From Stem Cells to Regenerative Medicine

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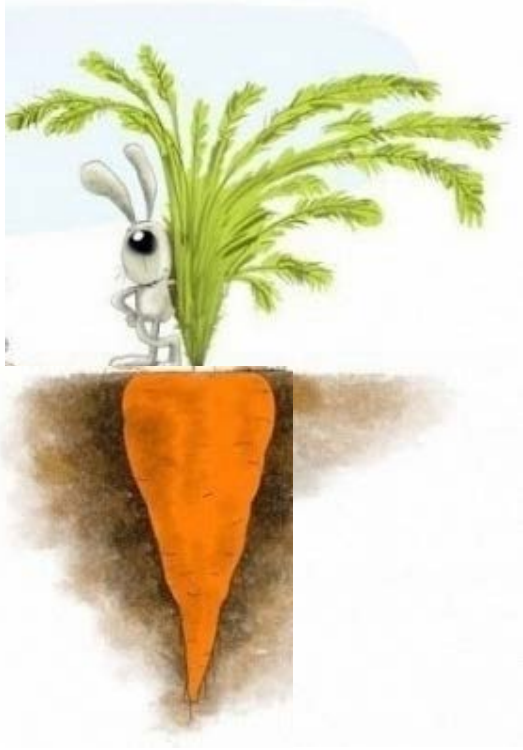
ROYAN

Our Vision and Mission

Application of science

Generation of science and translation of science



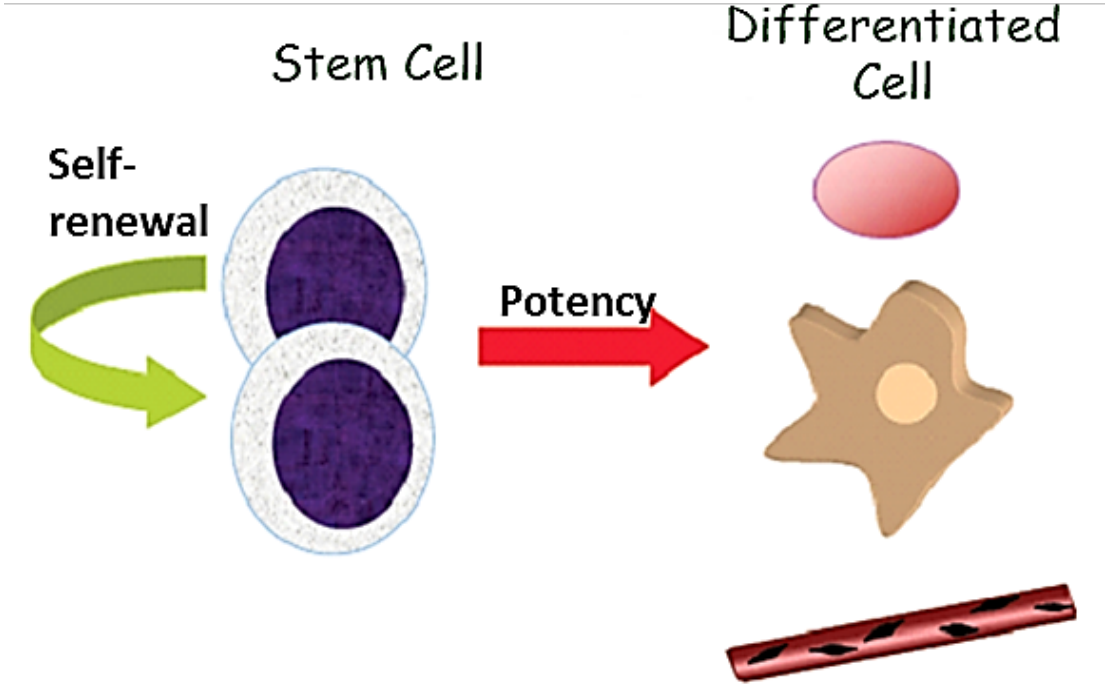
Applied science

Basic science

Generation of science → Translation of science (Animal models) → Translation of science (Clinical trials) → Application of science (e.g., Regenerative medicine And other services)

What is a stem cell?

Stem cells are generally characterized as cells with the potential for renewing themselves through cell division and the capacity to generate more specialized cells.



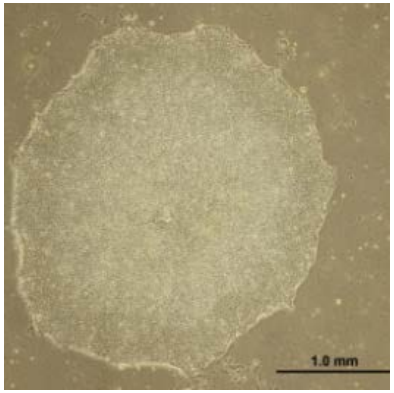
Sources of pluripotent stem cells

ICM isolation

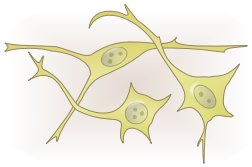
Directed differentiation

Transplantation

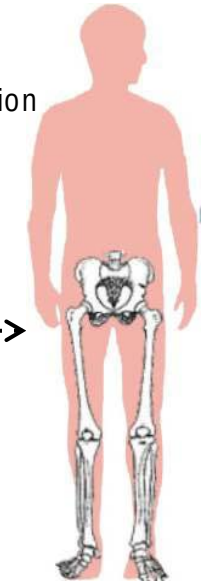
Preimplantation embryo



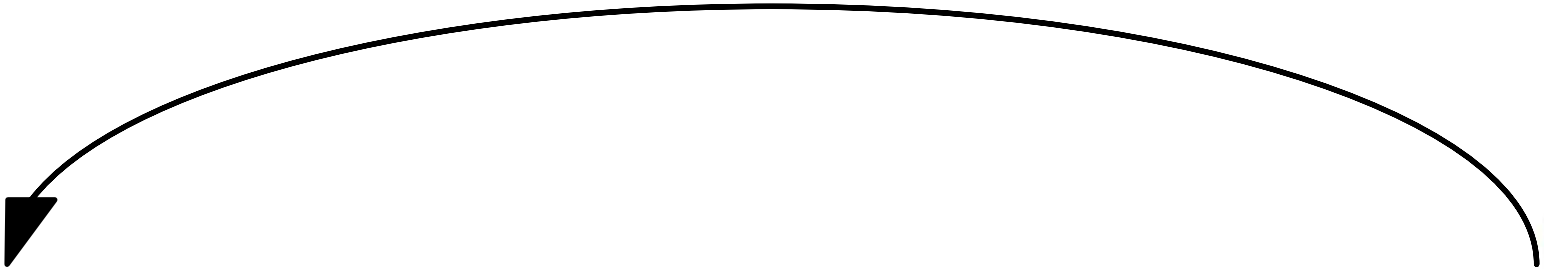
Embryonic stem (ES) cells



Neural lineage cells



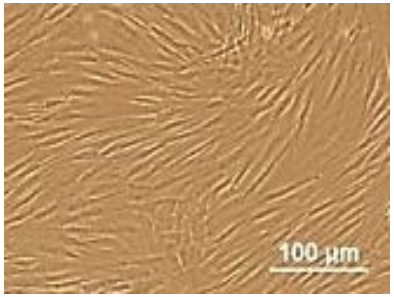
Sources of pluripotent stem cells



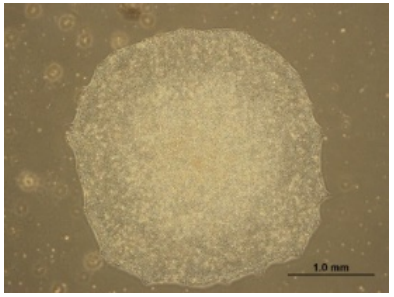
Pluripotent Reprogramming
by **Oct4, Sox2, Klf4, c-Myc**

Directed differentiation

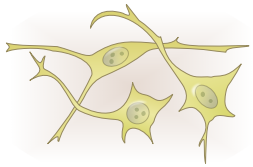
Transplantation



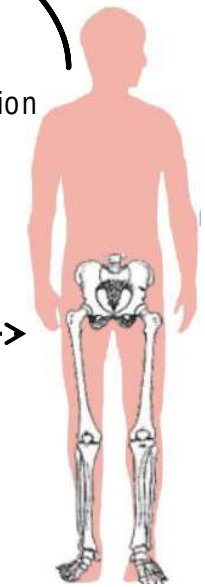
Somatic cells such as skin cells



Induced pluripotent stem (iPS) cells

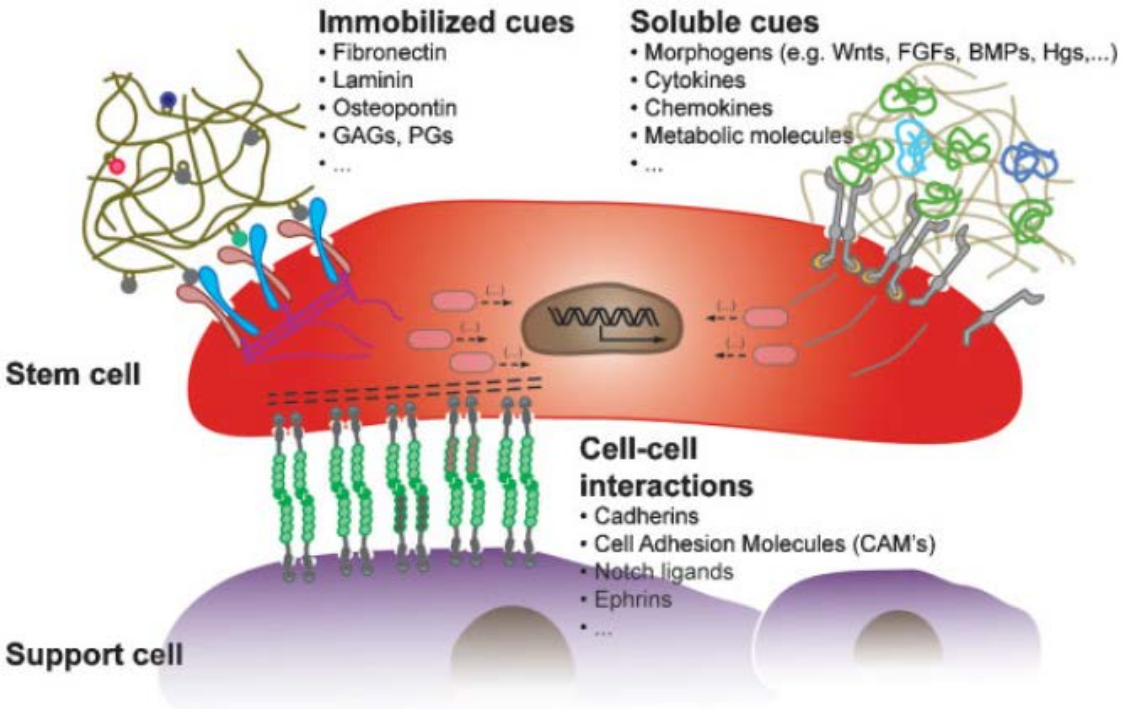


Neural lineage cells



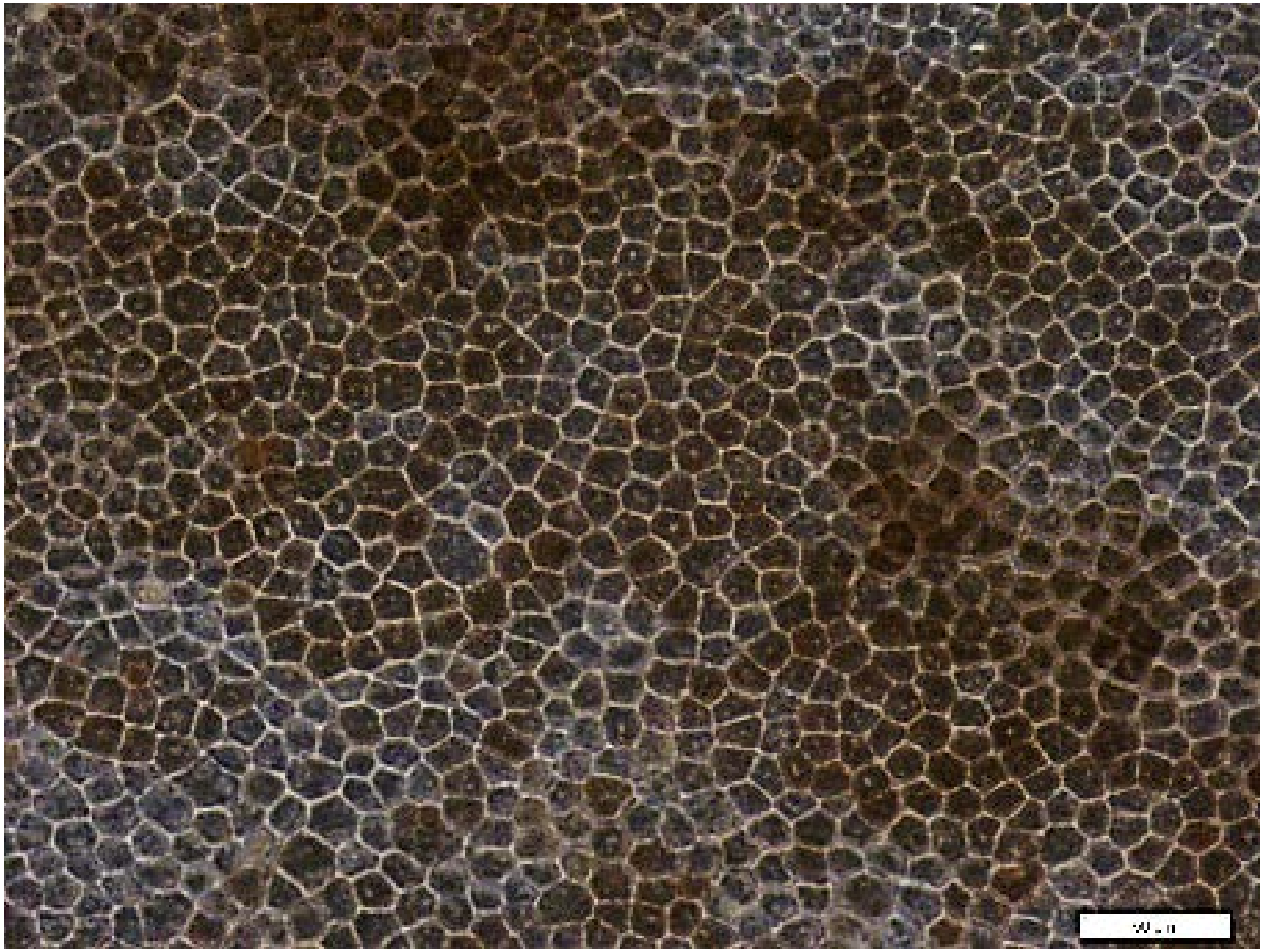
No place like home!

