Stem cells for regenerative medicine

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KU Leuven, Stem Cell Institute

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Content

- What are stem cells
- Use of adult stem cells for regenerative medicine
- Use of iPS cells in discovery medicine, preclinical drug assessment
- Use of iPS cells for regenerative medicine
- Need for clinical grade GMP iPS cell bank covering HLA types of Belgian population

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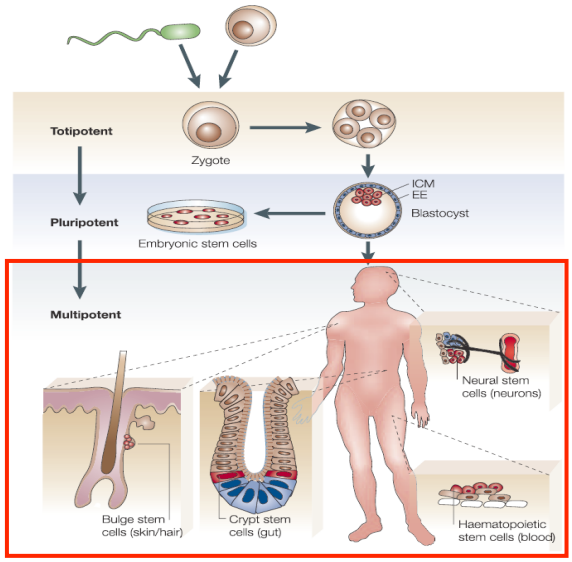
Different types of stem cells



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Eckfeldt, Nat Rev | Mol Cell Biol, 2005

Restrictions adult stem cells

- Senesces
- Differentiates to some not all cells

Use of adult stem cells

- No tumor formation
- Allogeneic or autologous
- Only cell used clinically (HSC, MSC and related cells, others)

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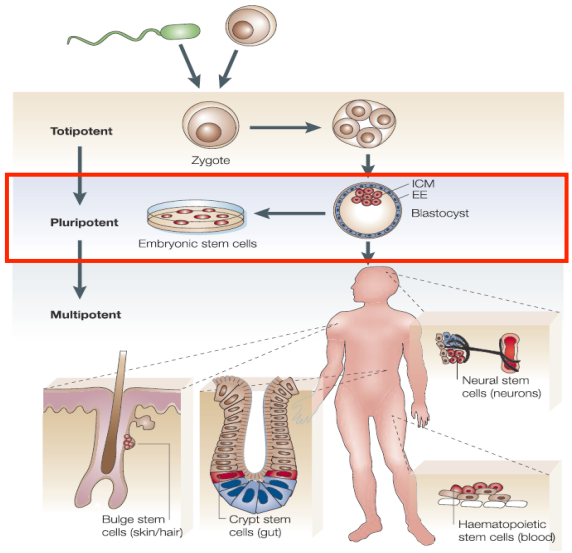
Different types of stem cells



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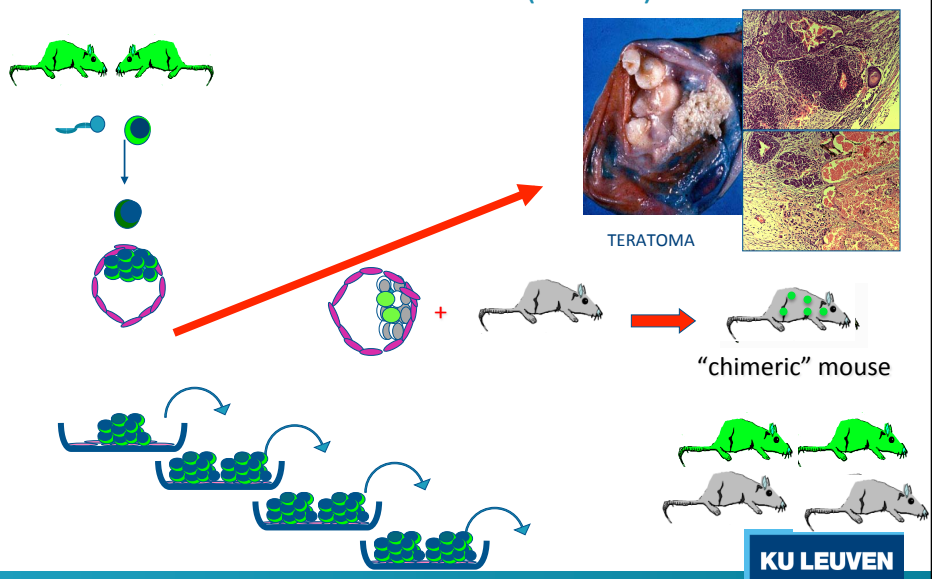
Eckfeldt, Nat Rev | Mol Cell Biol, 2005

