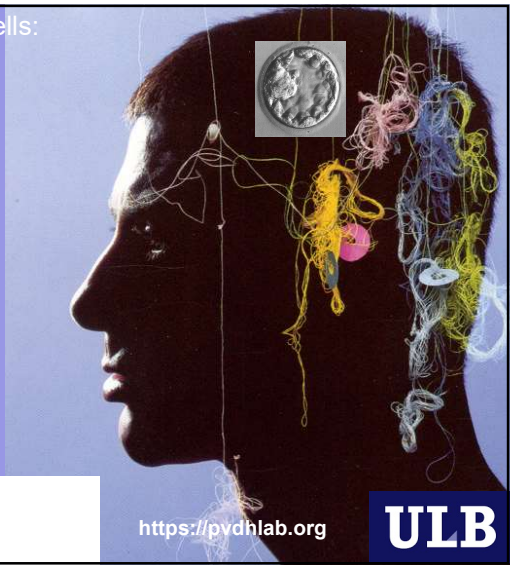
Embryonic Stem Cells: An Essential Tool for Human Biology and Medicine.

Pierre Vanderhaeghen

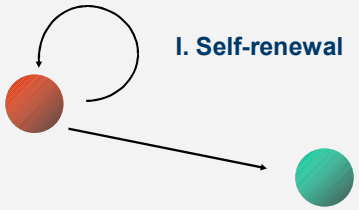


VIB-KU LEUVEN CENTER FOR BRAIN & DISEASE RESEARCH

https://pvdhlab.org

ULB

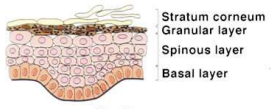
The two cardinal features of stem cells



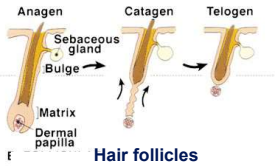
I. Self-renewal

II. Differentiation into more mature daughter cells

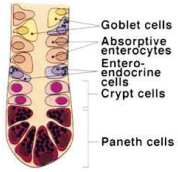
There are many types of stem cells. They are *specialized, so they only generate certain types of differentiated cells*



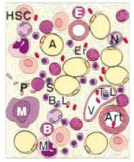
Skin



Hair follicles



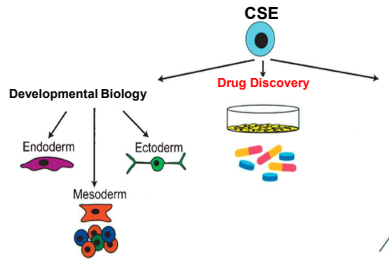
Intestinal epithelium

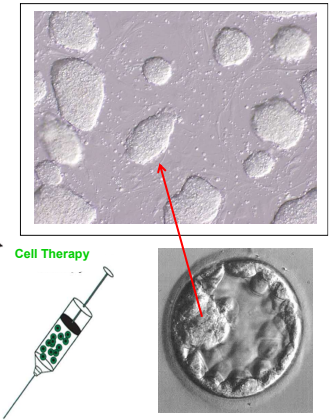


Bone marrow

Embryonic Stem (ES) Cells are PLURIPOTENT

- Derived from early embryos (blastocyst)
- Pluripotent (capable to generate any other cell type)
- « Immortal » (self-renewal)
- Available in mouse and human

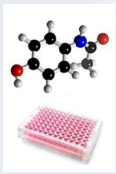




Why we need stem cells

life&brain

Drug development



Model systems

Non-human

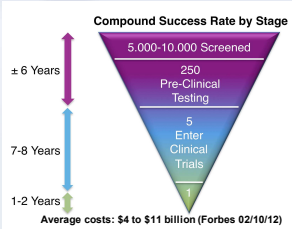
Transformed cells

Cell therapy

Donor tissue

Availability

Rejection

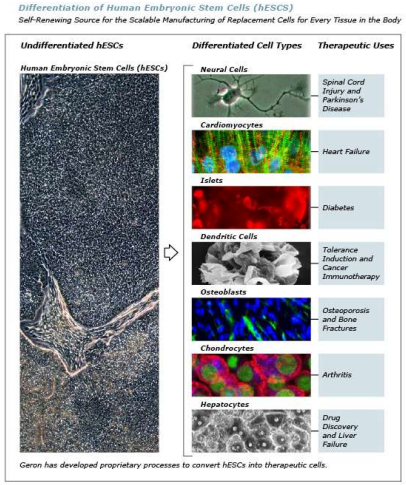


Average costs: $4 to $11 billion (Forbes 02/10/12)

The main expense is failure due to late clinical drop outs!

