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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Dr. Péter Balogh and Dr. Péter Engelmann

Transdifferentiation and regenerative medicine – Lecture 11

CARDIOVASCULAR REGENERATION

The projects are supported by the European Union.

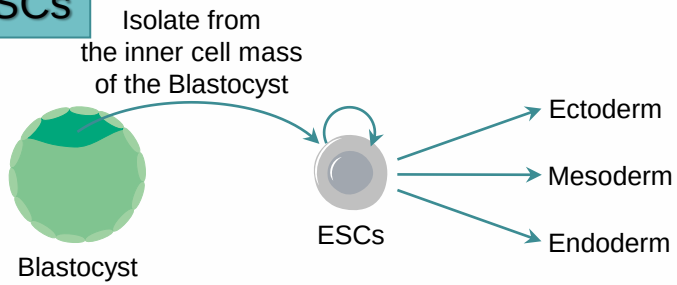
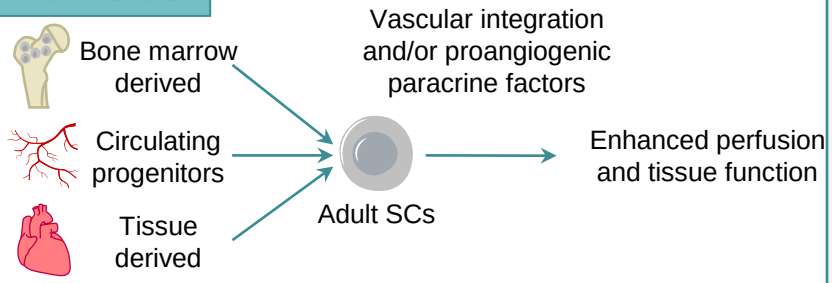
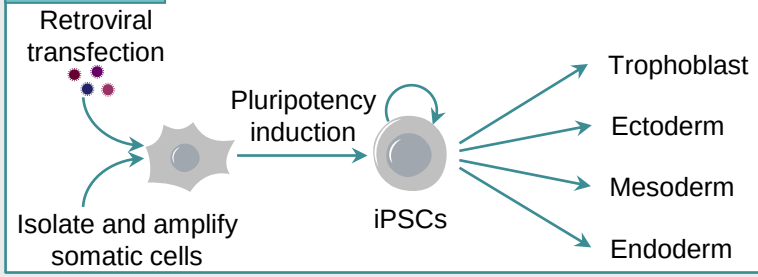
Structural heart diseases requiring regenerative therapy and cellular specialization

- Coronary artery diseases
- Congestive heart failure
- Cells to reconstitute:
  - pacemaker and atrial/ventricular cardiomyocytes
  - vascular smooth muscle cells
  - arterial/venous endothelial cells

Constrains of in vivo experiments

- Difficulties in identifying functional human CSCs (cardiac stem cells) or other precursors
- Transplantation into rodent hearts with different physiology (heart rate) limits survival
- Limited control for cardiogenic commitment

Cells with myocardial regeneration potential

	Origin	Advantages	Disadvantages
ESCs 	**Blastocyst of embryo**	• Pluripotent (3 germ layers) • Self-renewal and high replicative capacity	• Immunological concerns • Subject to ethical debate • Potential for teratoma and teratocarcinoma • Currently no clinical trial data
Adult SCs 	**Bone marrow, circulation or resident tissue**	• Autologous • Clinical safety and efficacy data • Typically lineage commited	• Limited number • Limited replicative capacity • Lineage restricted
iPSCs 	**Reprogramming of somatic cells**	• Totipotent (3 germ layers and trophoblast) • Autologous • Large reservoir of cells	• Potential for teratoma and teratocarcinoma • No clinical data