- **Niches:** house of stem cells
- Soluble and surface-bound
- Cell-ECM interactions
- Cell-cell interactions
- Mechanical forces
- Physicochemical cues
- Internal factors



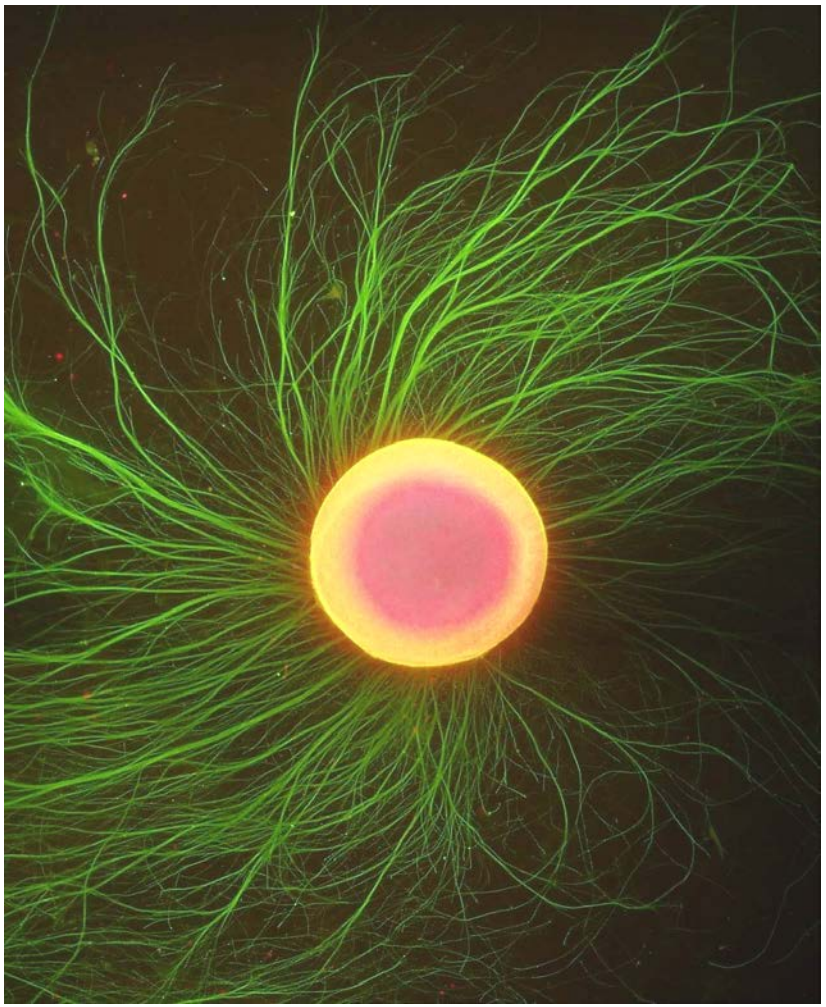
Lutolf et al. *Adv Mat* **2010**

Human pluripotent stem cell-derived Retinal pigment epithelium



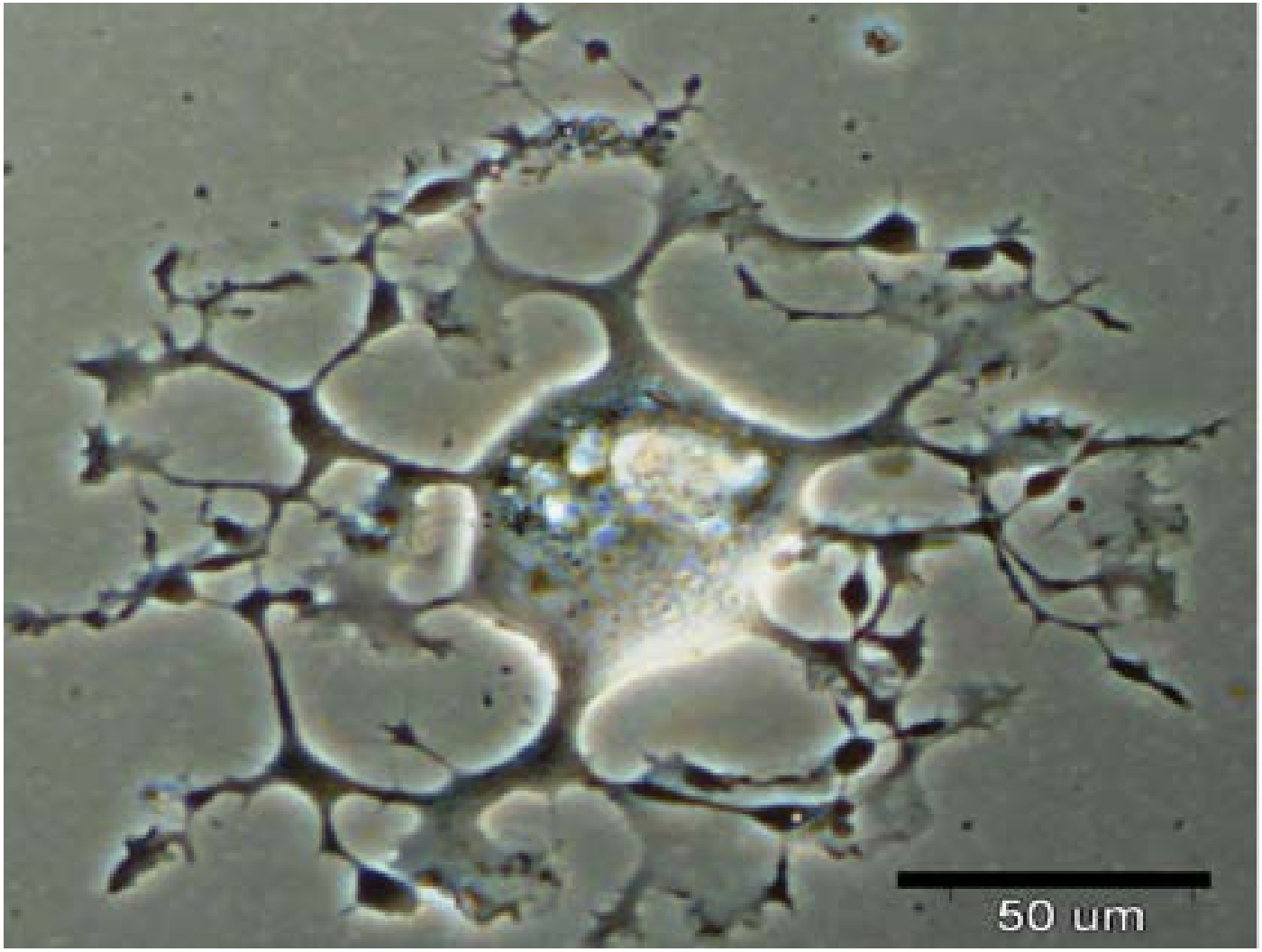
Zahabi et al., 2012, Stem Cells and Dev

Differentiation of hPSC into neuronal cells



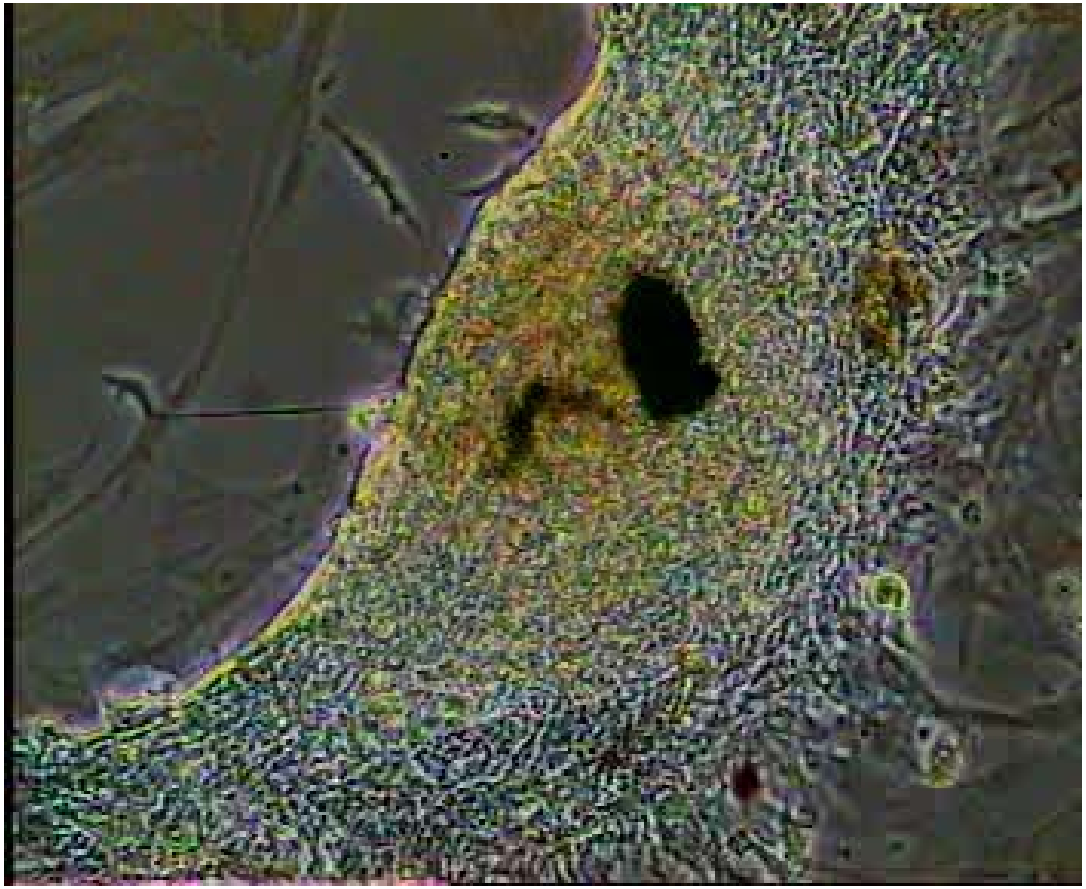
Baharvand et al., Int J Dev Biol. 2007

Differentiation of hPSCs into oligodendrocyte lineage



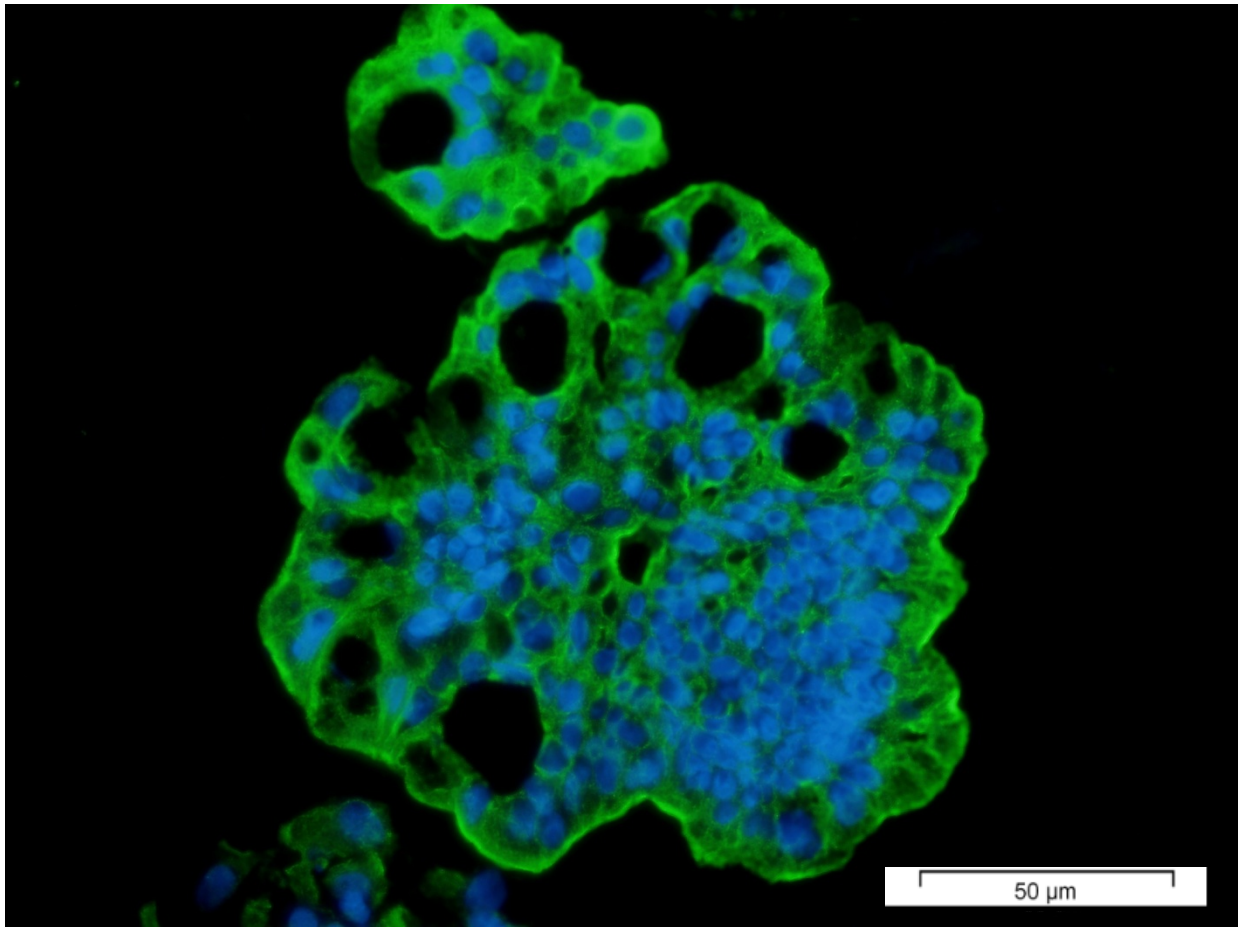
Pouya et al., PloS One, 2011

Human pluripotent stem cell-derived cardiomyocytes

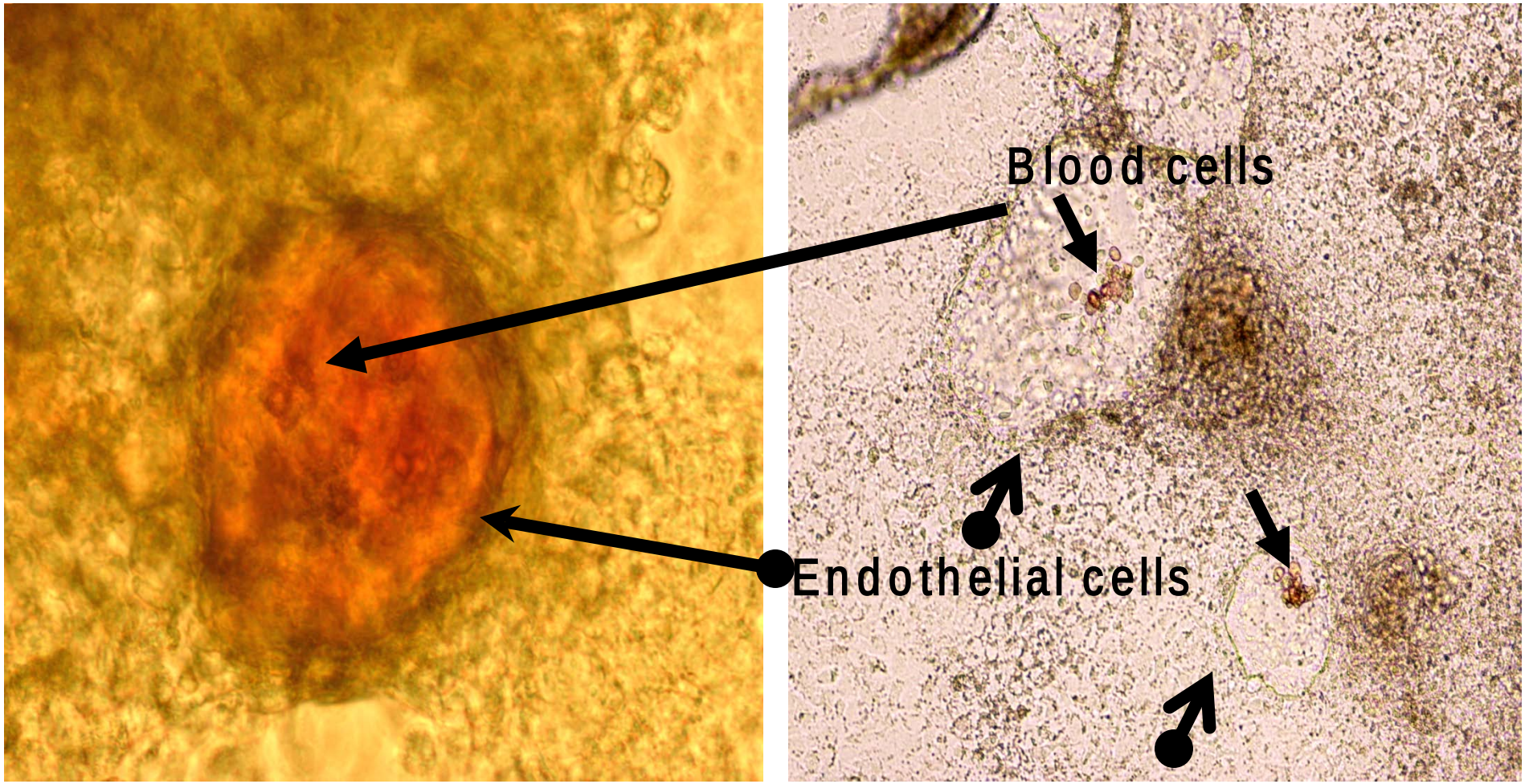


Baharvand et al., Differentiation, 2004

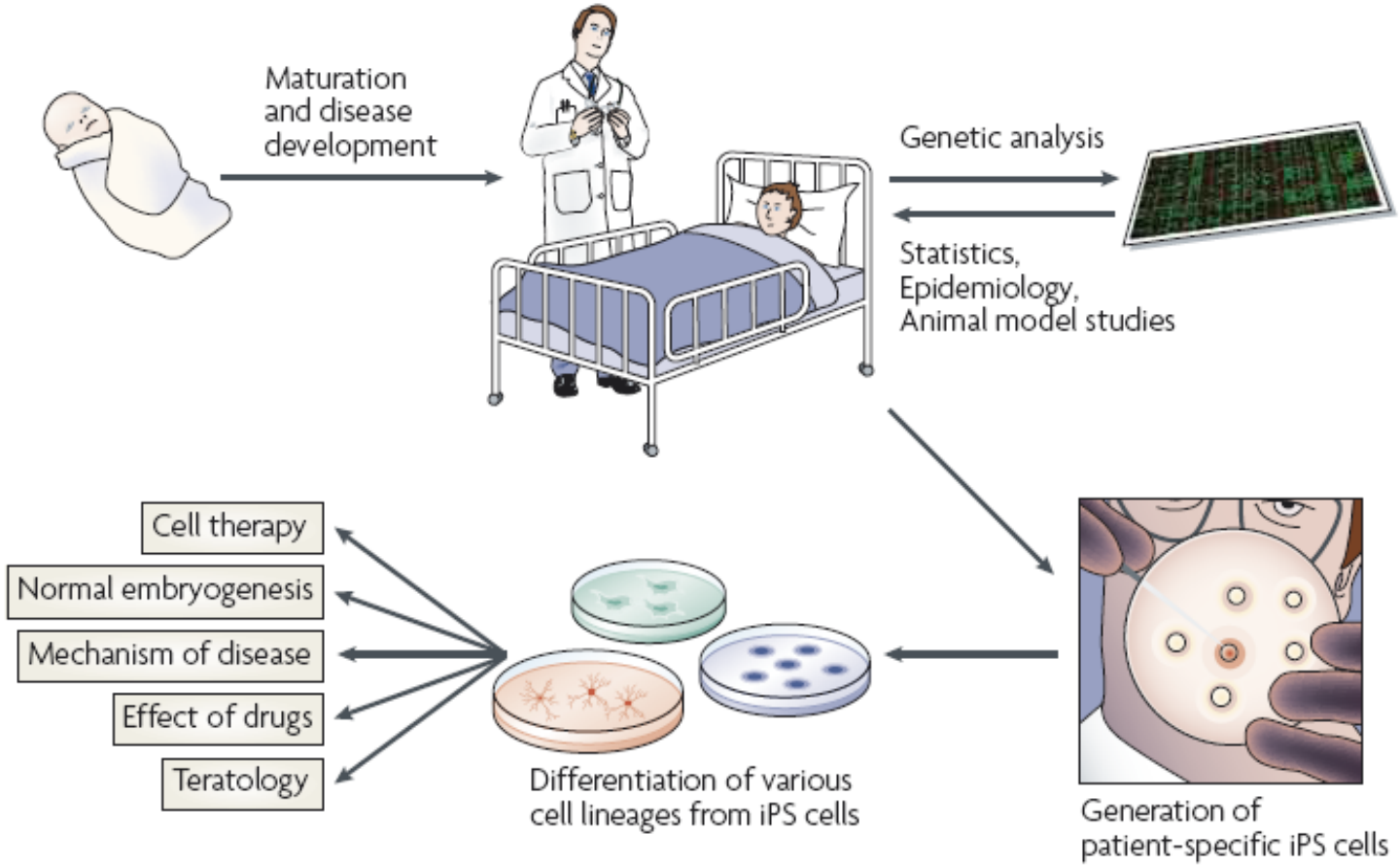
Differentiated Albumin positive cells



Blood cells and endothelial cells differentiated



Possible applications of pluripotent stem cells



Nishikawa *et al., Nature Biotech, 2008*