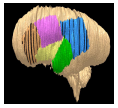
Urgent need for stem cells of human origin !

Embryonic stem cells are pluripotent



- **Depending on culture conditions (factors added to the culture medium) they will differentiate in any cell type of the body**

« Cortex in a dish »from pluripotent stem cells: an in vitro system to model human cerebral cortex development, evolution, and diseases.

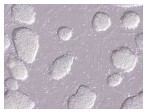


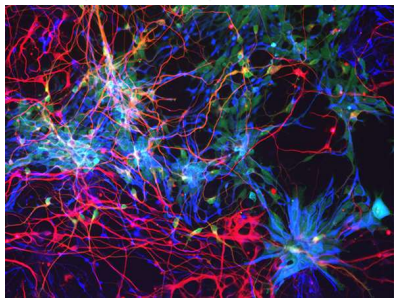
Human/mouse ES/iPS cell

DDM (Morphogen inhibitors)

Forebrain progenitor

Cortical progenitor

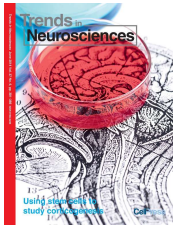




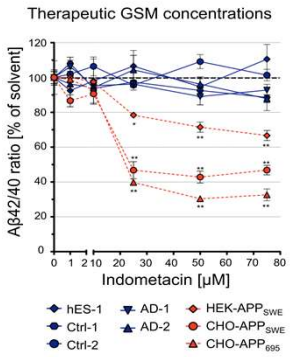
Gaspard et al Nature 2008
Tiberi et al. Nat. Neurosci. 2012
Espuny-Camacho et al Neuron 2013
Suzuki et al. Cell 2018

Human neurons in a dish can predict better the efficacy / safety of new drugs than non-neuronal cells

Embryonic Stem Cells for Drug Development



Example: Alzheimer Drugs



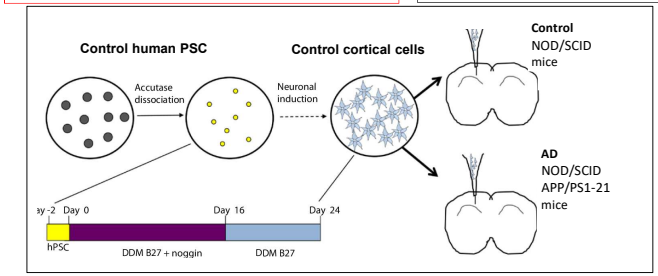
Mertens et al, Stem Cell Reports 2013

Human-mouse chimeric models to study human-specific features of disease

Alzheimer's disease

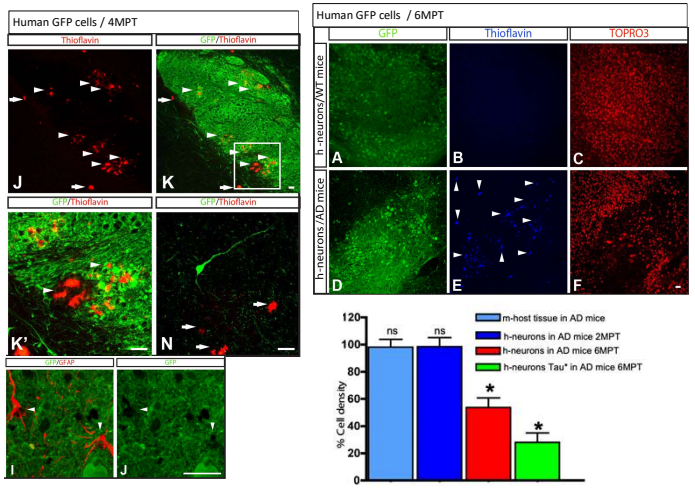
- Late onset
- Strikes pyramidal neurons
- amyloid-β (Aβ) plaques
- neurofibrillary pathology and ***tangles***
- Astrogliosis
- ***neuronal loss***