Embryonic stem cell: does not senesce and differentiates in all cells of a mouse (human)



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Pluripotency of embryonic stem cells

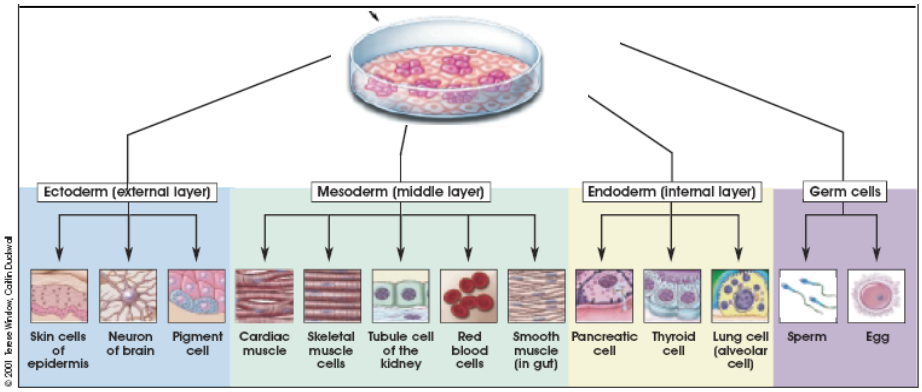

Figure 1.1. Differentiation of Human Tissues.

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ADAPTED FROM NIH STEM CELL WEBSITE

Enthusiasm surrounding embryonic stem cells

- Does not senesce
- Differentiates to all cell types; could this 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

- Teratomas
- Allogeneic
- Need to destroy early embryos (rest embryos from IVF)

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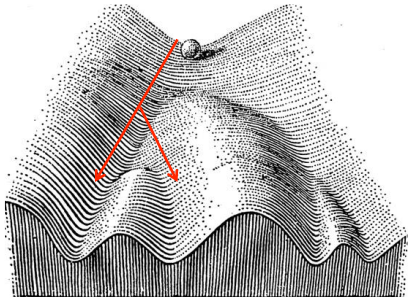
Differentiation one way street?

Waddingtons' epigenetic landscape (1957)

Development occurs through discrete changes in stem/progenitor cells



Irreversible cellular fate

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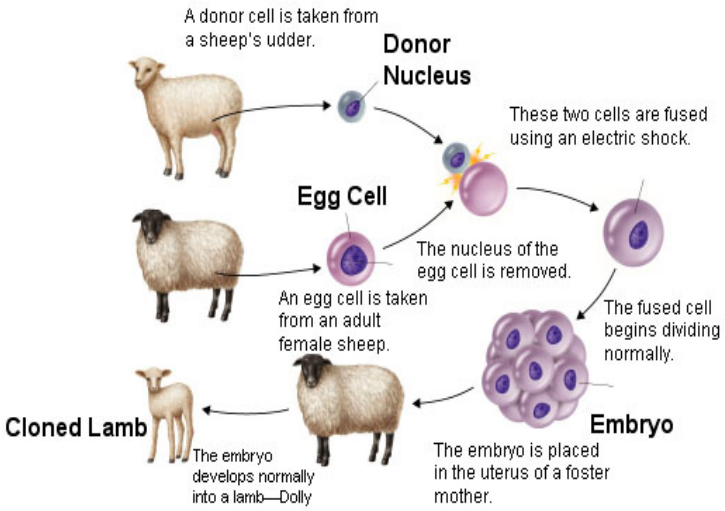
Waddington (1957)

But, Dolly!



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Wilmut *et al.* (Nature, 1997)

And also cloned frogs, in the early 60's

Nucleus Albino frog

Unfertilized egg

???

Albino frogs

Gurdon *et al.* (Nature, 1958)

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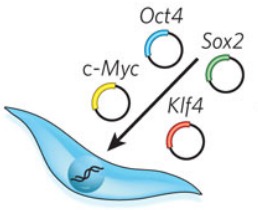
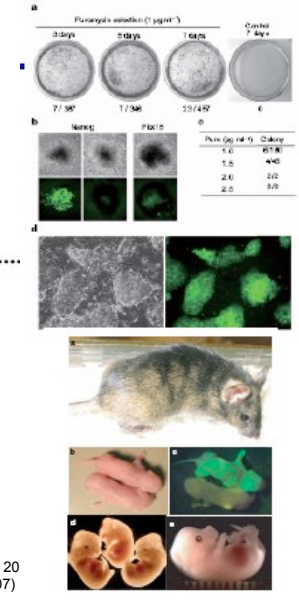
Induced pluripotent stem cells

c Transcription-factor transduction



Cell division
DNA replication



Takahashi & Yamanaka (Cell 20
Takahashi *et al.* (Cell 2007)