Transplantation of ESC-NPs Improves Cognitive Function in Alzheimerian Rats

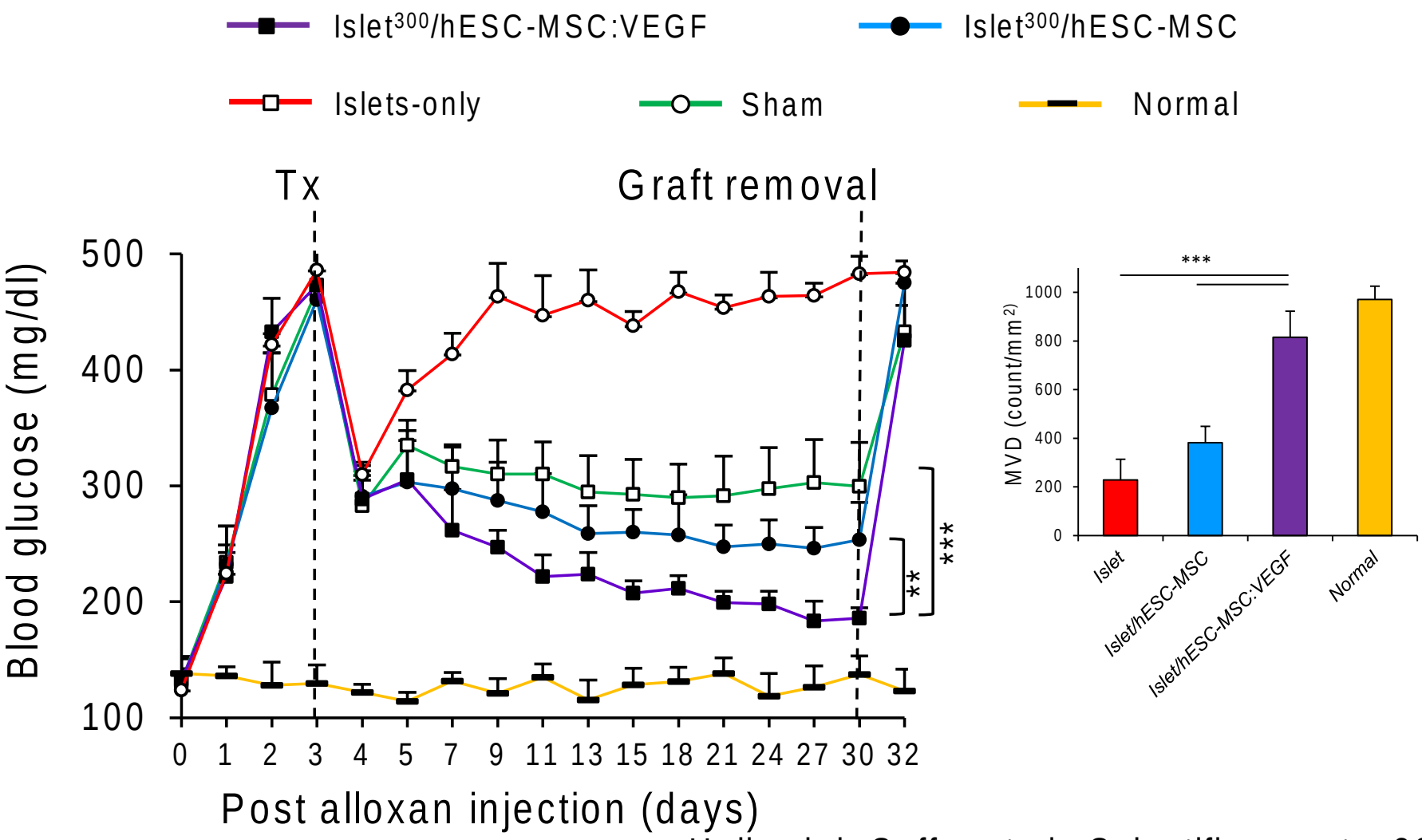
9s normal

39s nbM lesioned

22s PNPC transplanted

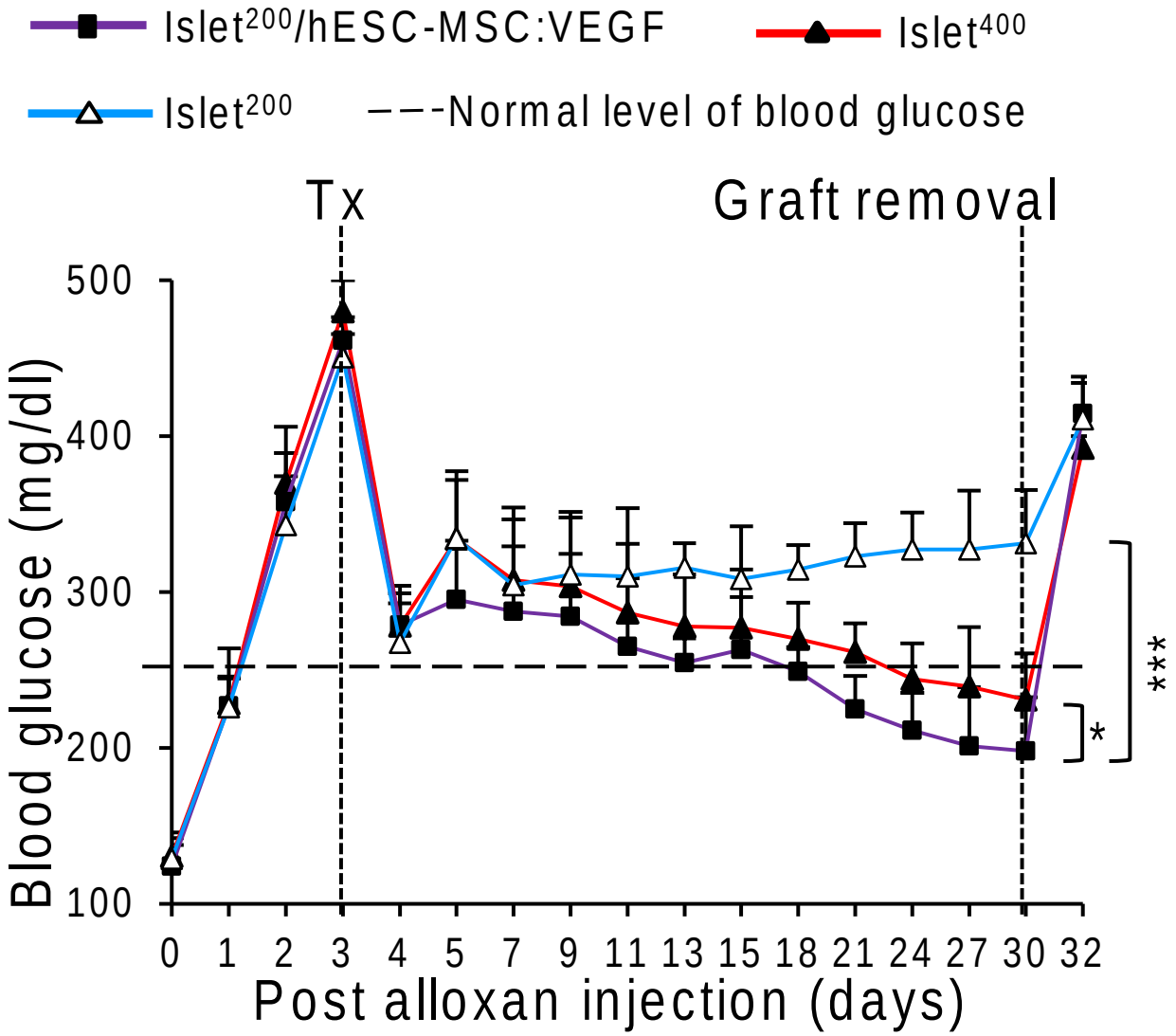
Moghadam et al., Differentiation, 2009

Inducible VEGF Expression by hESC-MSCs Reverses Diabetes



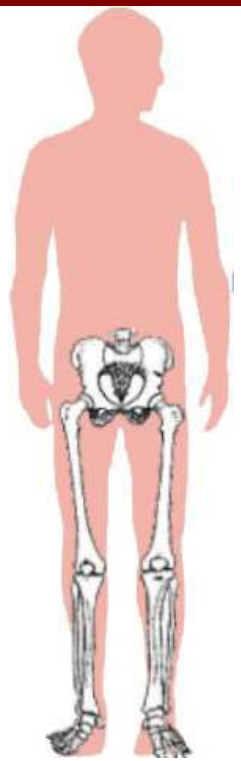
Hajizadeh-Saffar et al., Scientific reports, 2015

Inducible VEGF Expression by hESC-MSCs Reduces the Minimal Islet Mass Required to Reverse Diabetes

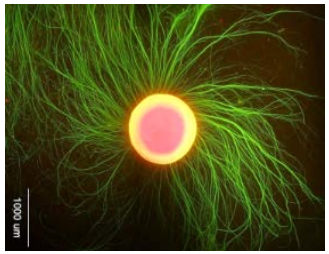


Hajizadeh-Saffar et al., Scientific reports, 2015

Could transcription factors directly induce other defined somatic cell fates without going back to, or through, a pluripotent stage?

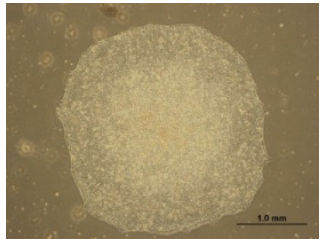


Desired cells

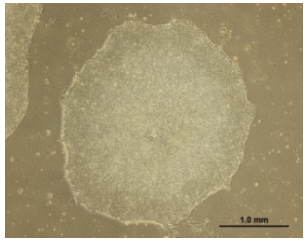


Directed differentiation

Programming



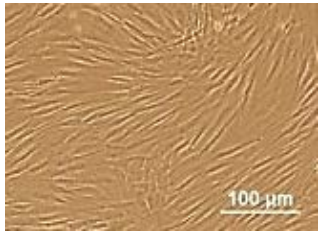
Induced pluripotent stem cells



Embryonic stem cells

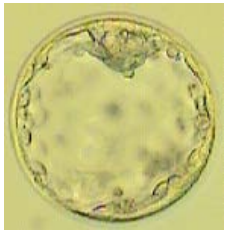
