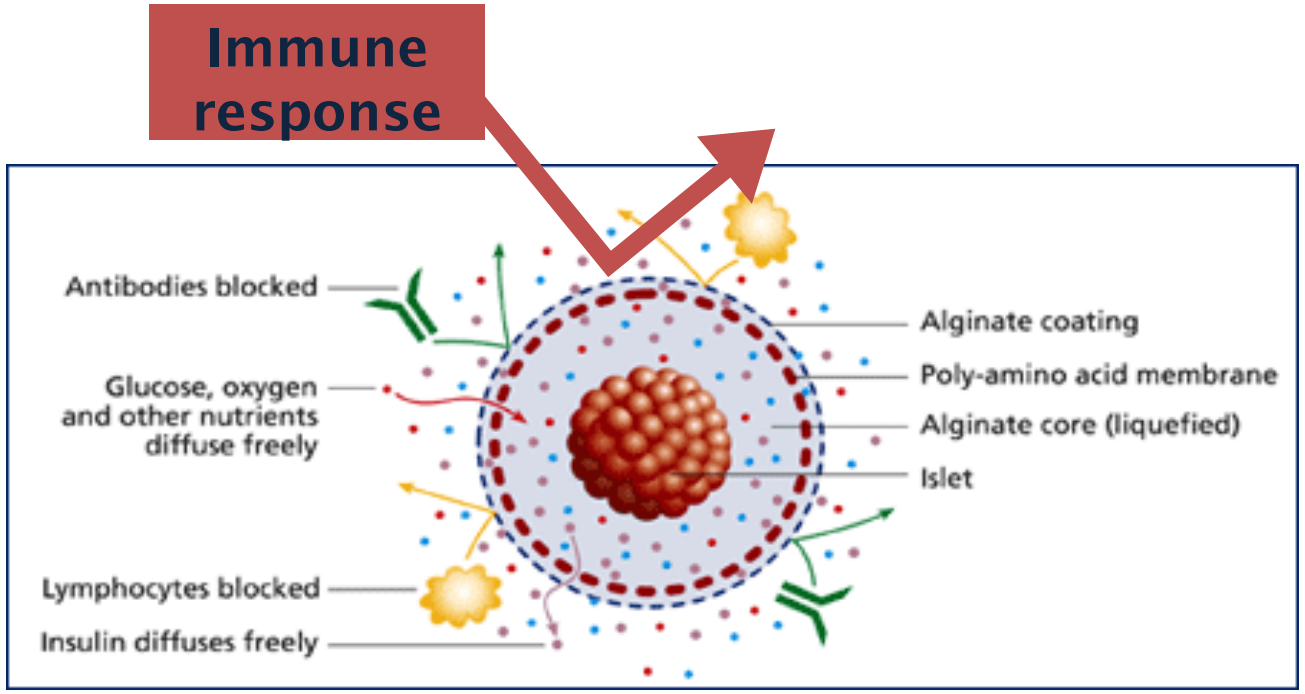


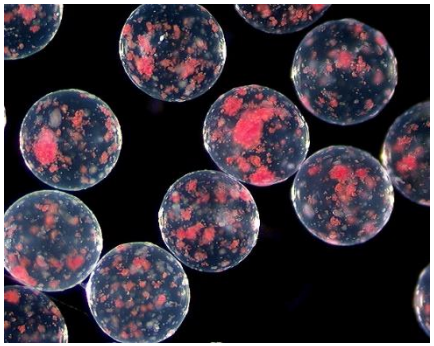
SAFETY

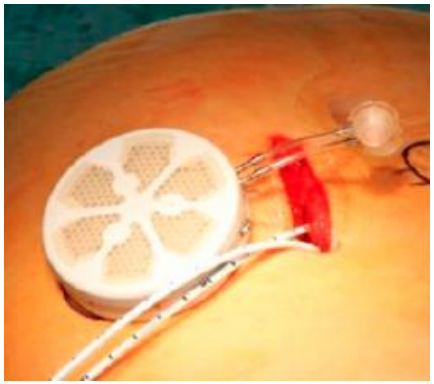
IMMUNITY

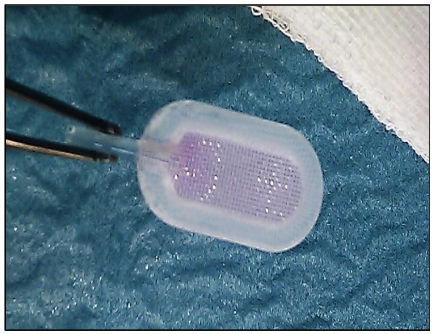
Motté E. et al. 2014

Encapsulation









Protects but does NOT prevent immune reactivity!!