2006-2007

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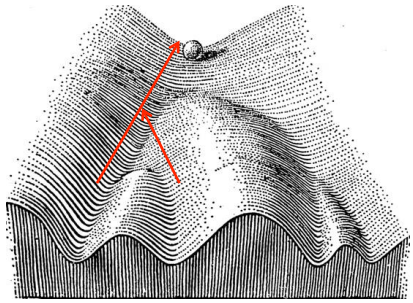
Differentiation one way street?

Development appears reversible



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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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Regenerative therapies with adult stem cells

- HSC:
  - first in the 60's, now an approved therapy for many diseases
  - Relatively high degree of HLA matching needed

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Regenerative therapies with adult stem cells

- MSC (Bone marrow, adipose tissue, …)
  - Not truly regenerative therapy, as most cells not detected beyond 1 or 2 weeks following transplantation
  - Exceptions might be restoration of some mesenchymal tissues?
  - Most effects are trophic
    - Support endogenous stem/progenitor cells (fistle healing) YES
    - Support of at risk ischemic cells (stroke, MI, PVD) YES??
    - Immunosuppressive YES??
  - HLA matching may not be needed for the "trophic" indications?

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Use of iPS cells in discovery medicine, preclinical drug assessment

- Creation of iPSC from patients with known (genetic) disease to then create tissue cells affected in disease
  - Examples: developmental diseases, autism, neurodegeneration, long-Qt syndrome, …
- Creation of iPSC from normal individuals (with different susceptibility to drug toxicity) and create tissue cells affected by toxicity
  - Examples: cardiac cells, peripheral neurons, hepatocytes, renal cells, …
- HLA not important, but genetic abnormalities or genetic trait of importance
- Can by using GLP grade iPSC

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Use of iPS cells in regenerative medicine Retinitis pigmentosa?

- **Human ESC-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy**: follow-up of two open-label phase 1/2 studies…
- Differentiate non-HLA matched ESC to retinal pigment epithelial cells
- Transplantation RPE in animal models can rescue photoreceptors
- Subretinal space is immune privileged, maybe allowing allogeneic therapy
- Clinical phase 1/2A trial with RPEs from human ESC in 18 patients
- Follow up 12-36 months (average 22 months)

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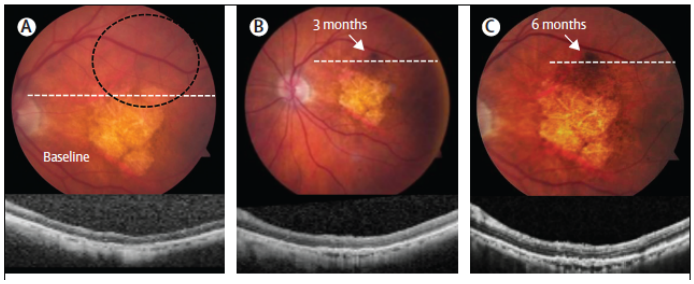
Lancet 2015; 385: 509–16

Fundus images of eyes: pigmentation after transplantation with hESC-retinal pigment epithelium



Presence of pigmented patches on fundus photographs of an eye from a patient with age-related macular degeneration (dotted circle shows an outline of the transplanted area) at 3 months and 6 months (arrows).

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Lancet 2015; 385: 509–16

Use of iPS cells in regenerative medicine ESC-RPE for Retinitis pigmentosa

- First evidence of medium- to long-term **safety** of ESC-derived cell transplantation
- First evidence of ESC-derived cell **graft survival**
- **Biological activity** of ESC-progeny (phase, thus cannot be defined)

- Number of cells needed small!
- Suggest ESC-derived cells may be a safe new cell source for treatment of medical disorders requiring tissue repair/replacement

- HLA matching needed?
- Phase II trails needed to demonstrate efficacy

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Use of iPS cells in regenerative medicine
Diabetes Mellitus?