Directed reprograming

The Alchemy of biology



Somatic cells such as skin cells

Pluripotent Reprogramming



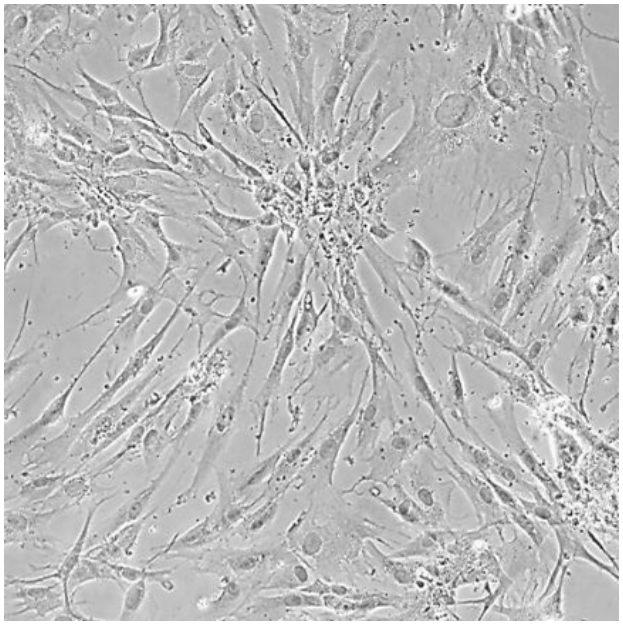
Preimplantation embryo

Transdifferentiation/ lineage reprograming: Direct fate switching from one somatic mature cell type to another functional mature or progenitor cell type without first undergoing reprogramming into or through a pluripotent intermediate.

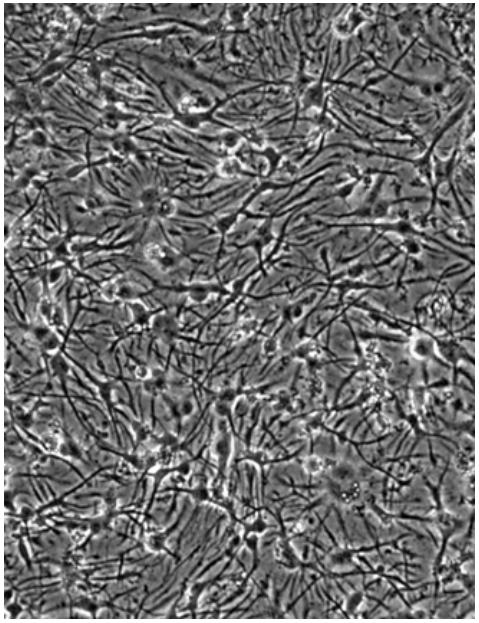
Pournasr et al., Stem Cells, 2011

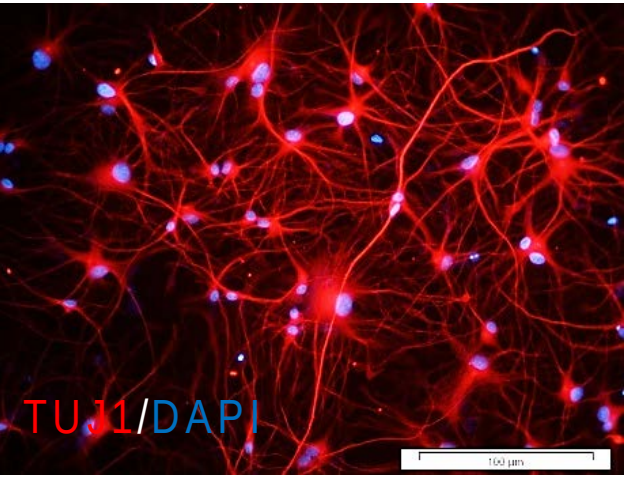
Transdifferentiation of human fibroblasts to Neural Stem

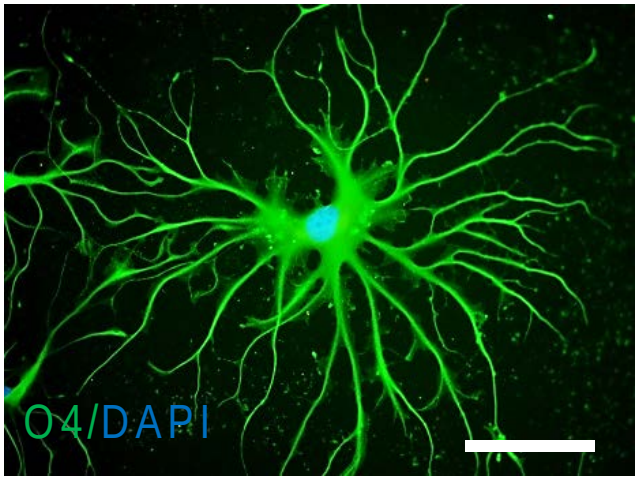
Fibroblasts

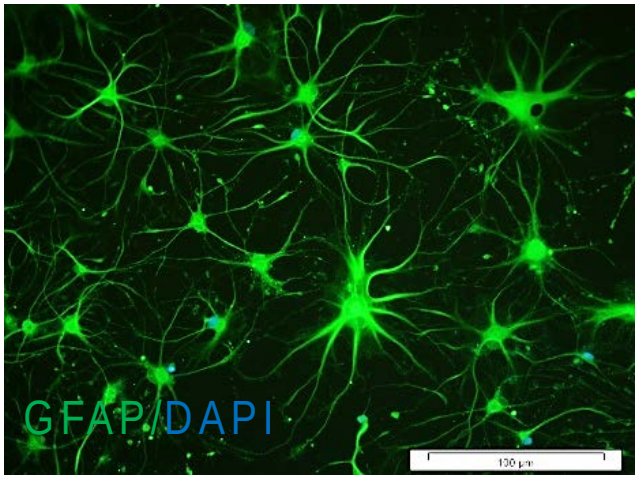


Neural stem cells

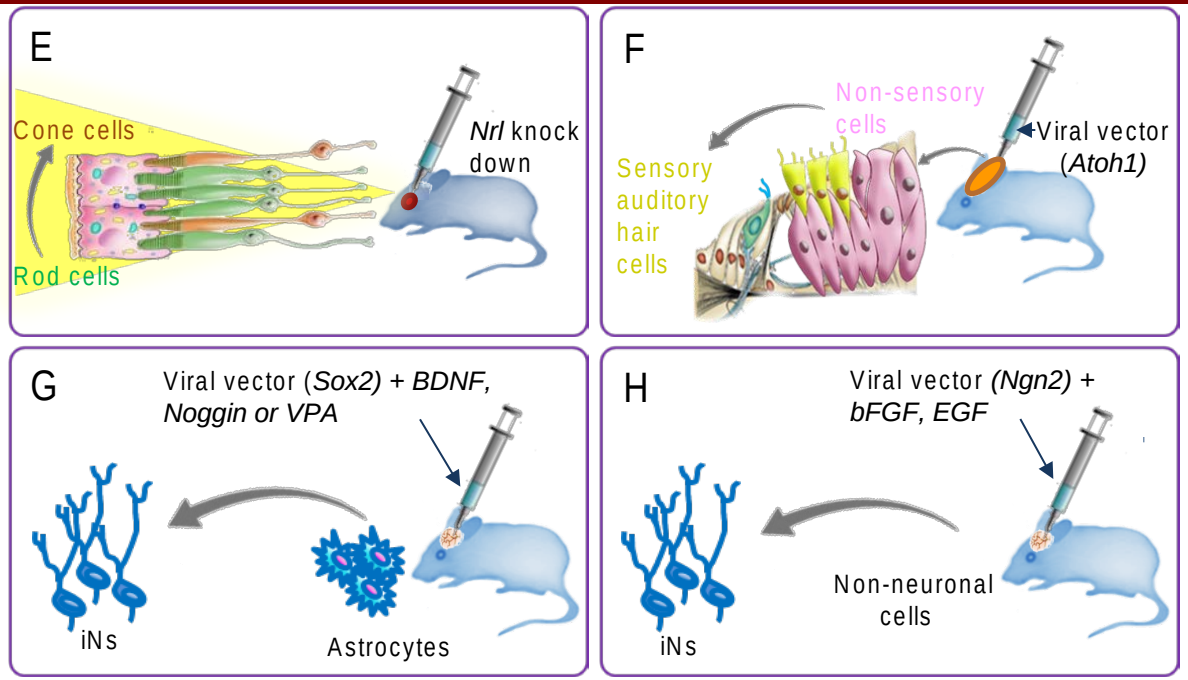








Schematic illustration of lineage conversion in vivo



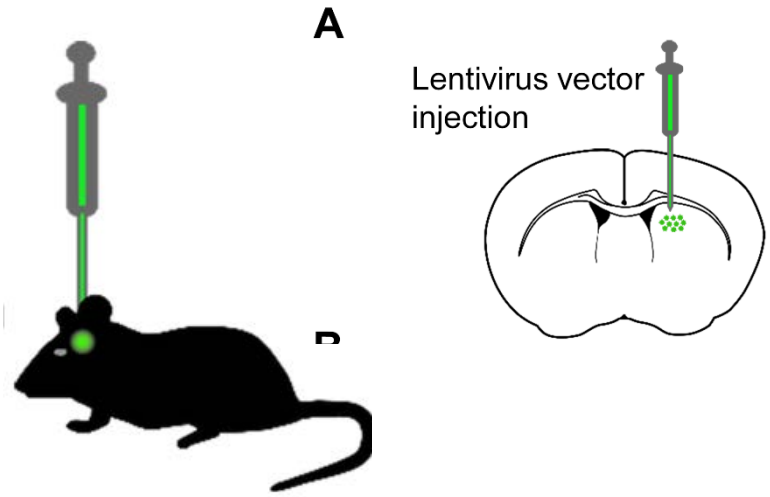
The proof of principle for therapeutic application of transdifferentiation has been established by treating diseases in animal models.

