Manifestation of Novel Social Challenges of the European Union
in the Teaching Material of
Medical Biotechnology Master's Programmes
at the University of Pécs and at the University of Debrecen

Identification number: TÁMOP-4.1.2-08/1/A-2009-0011

NEW SZÉCHENYI PLAN

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Transdifferentiation and regenerative medicine – Lecture 1

STEM CELLS AND TRANSDIFFERENTIATIO NINTRODUCTION, BASIC CONCEPTS

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Definitions

Stem cells: undifferentiated/resting cells that can divide and differentiate into mature cells of all three germ layers

Pluripotency: the capacity to produce several types with diverse biological characteristics

Self-renewal: the process in which stem cells preserve their pluripotency

Commitment: the capacity of cells to restrict their differentiation spectrum/direction

Differentiation: the gradual acquisition of cellular traits associated with specialization

Stem cell research – a brief history

- Early 1900's: all blood cells come from the same immature cells
- 1950-70's: Extensive studies on teratocarcinomas/teratomas in mice and humans
- 1963: Till and McCulloch: quantitative analysis of hemopoietic stem cell frequency (CFU-S)
- 1980-90's: production of Tg mice from inner cell mass of blastocysts
- 1998: isolation of human stem cells from embryos: beginning of political-ethical debate on the moral status of human embryos/stem cell research
- 2006: iPS technology begins (Yamanaka)

Abnormal multilineage differentiation: teratoma/teratocarcinoma

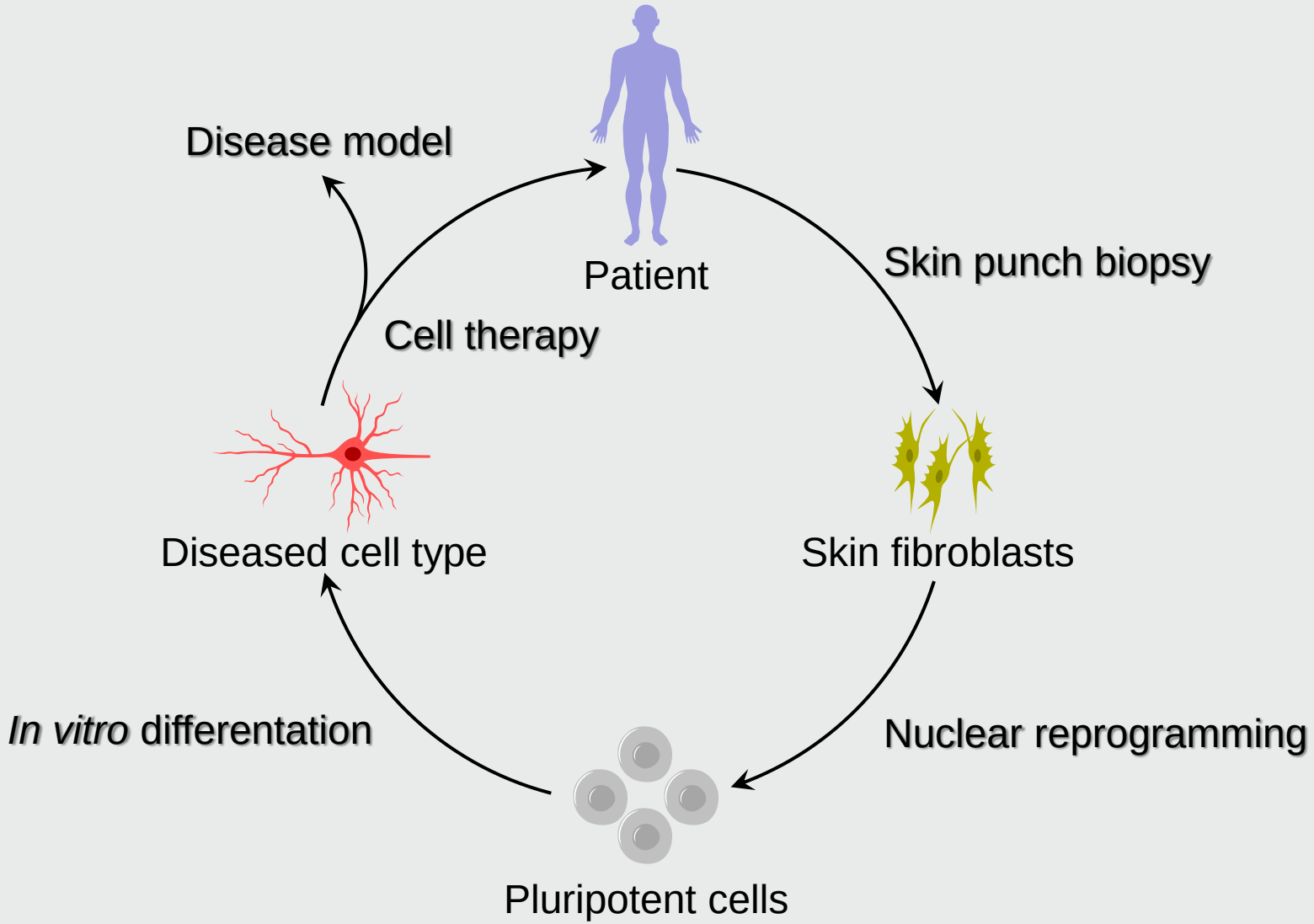
- Germ cell origin – testis or ovary
- Mixed cell composition – malignant cells with differentiated component (cartilage, epithelium)
- Potential use in human stem cell research *in vitro*