- **Tangles and neuronal loss are *not* observed in mouse models**
- **In vitro iPSC modelling lacks astrogliosis and genuine plaque formation / long term culture limitations**



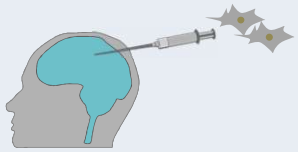
Ira Espuny, Bart De Strooper (KULeuven/VIB) / Jean-Pierre Brion, Karelle Leroy (ULB UNI)

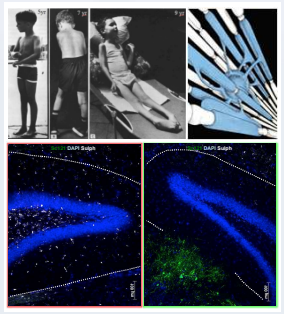
Human nerve cells are more sensitive to Alzheimer disease than mouse nerve cells



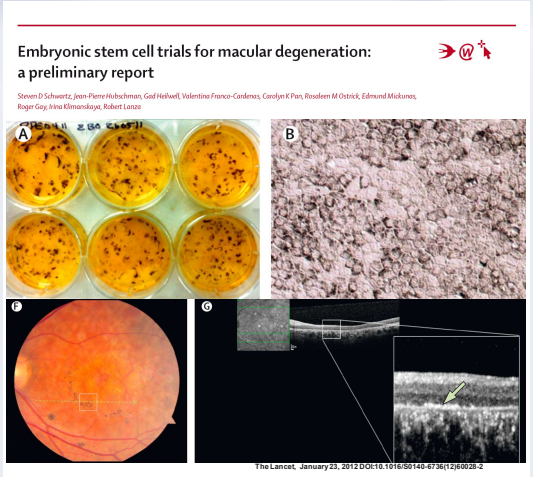
Embryonic Stem Cells for Transplantation: cell therapy for

Brain / eye / liver / pancreas





First human ES cell-based clinical trials for retinal macular degeneration



Cell replacement therapy is also focused on the brain:

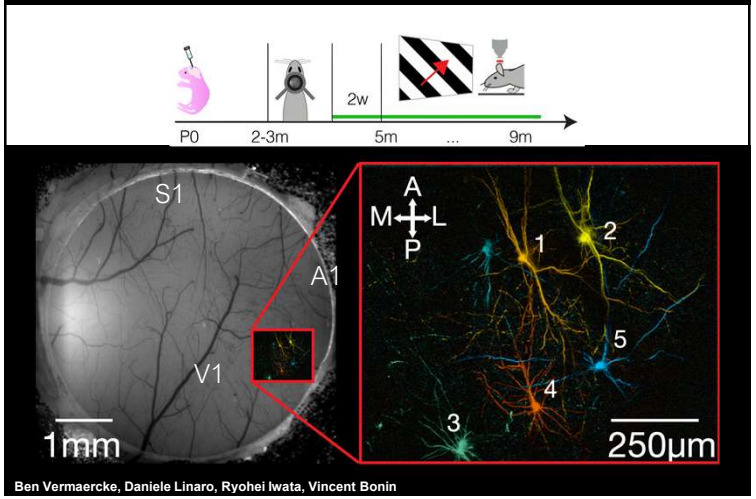
Parkinson disease (substantia nigra)
Huntington disease (basal ganglia)