For example, transplantation of inner ear hair cells converted from nonsensory cells by ***Atoh1 (Math1)***, in deaf animals substantially improves hearing thresholds (Izumikawa et al. Nat Med 2005).

Mirakhori et al., J Cell Physiol. 2014

In vivo reprogramming: Conversion of Astrocytes to neuronal cells

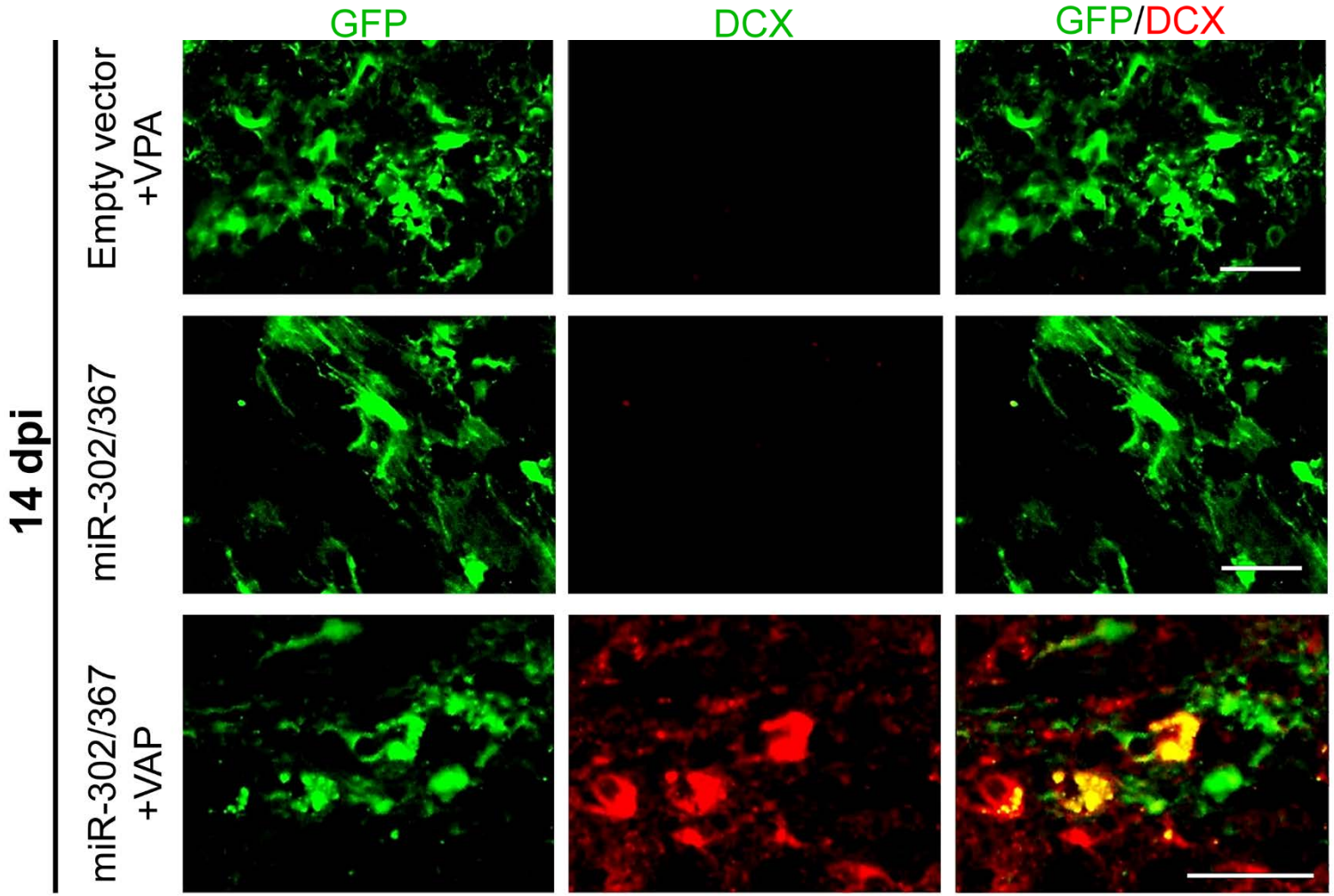
•The conversion of astrocytes to neuroblasts holds great promise for treatment of neurodegenerative and traumatic brain diseases.



Administration of GFP and miR-302/367 expressing lentiviral particles into the striatum

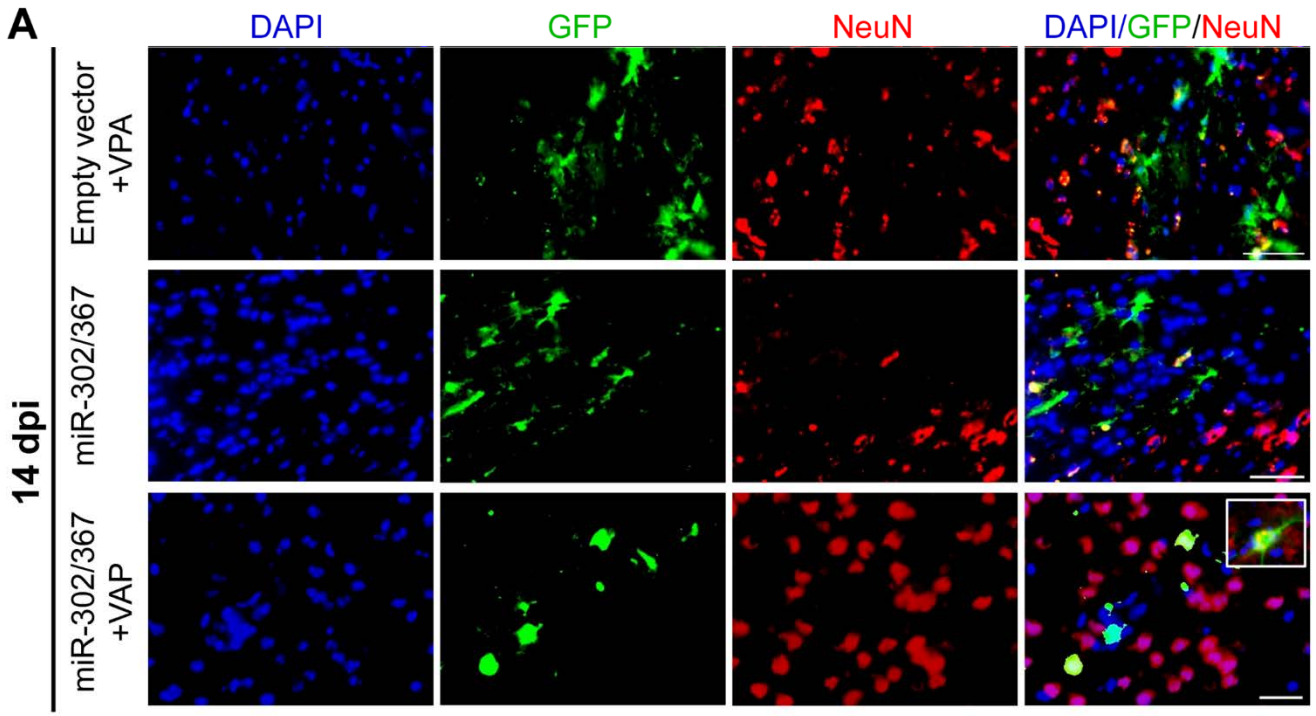
Ghasemi et al., Plos One. 2015

miR-302/367 and valproic acid converted the transducted cells into neuroblasts

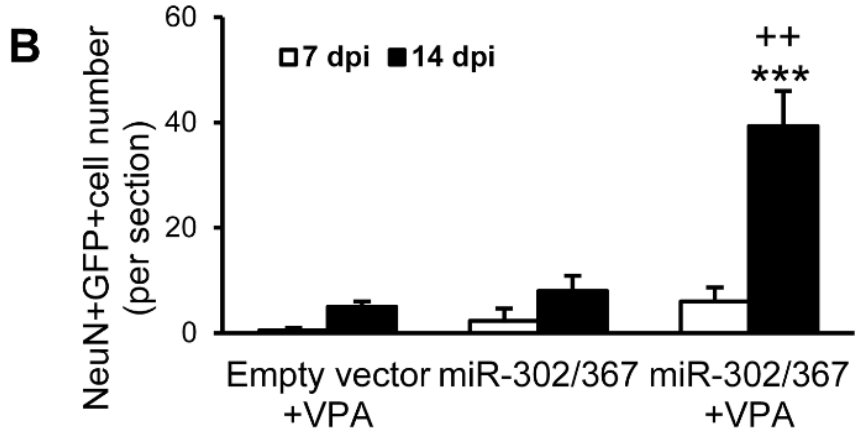


Doublecortin (DCX^+) cells were detected at 14 (dpi) in animals pre-treated with VPA that afterwards received miR-302/367. n=3 mice per group. Scale bar: 30 µm.

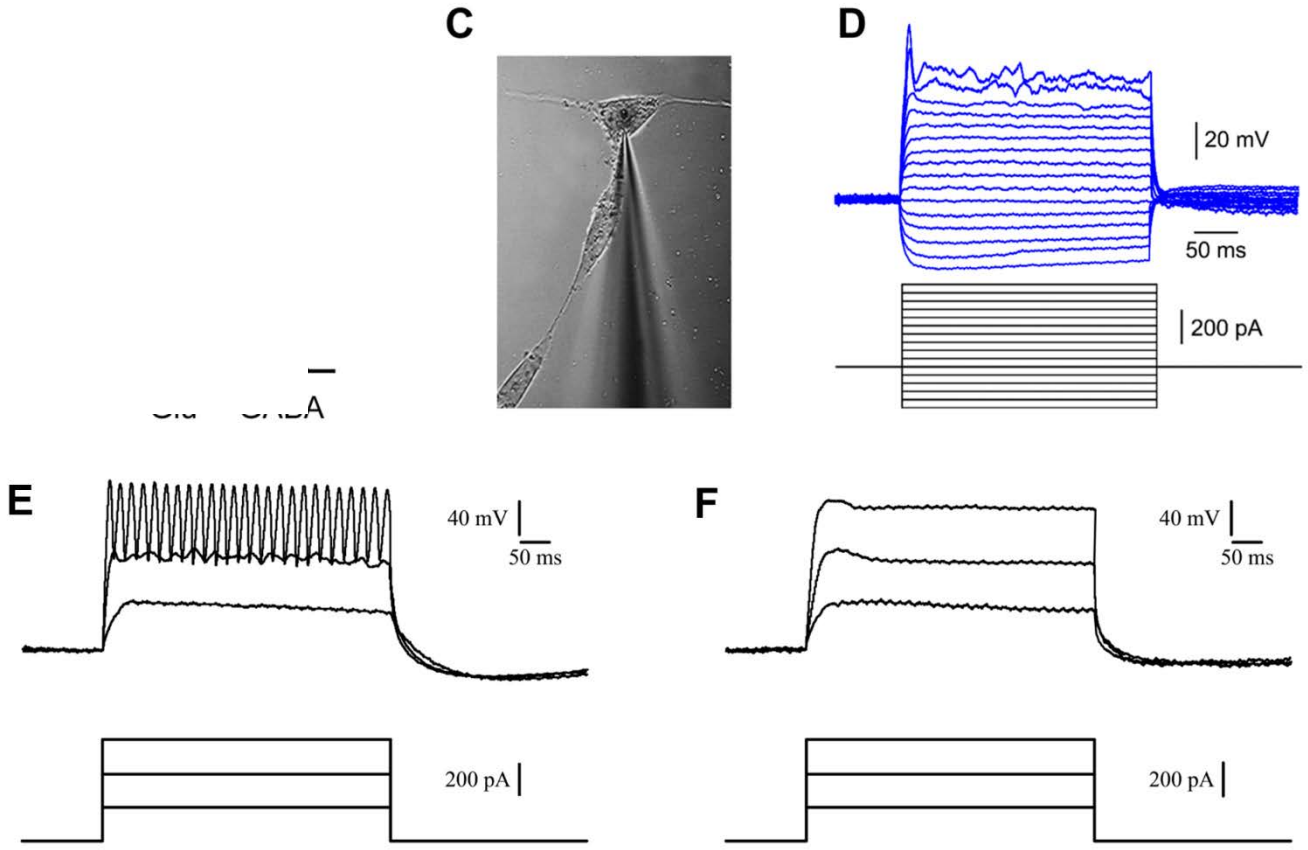
In vivo reprogramming: Conversion of mouse Astrocytes to neuronal fate



Scale bar: 50 μm.



Induced neurons showed mature neuronal properties at six and ten weeks after transduction in vitro



(C and D) Whole cell patch clamp recording from induced neuron-like cells at six weeks post-transduction (n=25) showed single action potential-like spikes. **(E)** Similar recording at ten weeks post-transduction (n=10) showed repetitive spike firing. **(F)** Treatment with 1 µM TTX as sodium channel blocker, inhibited spike firing. **p< 0.01.