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Encapsulation

- **Protection allo- & autoimmunity**
- **Protection innate immunity**
- **Support**
- **Vascularization**
- **Barrrier that avoids migration of cells with uncontroled growth**

- **With or without immunesuppression and anti-inflammatory strategies (systemic/local)**

Subcutaneous implantation

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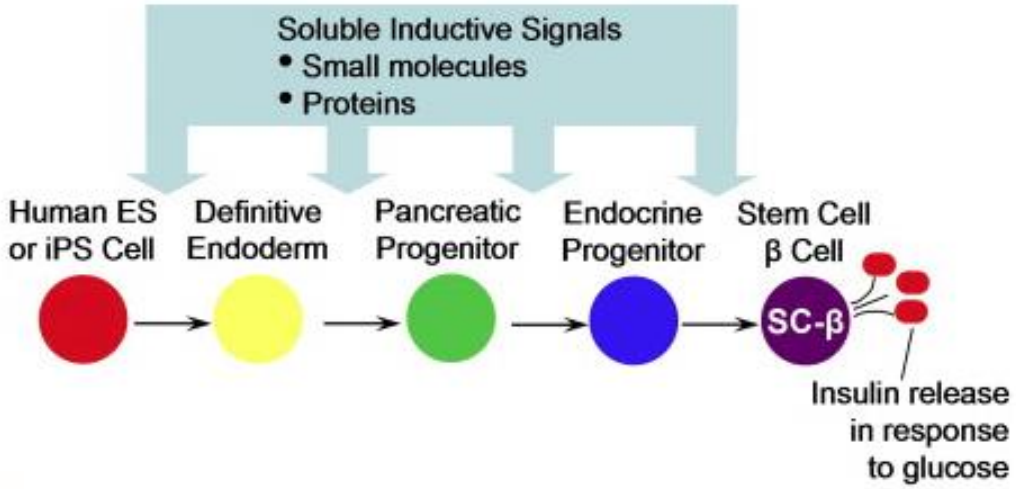
Directed differentiation into fully functional beta cell from ESC/iPSC

Cell

Resource

Generation of Functional Human Pancreatic β Cells In Vitro

Felicia W. Pagliuca,[1,3] Jeffrey R. Millman,[1,3] Mads Gürtler,[1,3] Michael Segel,[1] Alana Van Dervort,[1] Jennifer Hyoje Ryu,[1] Quinn P. Peterson,[1] Dale Greiner,[2] and Douglas A. Melton[1,*]
[1]Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Harvard University, 7 Divinity Avenue, Cambridge, MA 02138, USA
[2]Diabetes Center of Excellence, University of Massachusetts Medical School, 368 Plantation Street, AS7-2051, Worcester, MA 01605, USA
[3]Co-first author
*Correspondence: dmelton@harvard.edu
http://dx.doi.org/10.1016/j.cell.2014.09.040