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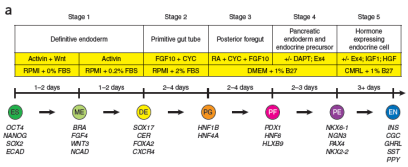
iPSC derived endocrine pancreatic cells

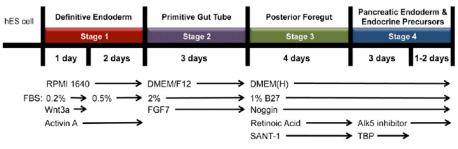
Production of pancreatic hormone–expressing endocrine cells from human embryonic stem cells

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



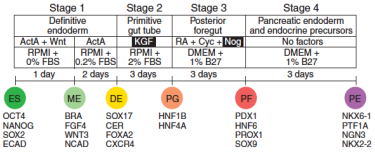
Maturation of Human Embryonic Stem Cell–Derived Pancreatic Progenitors Into Functional Islets Capable of Treating Pre-existing Diabetes in Mice

Alireza Rezania,[1] Jennifer E. Bruin,[2] Michael J. Riedel,[2] Majid Mojibian,[2] Ali Asadi,[2] Jean Xu,[1] Rebecca Gauvin,[1] Kavitha Narayan,[1] Francis Karanu,[1] John J. O'Neil,[1] Ziliang Ao,[3] Garth L. Warnock,[3] and Timothy J. Kieffer[2,3]



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



Limitations:

1) Immature beta cells
2) In vitro glucose unresponsive
3) Polyhormonal cells
4) Takes 3-4 months to differentiate into mature beta cells

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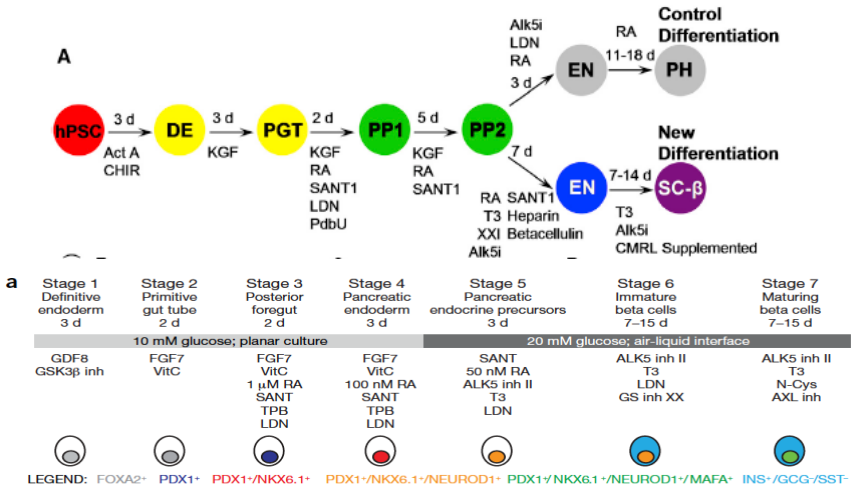
Generation of functional insulin producing beta cells from hESC



BetaLogics Venture, Janssen R&D LLC, Raritan, New Jersey, USA.
Timothy j Kieffer et al., 2014, Nature Biotechnology

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Use of iPS cells in regenerative medicine
iPSC-β-cells

- β-cells can be generated, that function equally well as β-cells from islets of Langerhans
- Transplantation paradigm is established (Edmonton protocol)

- HLA Matching: not needed and not desirable as autoimmune disease
- Specific HLA type needed to avoid immune system?

- How avoid allogeneic immune rejection?
- How perform safe?

⇒ Encapsulation?

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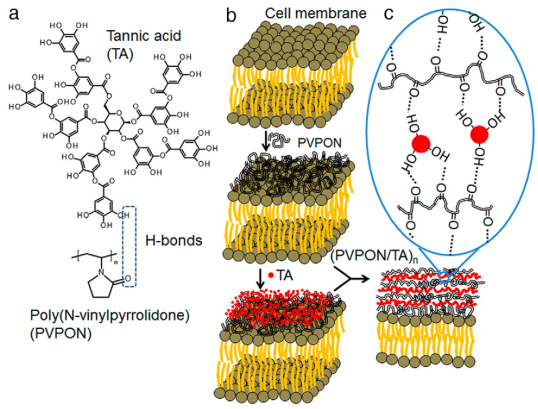
ENDOCRINE SOCIETY



Multilayer coating of hydrogen-bonded (H-bonded) tannic acid and poly(N-vinylpyrrolidone) (A) is adsorbed on islet cell surfaces in a stepwise manner (B) producing a nanothin conformal coating of H-bonded polymers (C).

Published in: Hubert M. Tse; Veronika Kozlovskaya; Eugenia Kharlampieva; Chad S. Hunter; *Molecular Endocrinology* **2015,** 29, 1388-1399.
DOI: 10.1210/me.2015-1085

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Use of iPS cells in regenerative medicine iPSC-β-cells

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- HLA Matching: not needed and not desirable as autoimmune disease
- Specific HLA type needed to avoid immune system?