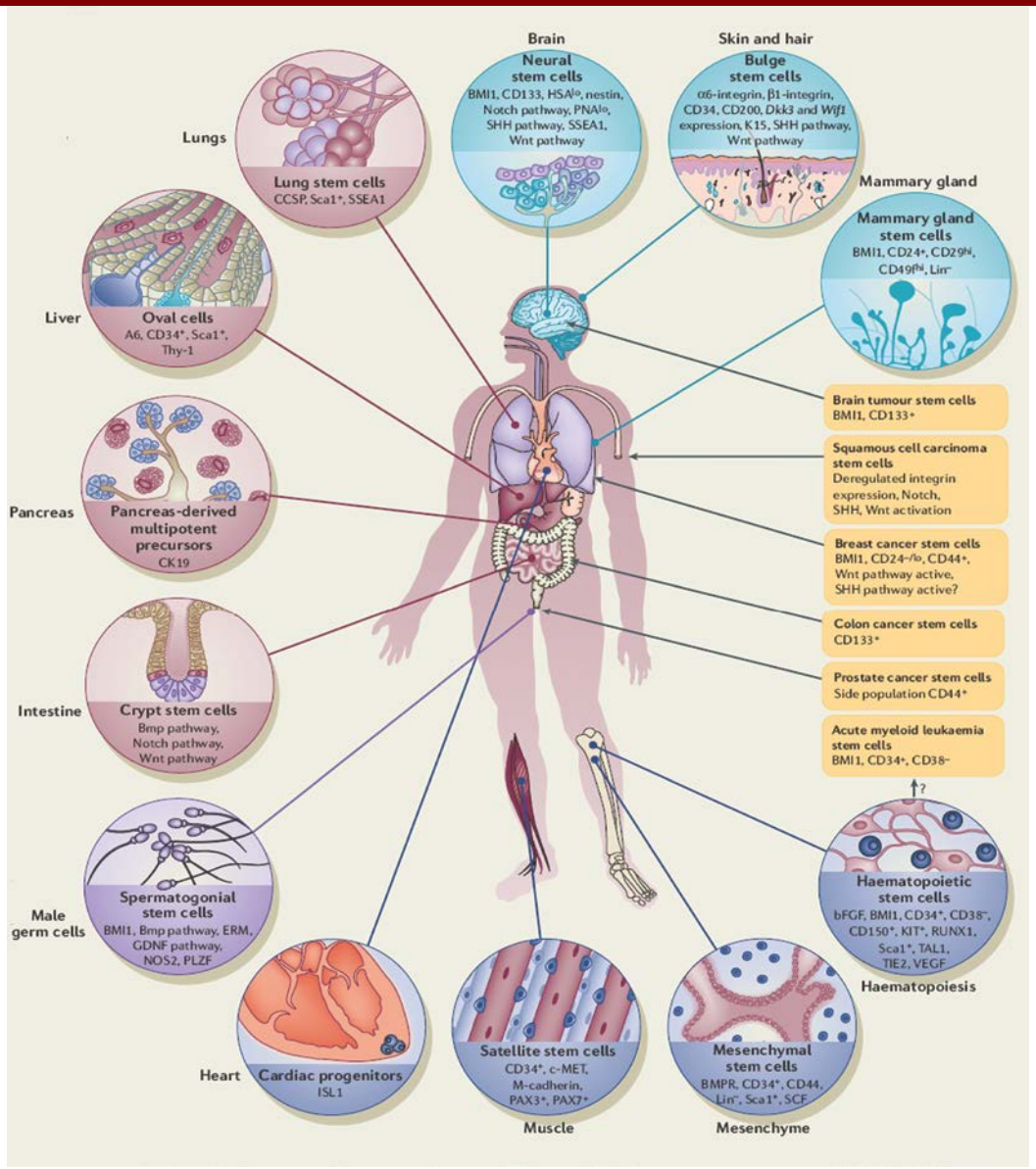
Human clinical trials using human pluripotent stem cells

- There are now 11 approved trials involving pluripotent stem cell-based therapies on the clinical trials website, (www.clinicaltrials.gov), and nine for ocular indications (eight from hESCs, one from induced pluripotent stem cell (iPSCs), one for diabetes and one for severe heart failure.

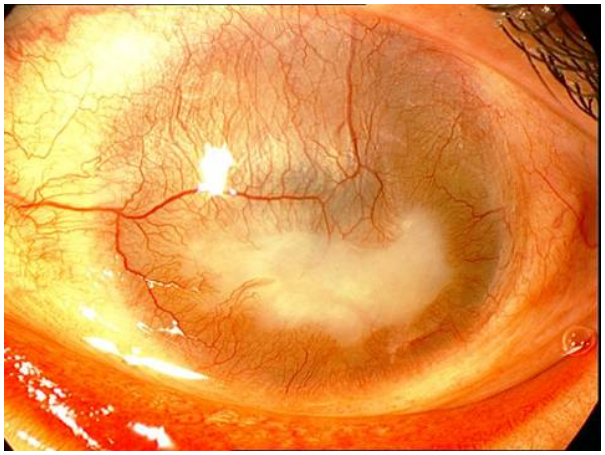
- This is not surprising since, compared with other organs and tissues, the eye is particularly well suited for first-in-man cellular therapies. It is a relatively immunoprivileged site, allowing non-HLA matched cells to be injected into patients'eyes with reduced risk of immune rejection and providing an isolated environment for containment of injected cells, thus limiting the potential area in which cells may travel or form tumors.

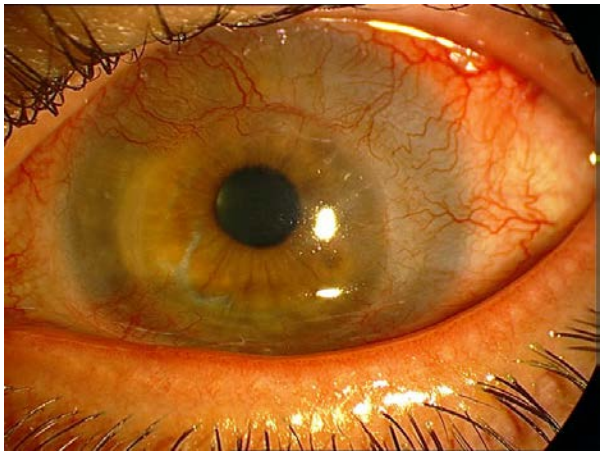
Schwartz et al., Lancet. 2015
Schwartz et al., Lancet. 2012

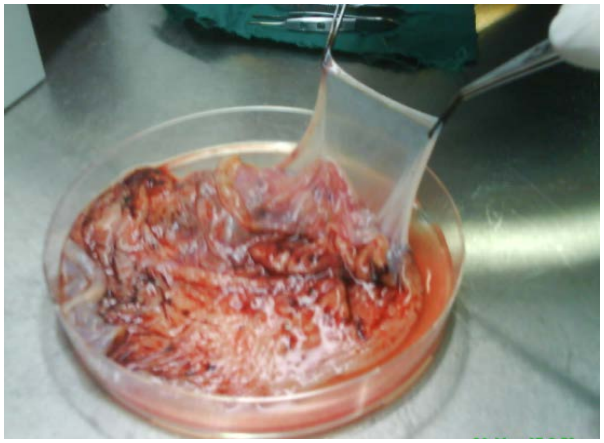
Tissue-specific stem cells

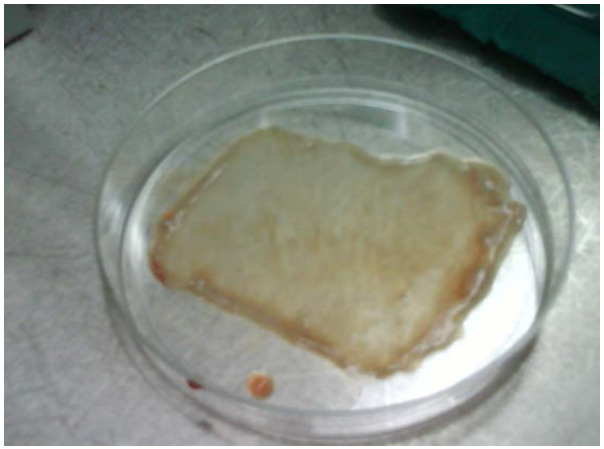


Limbal stem cell transplantation





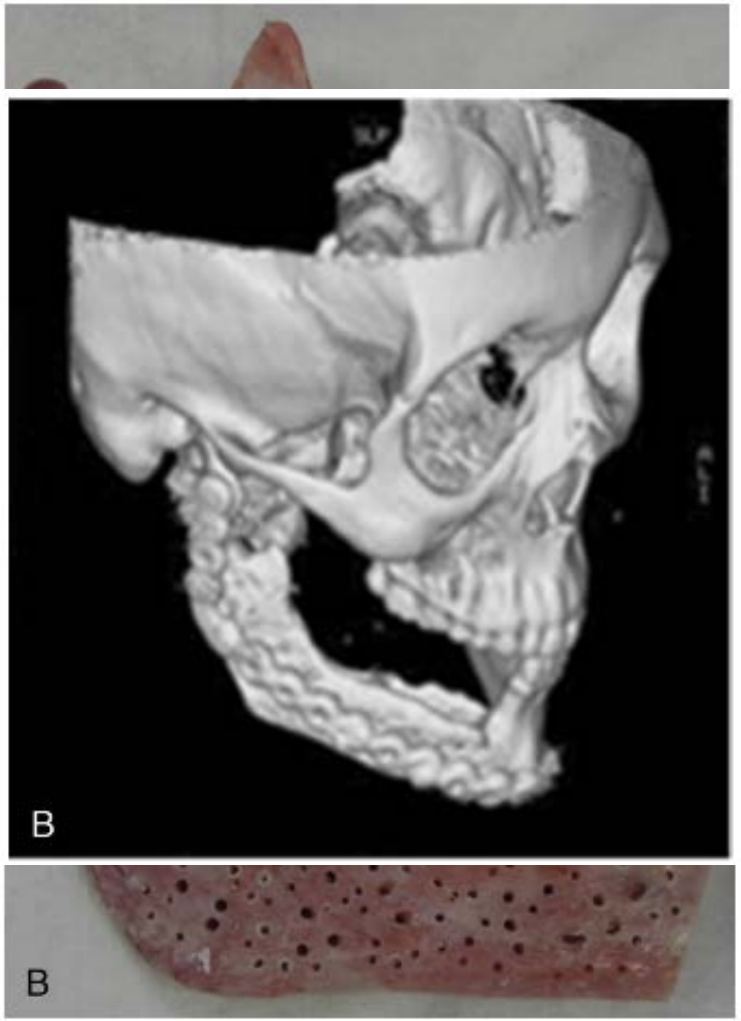




Baradaran et al., Cornea, 2010, Labafinejad hospital

Repigmentation by cell transplantation

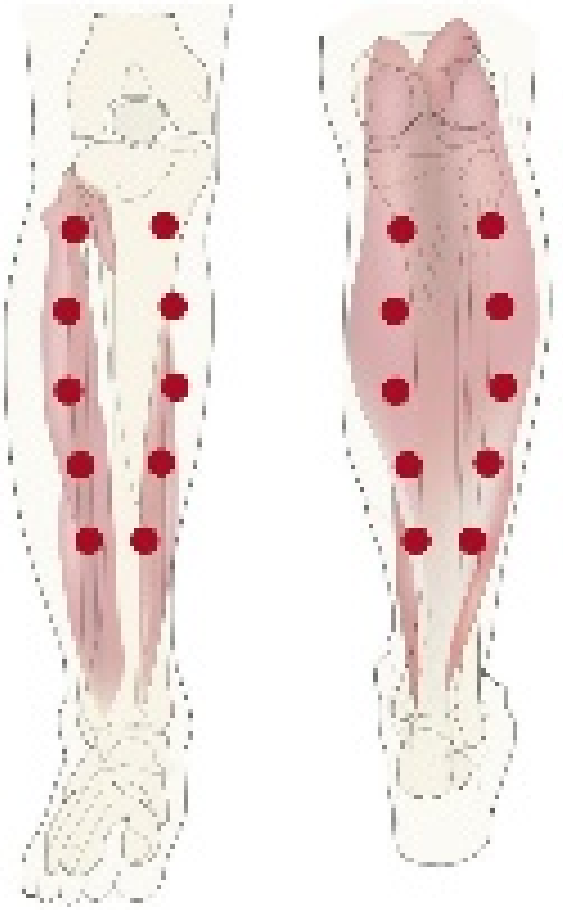
Reconstruction of human mandibular continuity defects with allogenic scaffold and autologous marrow mesenchymal stem cells

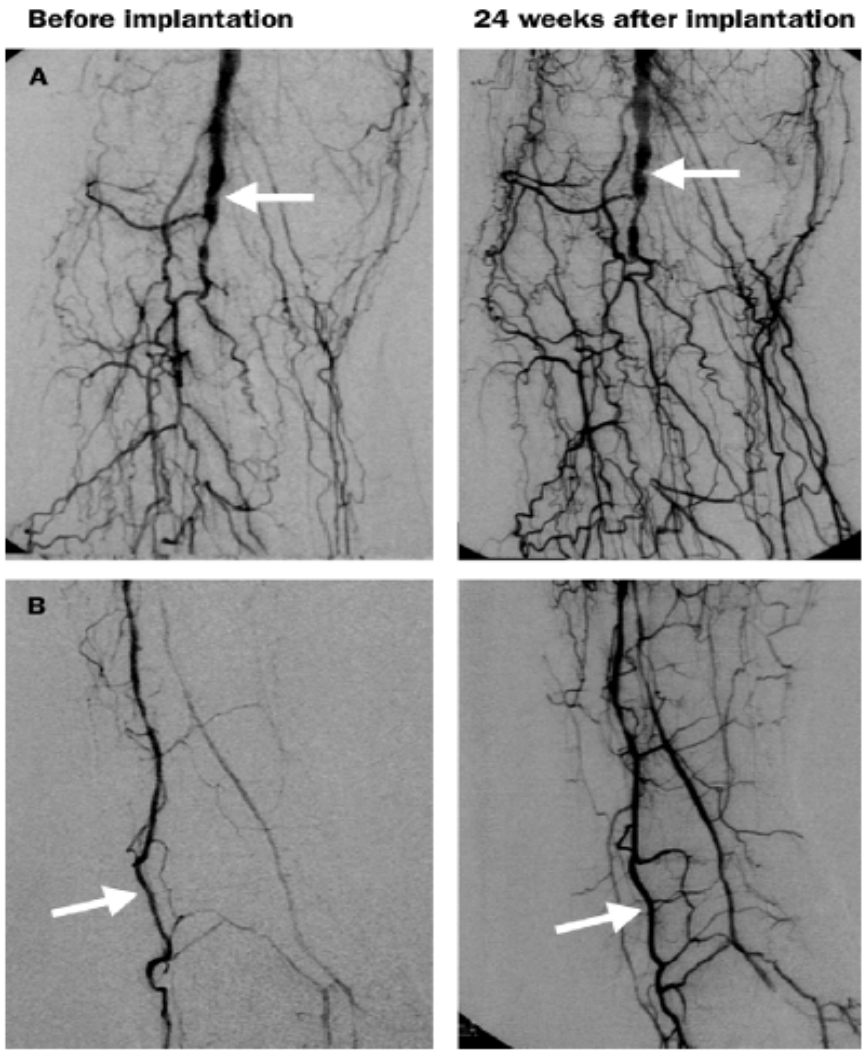


A, Preoperative spiral CT scan of mandibular continuity defect that is bridged with a reconstruction plate. B, Postoperative spiral CT scan showing normal bone healing and osteointegration to the adjacent host bone after reconstruction with MSCs reinforced allograft.