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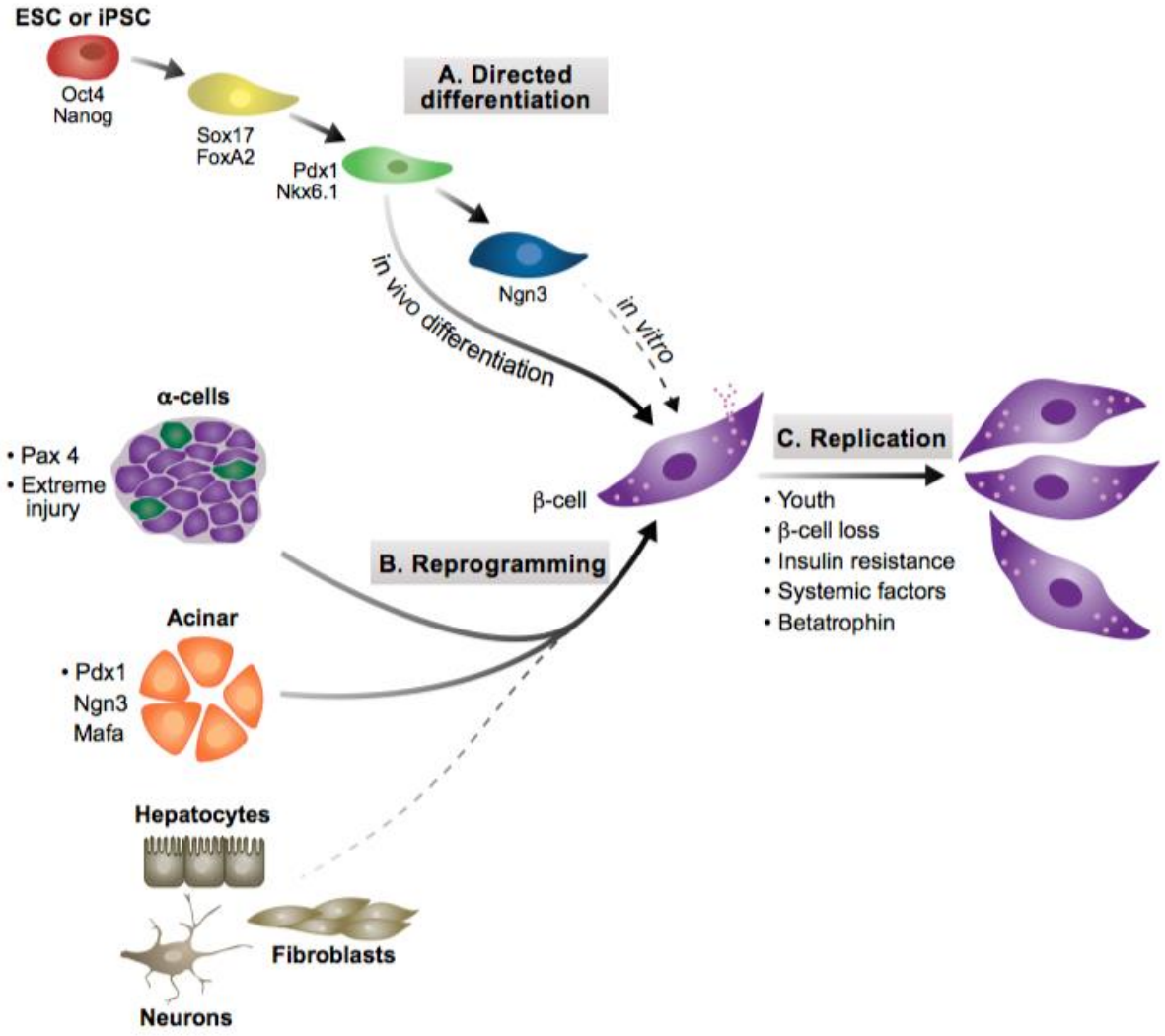
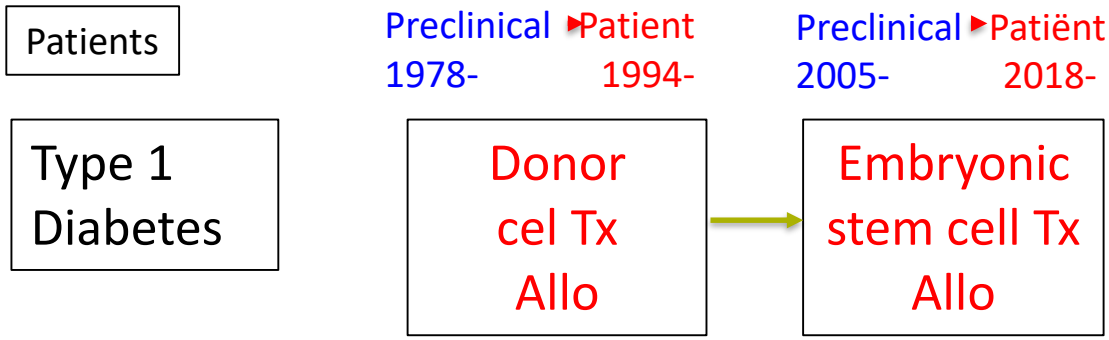
Cell, 2014