- How avoid allogeneic immune rejection?
- How perform safe?

⇒ Encapsulation?

- Currently not yet possible, as encapsulation technique needs further improvement
- How long will β-cells persist?
- Tumor formation?

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Use of iPS cells in regenerative medicine
iPSC-dopamine neurons for Parkinson disease?

- Proof of principle that this may work: studies from Lund University using fetal brain dopamine progenitors
  - Non-placebo controlled Phase I/II studies encouraging
  - With immunosuppression
- However, subsequent placebo controlled muti-center studies not as successful
  - Loss of graft after stopping immunosuppression
  - In some patients development of chorea like symptoms
- Thus problems:
  - HLA matching needed?
  - Correct cells should be generated to avoid chorea development

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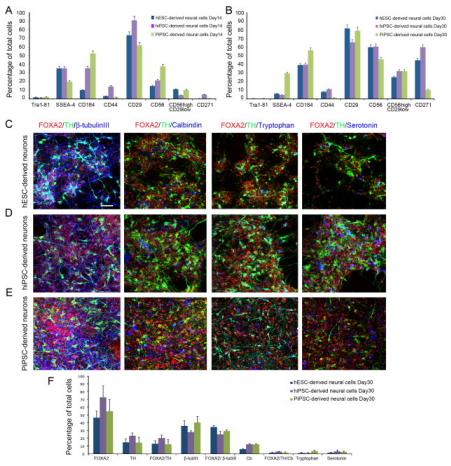
Improved Cell Therapy Protocols for Parkinson's Disease Based on Differentiation Efficiency and Safety of hESC-, hiPSC-, and Non-Human Primate iPSC-Derived Dopaminergic Neurons



STEM CELLS
Volume 31, Issue 8, pages 1548-1562, 23 AUG 2013 DOI: 10.1002/stem.1415
http://onlinelibrary.wiley.com/doi/10.1002/stem.1415/full#fig2

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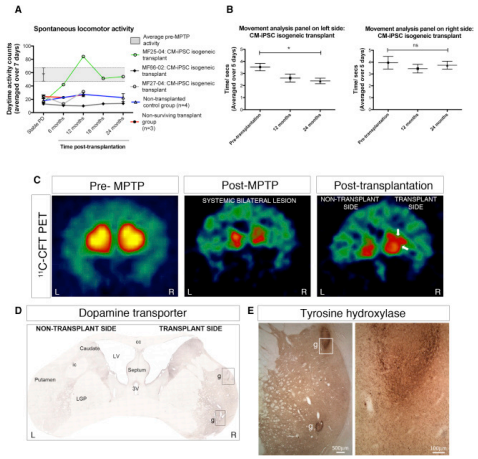
Functional Improvement of PD Motor Symptoms, Increased Dopamine Reuptake, and Reinnervation of the Transplanted Putamen after Autologous Transplantation of CM iPSC-Derived Dopamine Neurons



Penelope J. Hallett, Michela Deleidi, Arnar Astradsson, Gaynor A. Smith, Oliver Cooper, Teresia M. Osborn, Maria Sundberg, Michele A. Moore, Eduardo Perez-Torres, Anna-Liisa Brownell, James M. Schumacher, Roger D. Spealman, Ole Isacson
http://dx.doi.org/10.1016/j.stem.2015.01.018

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Use of iPS cells in regenerative medicine Parkinson disease

- Data available that pure dopaminergic cells representing the zone A8 dopaminergic cells in midbrain can be generated, which should decrease chorea problems seen in randomised trials
- Number of cells needed, relatively small (400,000 in the human brain)

- Primate-primate, and human-primate transplants possible, and improve phenotype
- No tumors found

- But: grafts done in dorsal striatum, not substantia nigra, as projection from the latter is not yet possible in adult brain- Implications for regulation output?
- But: PD is more than loss of dopamine neurons
- HLA matching likely needed

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Conclusion

- Established that HSC serve as regenerative therapy: HLA matching needed
- For MSC (different origins): in most cases not regenera… A matching may not be needed
- MSC therapies awa…
- iPSC deri… …ears, with as likely indicatior… …itus, PD, others?
- Risks: tum…
- HLA identical?
  - Likely true for PD;
  - Not known for RP, but may also be as retina is as immunoprivileged as brain;
  - Type I diabetes: avoid certain HLA types; encapsulation not yet fully developed

Need for clinical grade GMP iPS cell bank covering HLA types of Belgian population?

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