Most prevalent brain diseases strike the cerebral cortex

Stroke
Trauma
Epilepsy

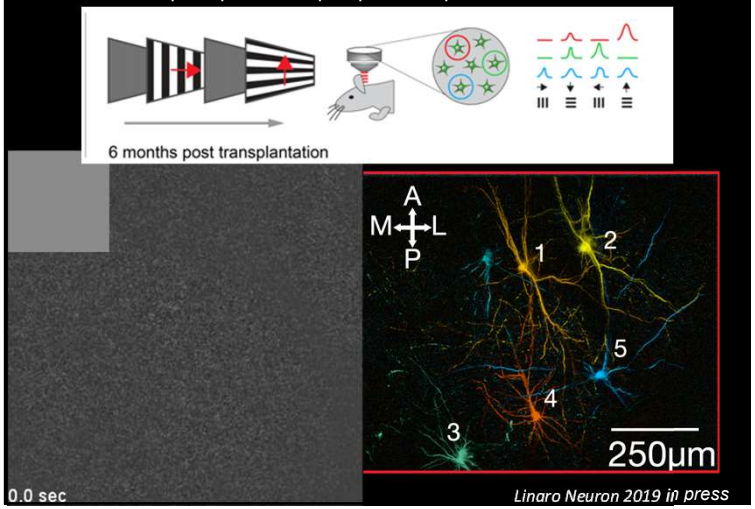
Can we envision cell therapy for diseases of the cerebral cortex, despite its complexity?

Testing the function of transplanted human neurons in a living brain: can they work properly in the host brain circuit?



Ben Vermaercke, Daniele Linaro, Ryohei Iwata, Vincent Bonin

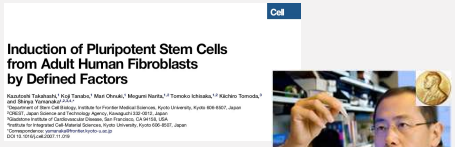
Transplanted neurons can integrate and function into the host brain circuits: Proof of principle for the prospect of repair of cortical diseases



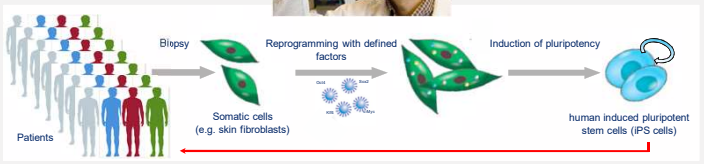
How are ES cells generated

- Typically derived from supernumerary embryos (IVF) donated for research (informed consent / no intellectual property associated)
- All of them were generated in the last 20 years. Only few actually used throughout the world (little human diversity / we will run out).

Do we still need human embryonic stem cells ?



Shinya Yamanaka
Nobel Prize 2012



Reprogramming of adult cells into ES-like cells: induced Pluripotent Stem Cells (iPSC)

Why we still need human embryonic stem cells

- Until now it is unclear, to what extent the properties of iPS cells equal those of ES cells, which have remained the golden standard.
- Currently used reprogramming procedures still pose the risk of mutagenesis.
- **Mutations naturally acquired during the aging process are preserved in iPS cells.**

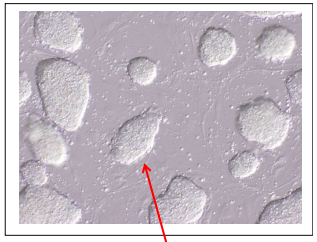
→ ***The best iPS cell will never be as good as an ES cell !***

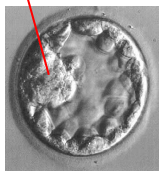
→ ***ES cells are an indispensable 'gold standard' for further optimization of cell reprogramming technologies.***

→ ***Future stem cell applications will be based on a 'best fit' selection from a growing spectrum of cell sources and methods, ranging from ES cells to direct fate conversion. No 'best source' paradigm !***

Human Embryonic Stem Cells have become essential tools for biomedicine, today and tomorrow

- **Wide perspective for human disease model to complement animal studies**
- **New tool for drug discovery and safety**
- **Important prospect for cell therapy repair for multiple organ deficiencies**





- **We need more ESC cell lines (number / diversity)**
- **Researchers need easier access to ESC research at the European level (regulatory hurdles are blocking research in many countries in Europe today)**

VIB-KU LEUVEN CENTER FOR BRAIN & DISEASE RESEARCH

Sofie Beckers
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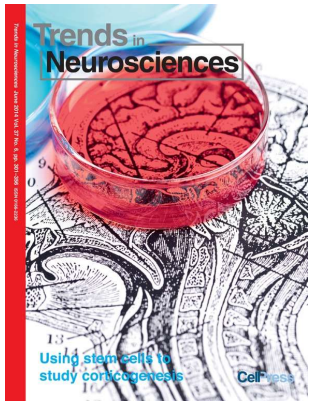
Vincent Bonin