Alternative Cell Sources – directed differentiation and reprogramming



Pagliuca, Melton Development, 2013



1st insulin independence: 2000

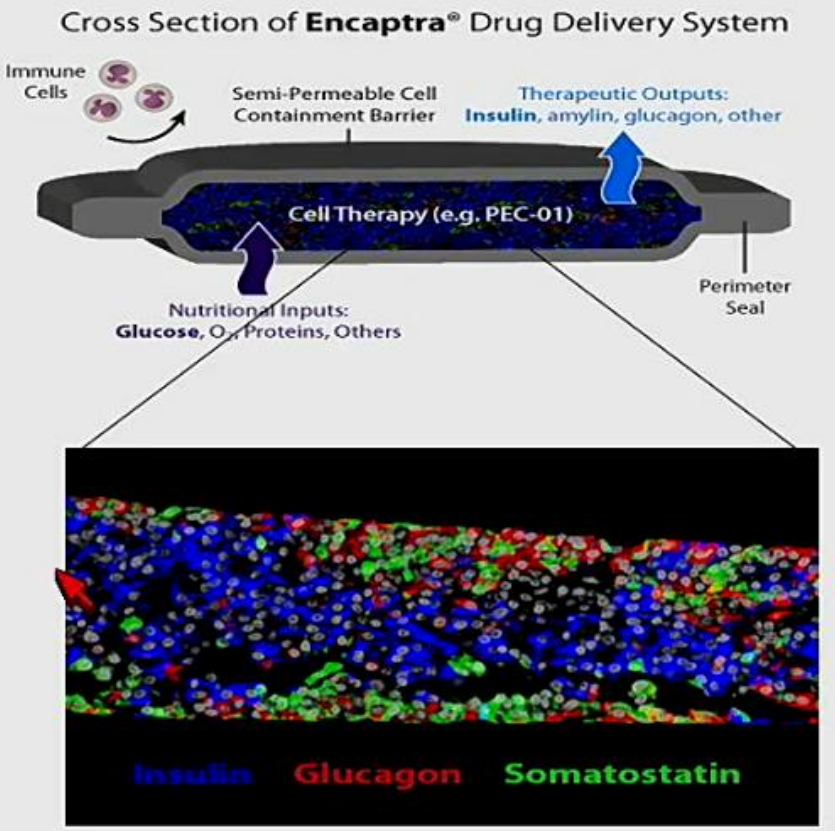
Preclinical = research in animal models Tx = Transplantation

Today – USA, Canada and Belgium

VIACYTE

VC-01™ Combination Product

- **PEC-01 cells:**
  A proprietary pancreatic endoderm cell product derived through direct differentiation of an hESC line CyT49.
- **Encaptra Drug Delivery System:**
  A Proprietary immune-protecting and retrievable encapsulation medical device.
- **Phase 1/2 trial - STEP ONE**: or Safety, Tolerability, and Efficacy of VC-01 Combination Product in Type 1 Diabetes, was launched in September 2014.