Issues of plasticity

Plasticity: existence of parallel differentiation programs

- Directionality: reversible/irreversible (switchable), *i.e. inhibition of Pax5 suspends B-cell identity; neuronal → hemopoietic transdifferentiation/switch*
- Homeostasis: measured degree of commitment along various directions, responsive to external effects (*altered blood cell production in infections*).

Concept of regenerative medicine



Aims and concepts behind cellular reprogramming

- Personalized cellular replacement therapy
- Absent/diseased cells (genetic, degenerative, traumatic etc. causes) and tissues corrected in a controlled cellular differentiation way

Obstacles of cellular reprogramming

Stem cell-related:

- rare cell type
- difficult isolation procedures
- uncertain differentiation capacities (lineage/normal/malignant)

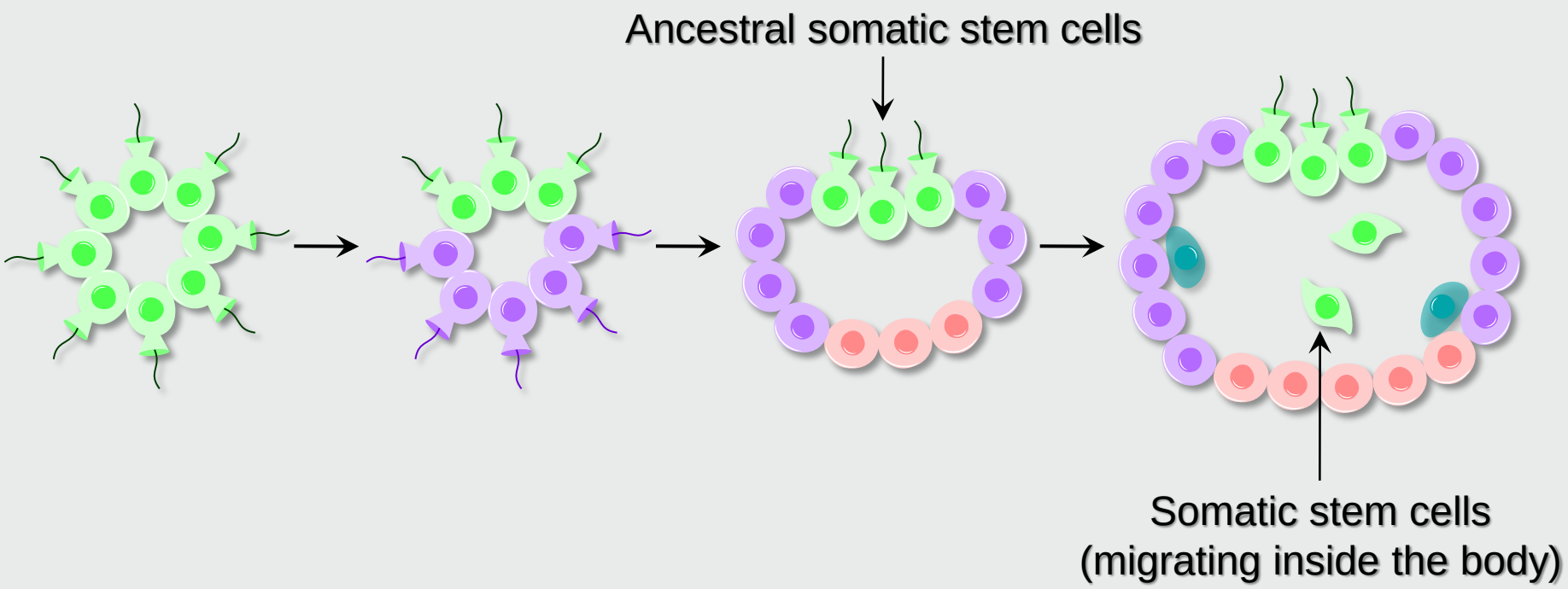
Recipient-related:

- effect of previous medical treatment
- problems of tissue delivery and stem cell positioning
- immunological responsiveness against the donor cells/molecules

Evolution of tissue regeneration

- Uniform composition of early multicellular organisms – all cells can individually regenerate
- Later the ability to proliferate became restricted to a subpopulation of the cells
- Ancestral somatic stem cells (site-bound)
- Migratory stem cells

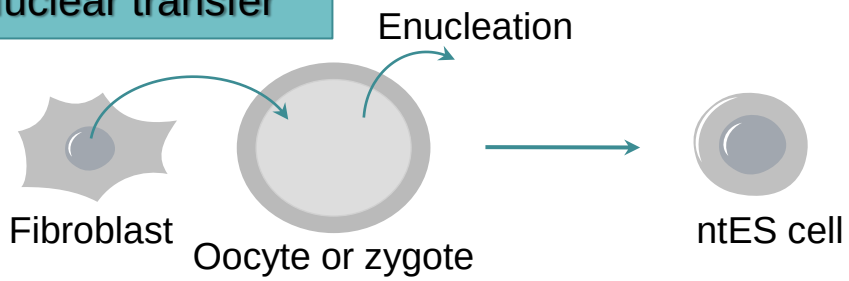
Evolution of tissue regeneration



Types of stem cells

- As defined by the developmental origin:
  - embryonic (neonatal)
  - postnatal, adult
- As defined by their physiological turnover/differentiation kinetics:
  - continuous, migratory (hemopoietic stem cells)
  - slow, sessile (liver, muscle etc)
- As defined by their differentiation spectrum:
  - totipotent
  - pluripotent
  - oligopotent

Methods for reprogramming

	Advantages	Disadvantages
Nuclear transfer 	• Indistinguishable from embryo-derived ES cells	• Technically challenging • Sources for oocytes or zygotes
Cell fusion 	• Technically straightforward	• Fusion is inefficient • Reprogrammed cells are tetraploid
Direct reprogramming 	• Technically straightforward • Autologous to fibroblast donor	• Uses oncogenic retroviruses and transgenes

Experimental approaches for reprogramming

- Nuclear transfer: introduction of somatic cell nucleus into enucleated oocyte/zygote
- Cellular fusion: the fusion of ES and somatic cells (induced by viruses, chemical agents and electronic current)
- Cell explantation: the generation of pluripotent cells directly by explanting cells into appropriate culture/co-culture conditions
- Direct reprogramming: iPS

Safety issues related to stem cell research/regenerative medicine

- Human ES cell culture – xenogenic exposure to mouse fibroblasts
- Transmission of human viral pathogens
- Error in reprogramming
- Serum-derived factors

Summary

- Stem cell research is relatively new, with substantial progress achieved and raising even more widespread hype (scientific as well as public).
- Different cells and procedures have been employed – no magic cure as yet.
- Issues to be solved: cell isolation, maintenance, reprogramming, overcoming alloreactivity and pathological differentiation.