Zamiri et al., J Craniofac Surg. 2013
Shiraz university of Medical Sciences

Transplantation of MNCs in patients with advanced lower limb ischemia



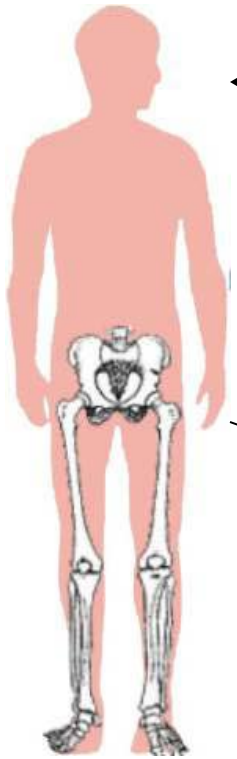


Zafarghandi et al., Cytotherapy, 2010, Tehran University of Medical Science, Sina Hospital

Limb salvage after autologous BM-MNC therapy

Zafarghandi et al., Cytotherapy, 2010, Tehran University of Medical Science, Sina Hospital

How to produce large scale of transplanting NSCs/NPCs?

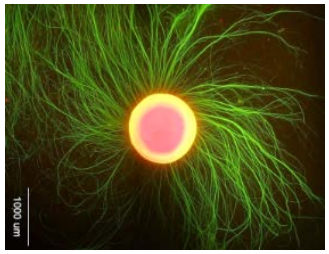


Scale up culture

Translational medicine

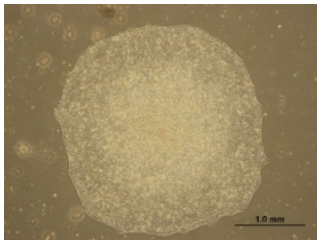
Transplantation

Desired cells

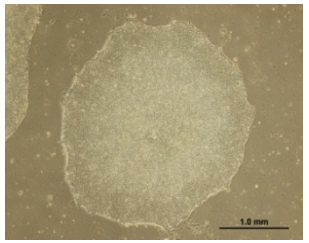


Directed differentiation

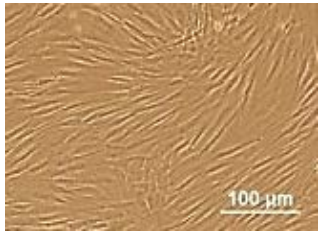
Programming



Induced pluripotent stem cells



Embryonic stem cells



Somatic cells such as skin cells

Pluripotent Reprogramming

Preimplantation embryo

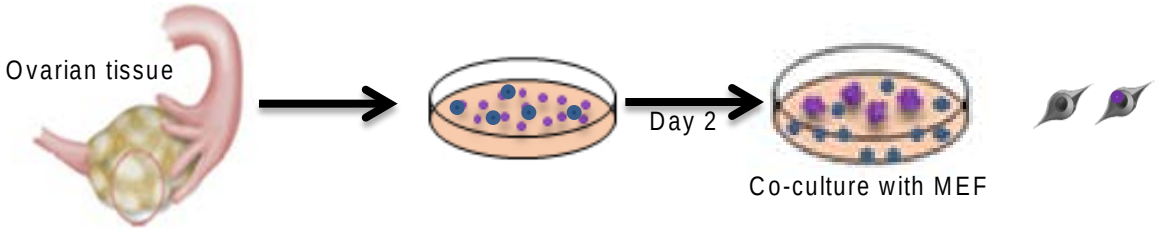
Cell engineering

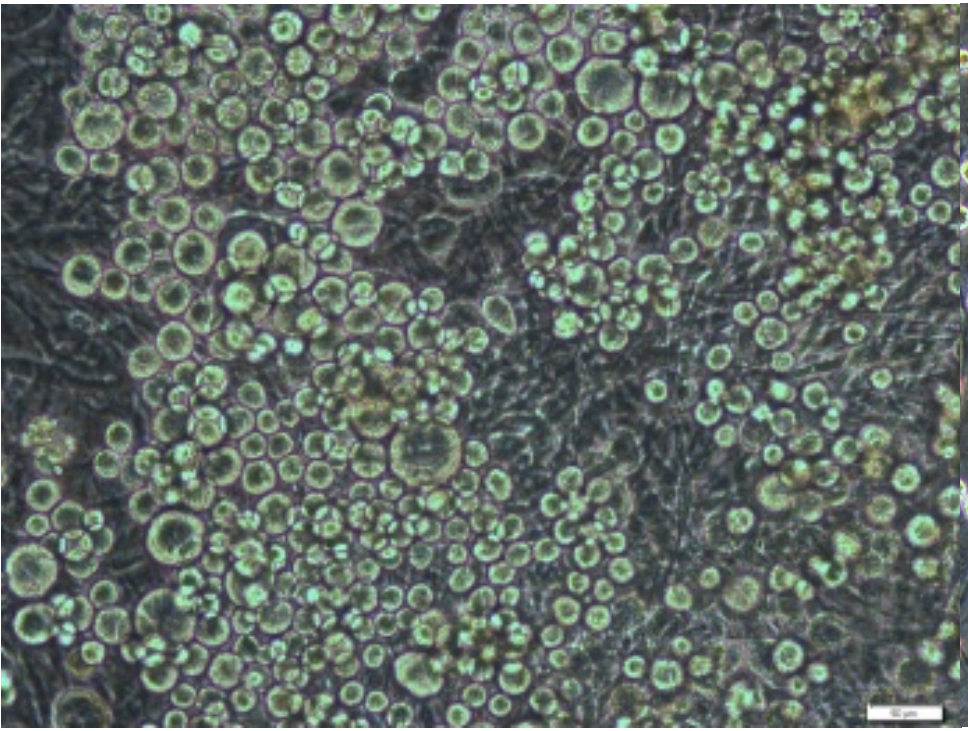
Cell engineering: Scale up culture

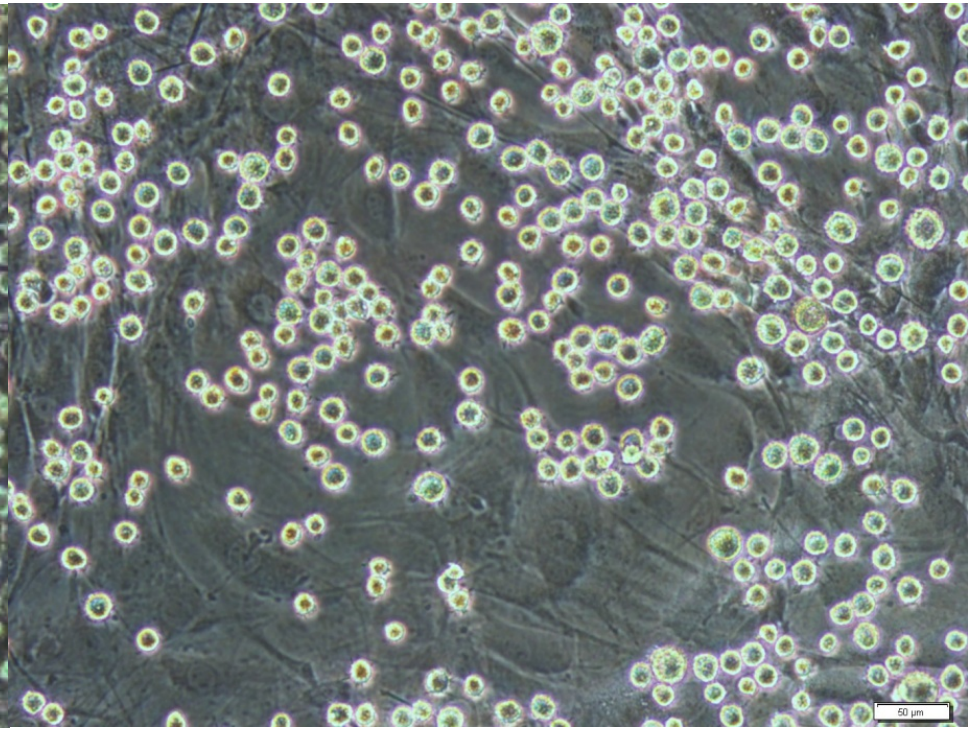
"The two communities—biologists and engineers—have been disconnected for a very long time but are now starting to effectively communicate in order to establish an entirely new interdisciplinary field of stem cell bioengineering."

Gordana Vunjak-Novakovic et al. *Cell Stem Cell* **2011**

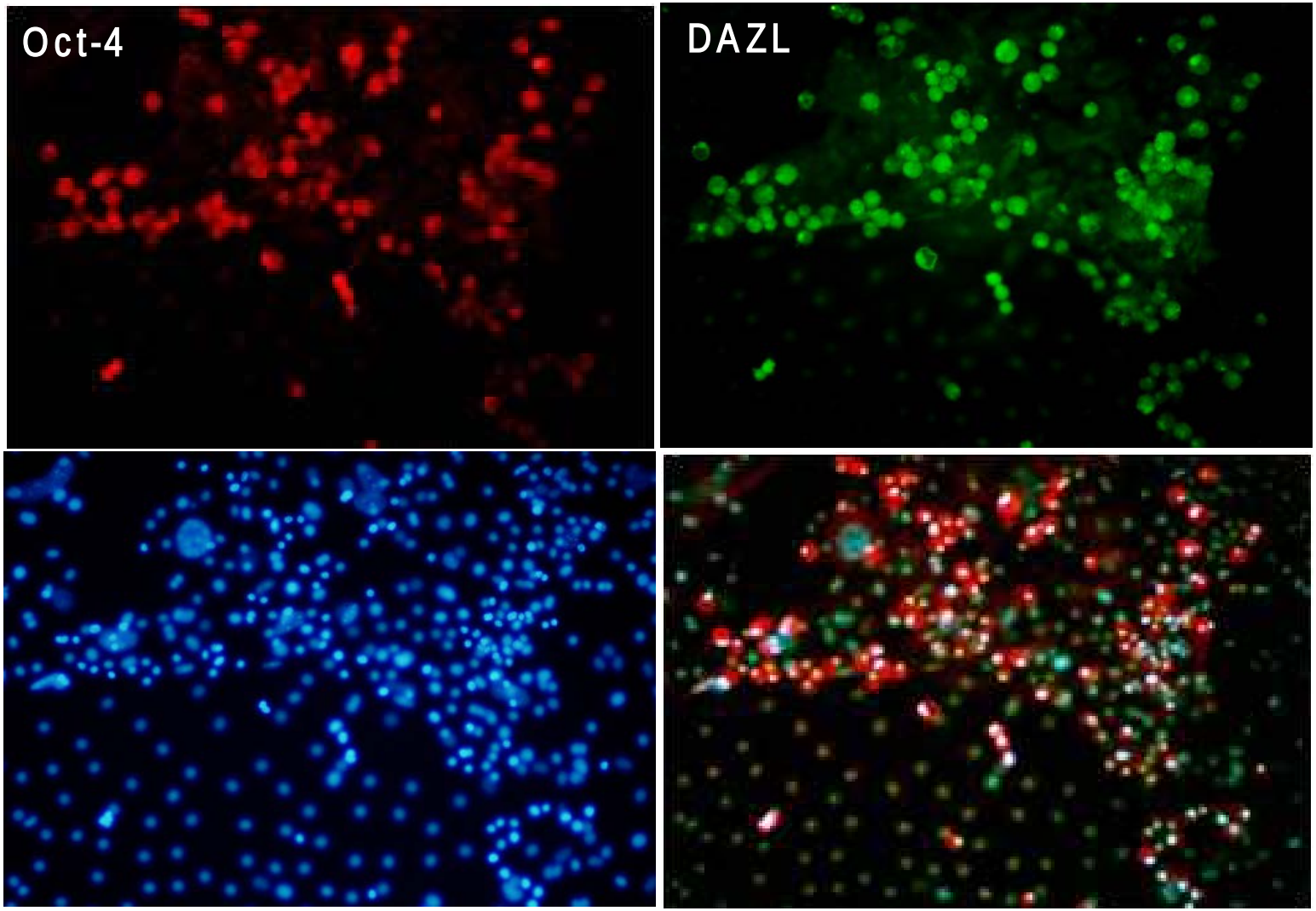
Oogonial stem cells







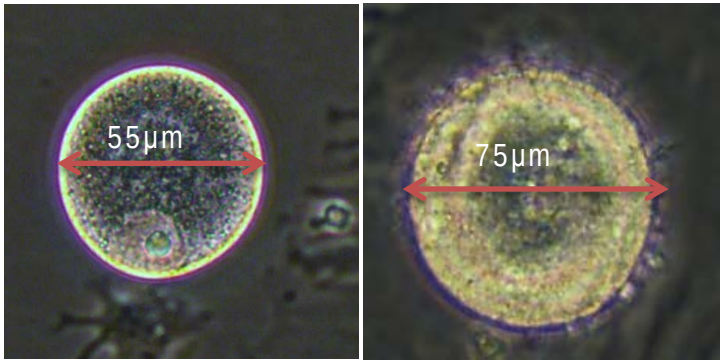
Oogonial stem cells



Saberi et al., Unpublished data

Oogonial stem cells

A



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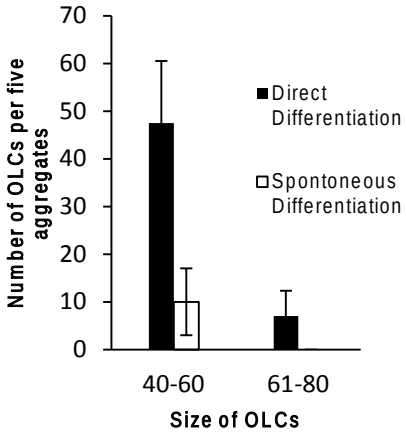