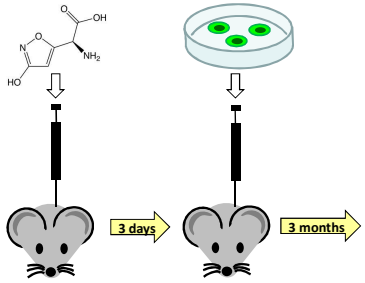
IRIBHM/ULB
David Gacquer
Vincent Detours

From stem cells to cortex in a dish



- Research tool to study human cortex development and function at the neuronal level
- Modelling for human-specific diseases (mental retardation, autistic disorders, Alzheimer disease,…).
- Source of cortical cells of highly defined identity for brain repair?

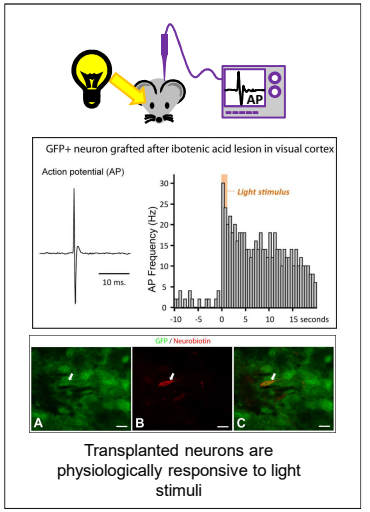
Les neurones dérivés à partir de cellules souches embryonnaires peuvent-ils contribuer à la réparation Cérébrale?



6-8 weeks old mice
Neurotoxic lesion
In visual cortex

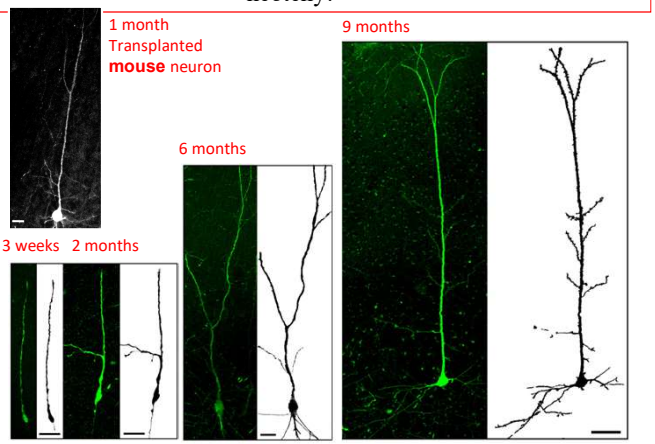
Grafting of mouse ESC-derived cortical cells of Visual identity

Michelsen, Acosta-Verdugo et al.

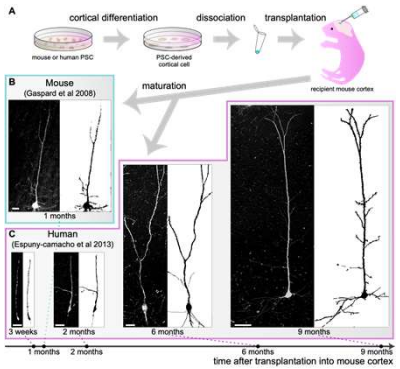


Transplanted neurons are physiologically responsive to light stimuli

Months-long maturation from transplanted human PSC-derived cortical pyramidal neurons, but not mouse neurons: intrinsic neuronal neoteny?

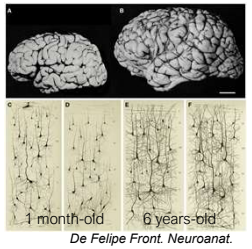


Human/mouse chimeric cortex recapitulates *species-specific* timing of neuronal maturation



Neoteny: retention of juvenile properties in a mature organism

Intrinsic cellular basis of neoteny /prolonged maturation of the human cortex?



De Felipe Front. Neuroanat.

Extraordinary neoteny of synaptic spines in the human prefrontal cortex

PNAS | August 9, 2011 | vol. 108 | no. 32 | 13281–13286

From stem cell simplicity to brain complexity?
Example of the cerebral cortex, the most complex structure in our brain