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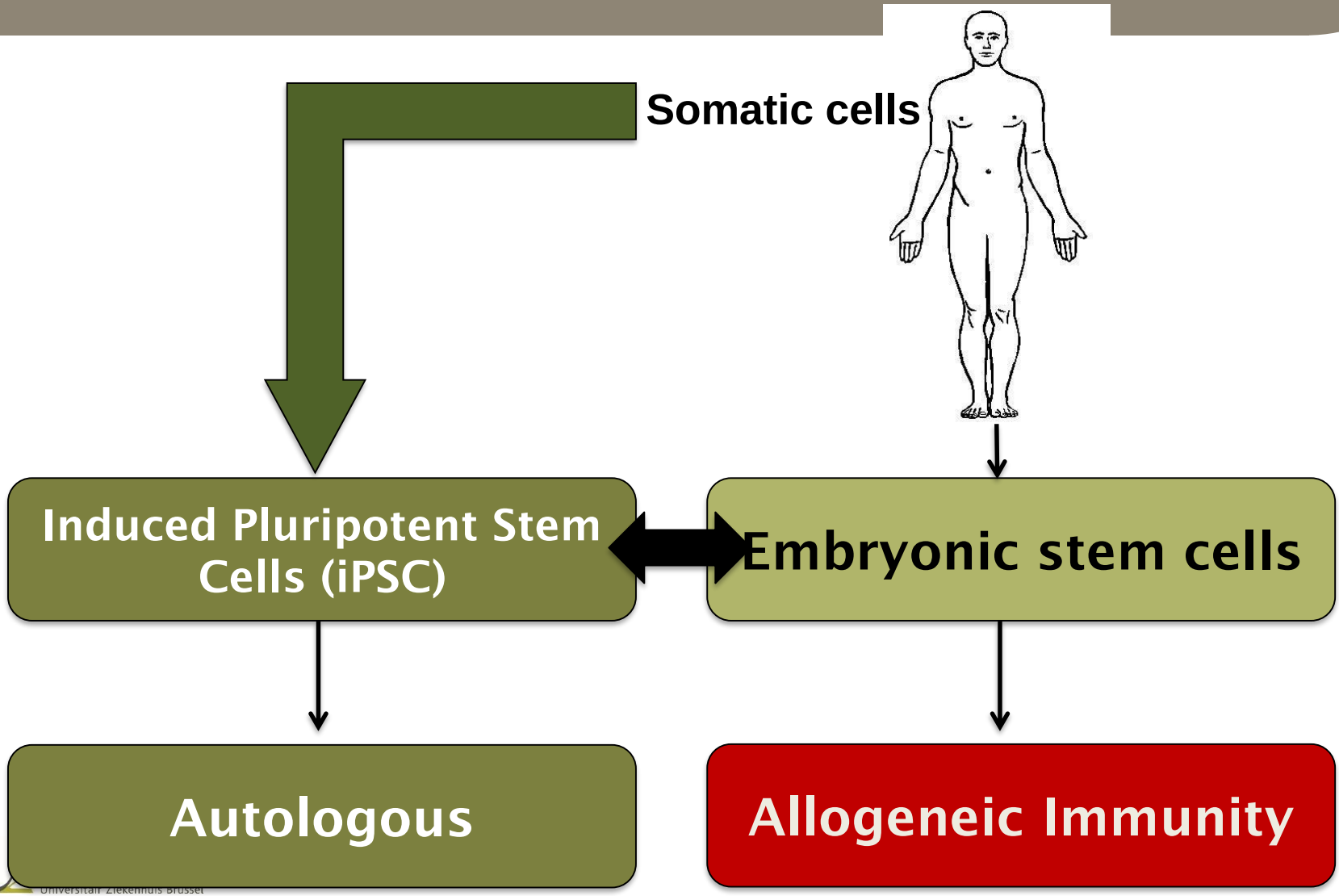
Clinical trial - endpoints