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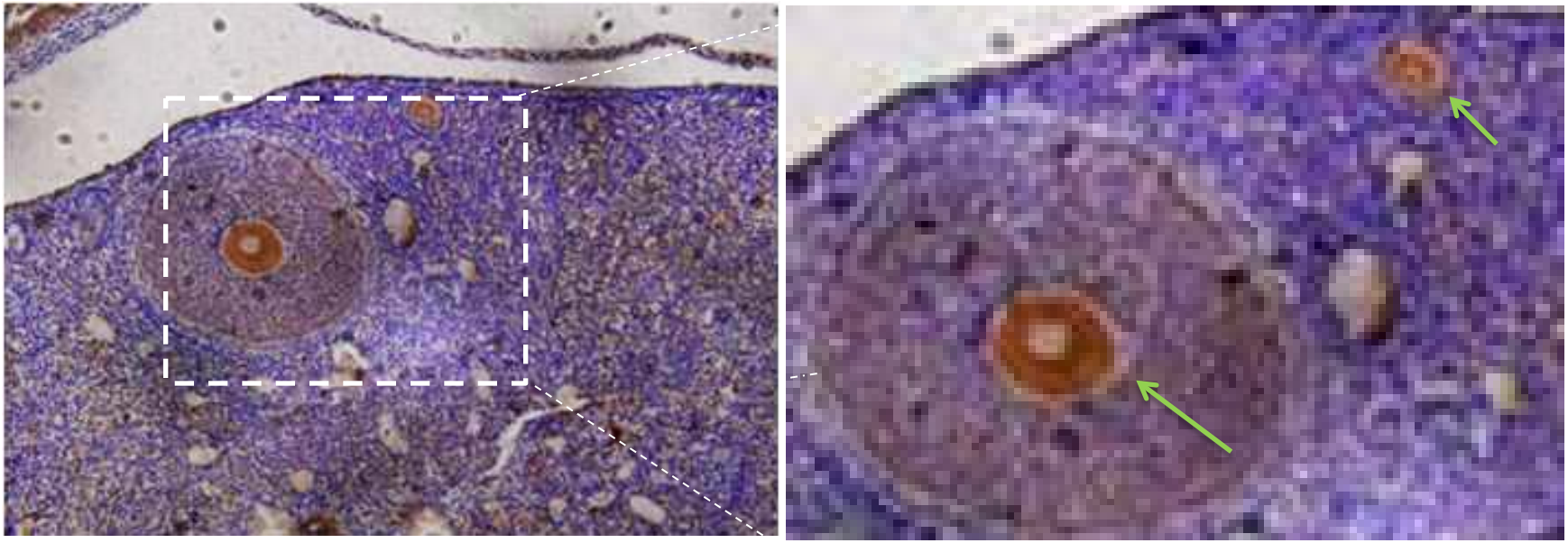
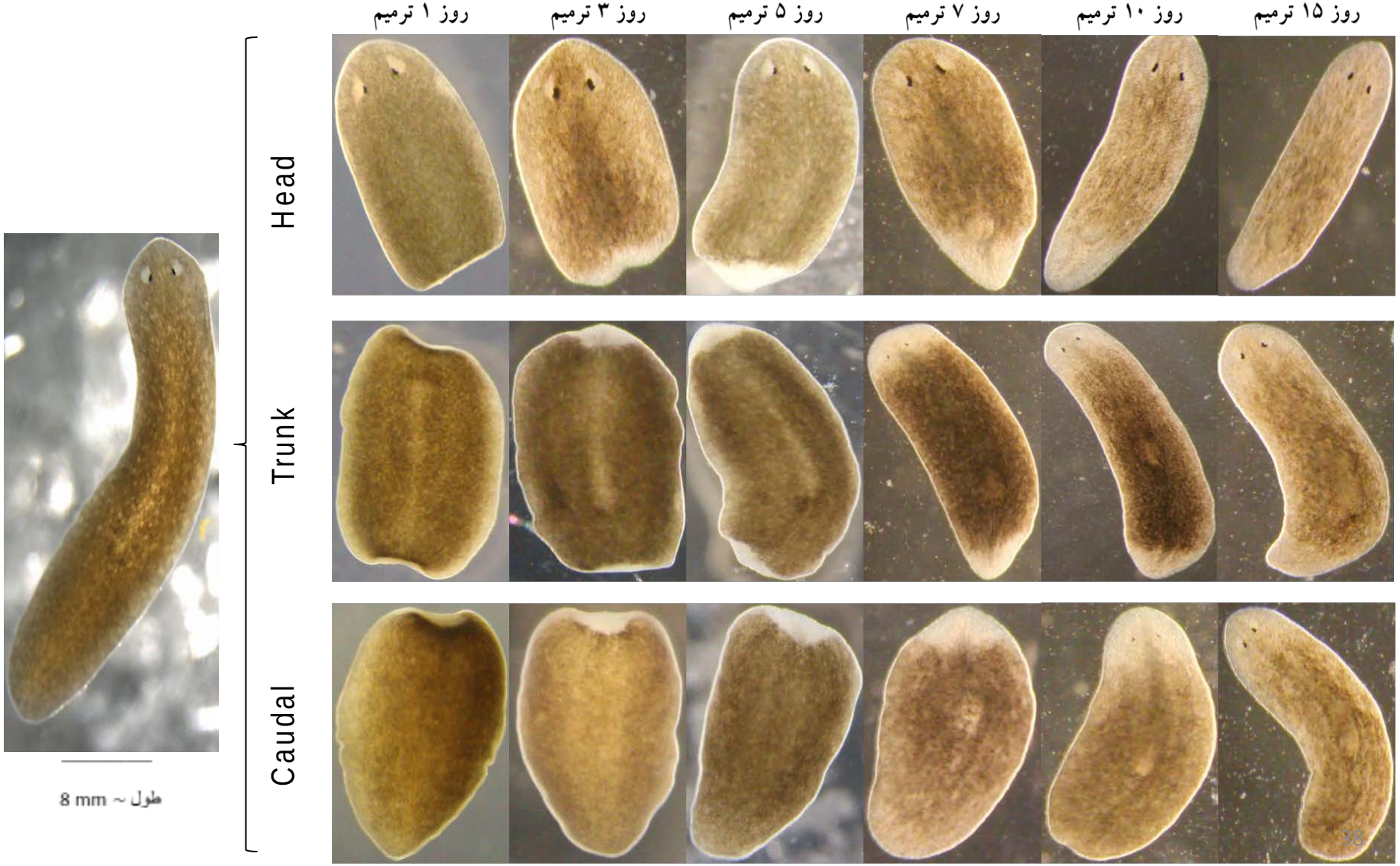


Saberi et al., Unpublished data

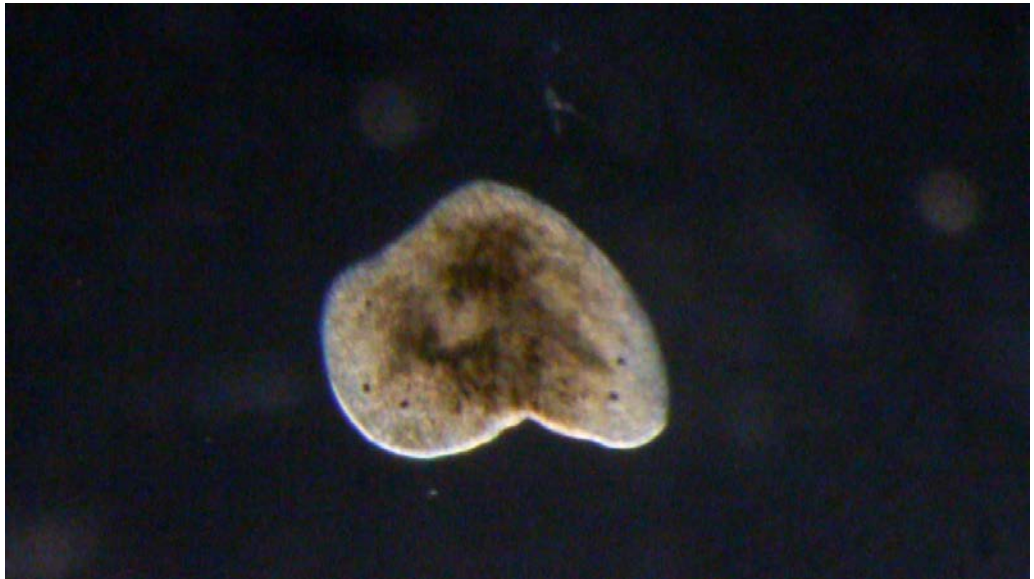
Planaria: King of Regenerative biology

ROYAN



Regeneration in Planaria

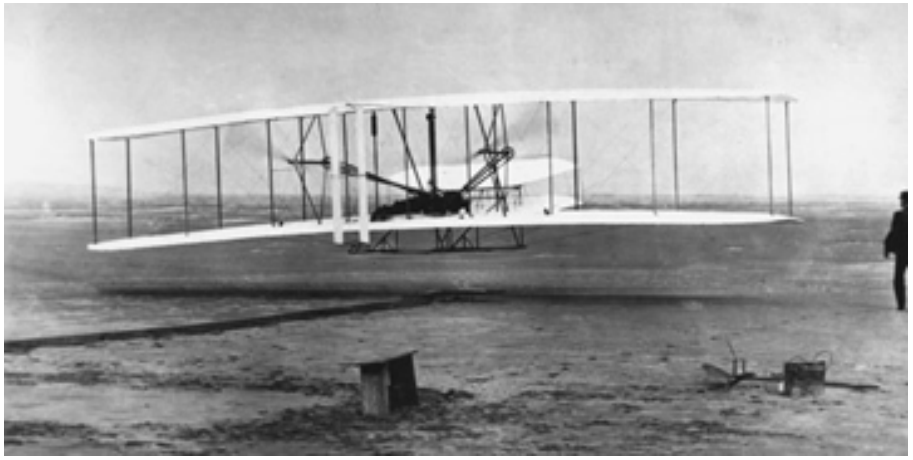
ROYAN



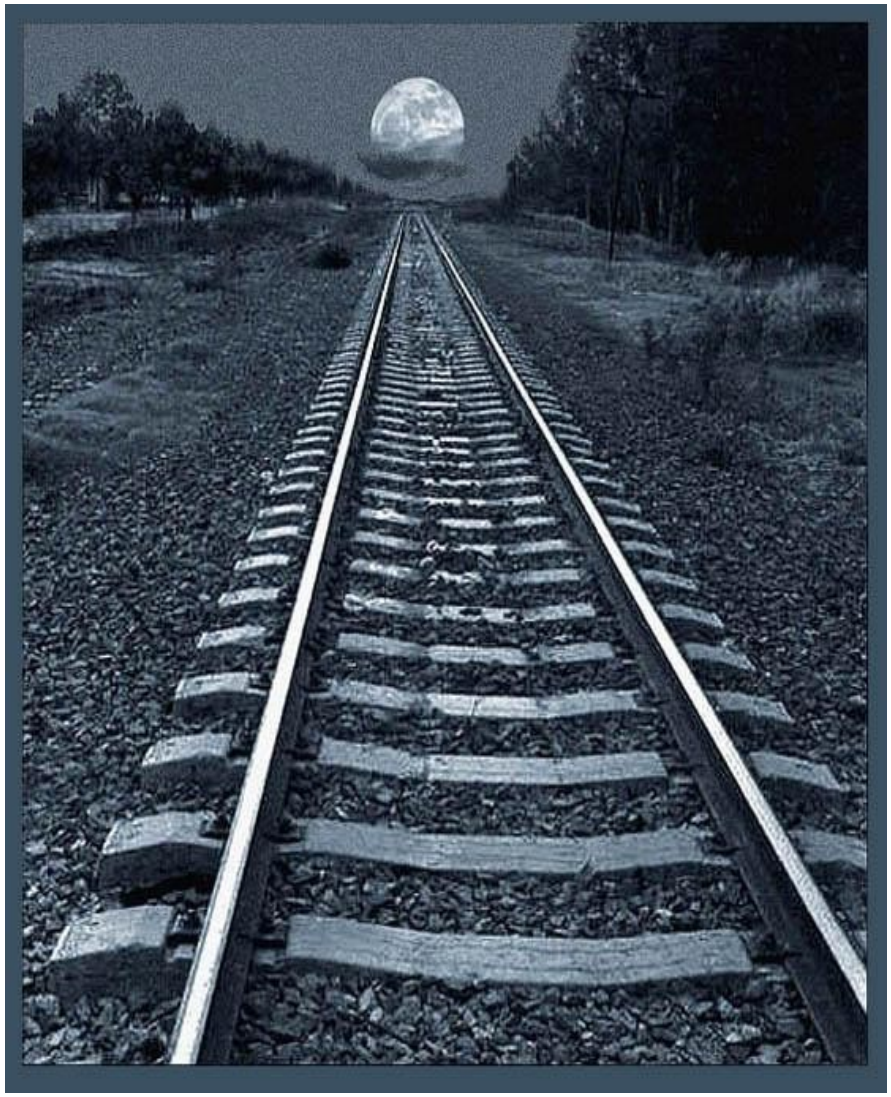
Conclusion 1

- It is important to acknowledge that stem cell field is still in infancy and the initial studies are promising.
- **Current medicine** is based on drug therapy dominated by antibiotics, chemotherapy, antipsychotic agents, and other pharmaceutical.
- **Scientific medicine of the future** will likely be based upon cellular therapies, focused on repair and regeneration of tissues by transplantation.

Conclusion 2



Conclusion 3: Vision (Ponzo effect)



- Impossible to assess the magnitude of an object on the horizon
- Similarly, difficult to assess the ultimate effect of a new study or procedure when it first appears on the ‘horizon’

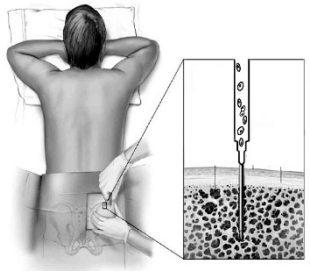
Acknowledgement

- Gratefully thank all Colleagues at Royan institute
- These studies was funded by grants provided from Royan Institute and Iranian Council for Stem Cell Research and Technology.

Transplantation of BM-HSCs in CABG candidats

Ficoll

MNC cells



Bone marrow aspiration

Clinimacs

CD133 cells

Flow cytometry analysis