SAFETY

Survival
Maturation
In vivo function



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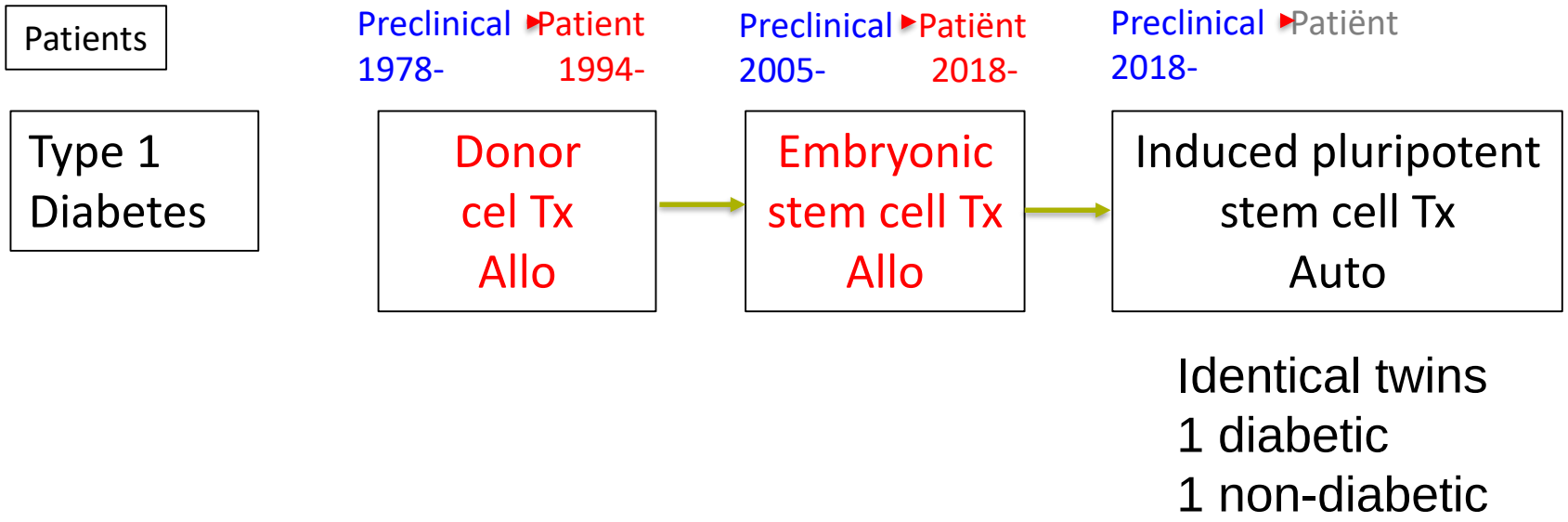
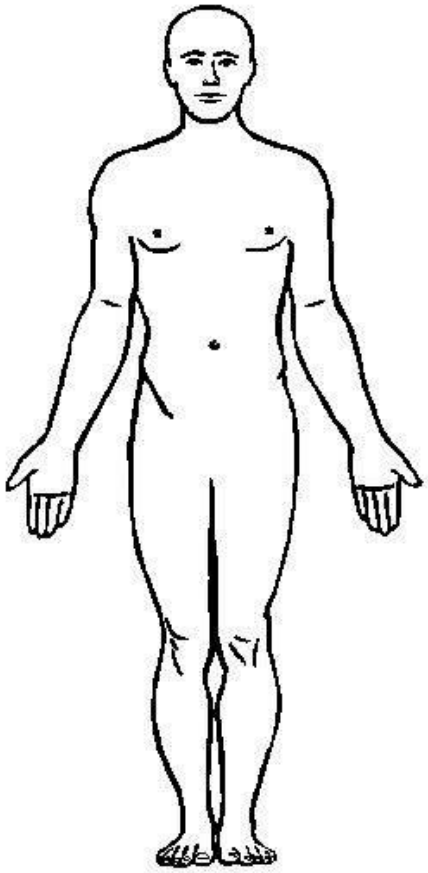


Preclinical = research in animal models Tx = Transplantation

Personalized medicine



Induced pluripotent stem cells (iPSC)

Autologous origin BUT economics of scaling up personalized therapy challenging (i.e. quality/safety controls)

Pragmatic approach ➔ bank of iPSC lines

Autoimmune response remains!

Fairchild P, Nat. Rev Immunology 2010, p 868

TODAY

Future

EU
Horizon 2020

Collaborators

San Raffaele Hospital

Lorenzo Piemonti

Brussels Free University-VUB
University Hospital Brussels

Daniel Pipeleers
Krista Suenens and team animal studies
Ines De Mesmaeker, Thomas Robert
Geert Stange and lab team
Zhidong Ling and staff Beta Cell Bank
Frans Gorus and team clinical chemistry
Bart Keymeulen, Pieter Gillard, Daniel Tulleneers, Robert Hilbrands, Freya Van Hullle
Diedert De Paep, and teams diabetes clinic in Brussels and Kath. Univ. Leuven

ViaCyte, San Diego

Evert Kroon

Leiden Univ

Bart Roep

Nestle Inst Health Sci
Ed Baetge
Marine Kraus

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