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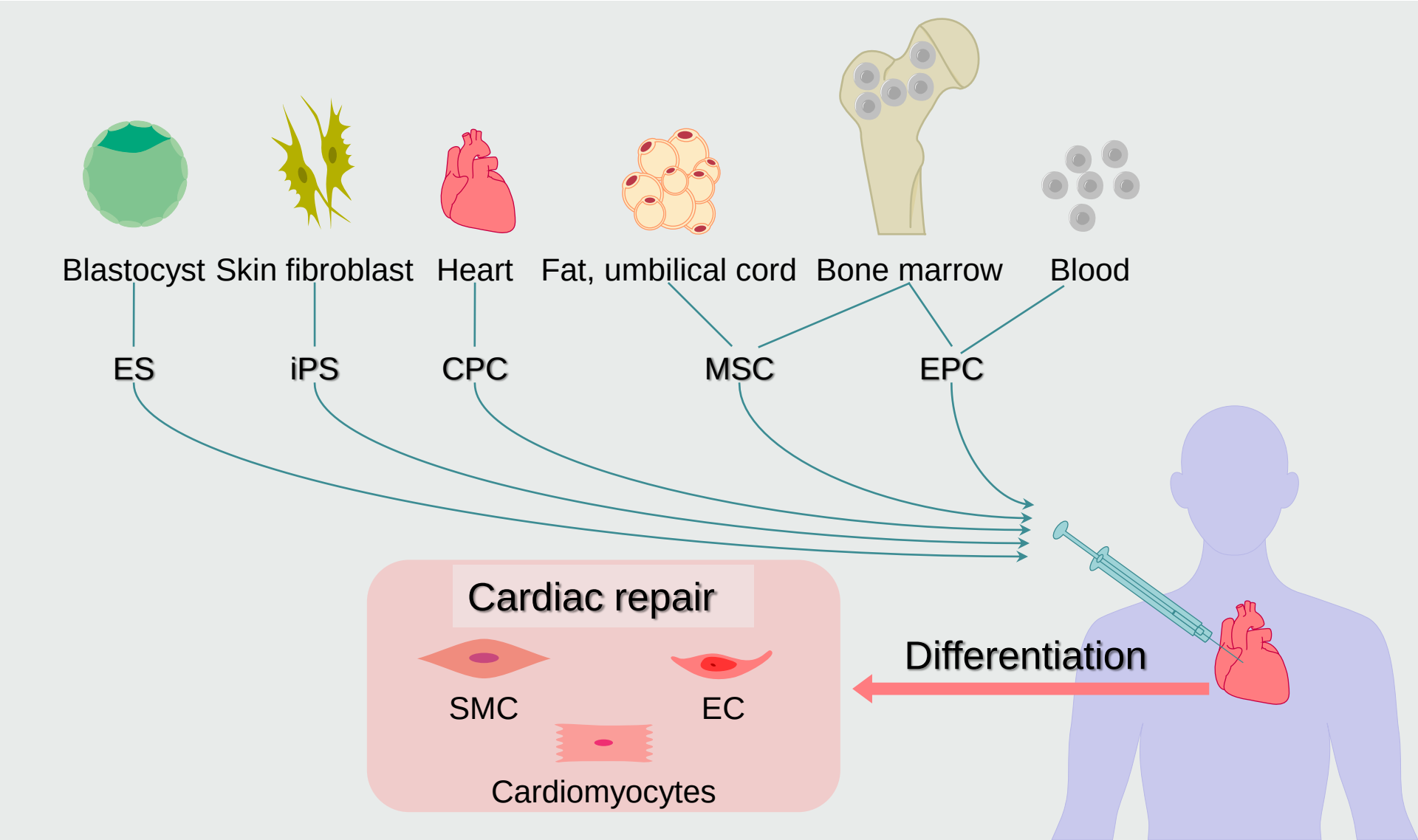
Tissue sources for myocardial regeneration



Bone marrow-derived mononuclear cells – a controversial field

- Improved (early) LV functions
- Variable results depending on the way of cellular delivery (intracardiac, intracoronary)
- Early response enhancement with subsequently diminishing difference to the recovery with placebo control
- BOne marrOw transfer to enhance STT-elevation infarct regeneration (the BOOST trial)

Endothelial progenitors cells

- Induction of neoangiogenesis (vasculogenesis – new vessels, angiogenesis – sprouting from preexisting vessels)
- New vessels supply hypertophic periinfarct myoblasts/myocytes from endothelial progenitor cells following G-CSF mobilization
- Sustain regeneration from endogenous cardiomyocytes

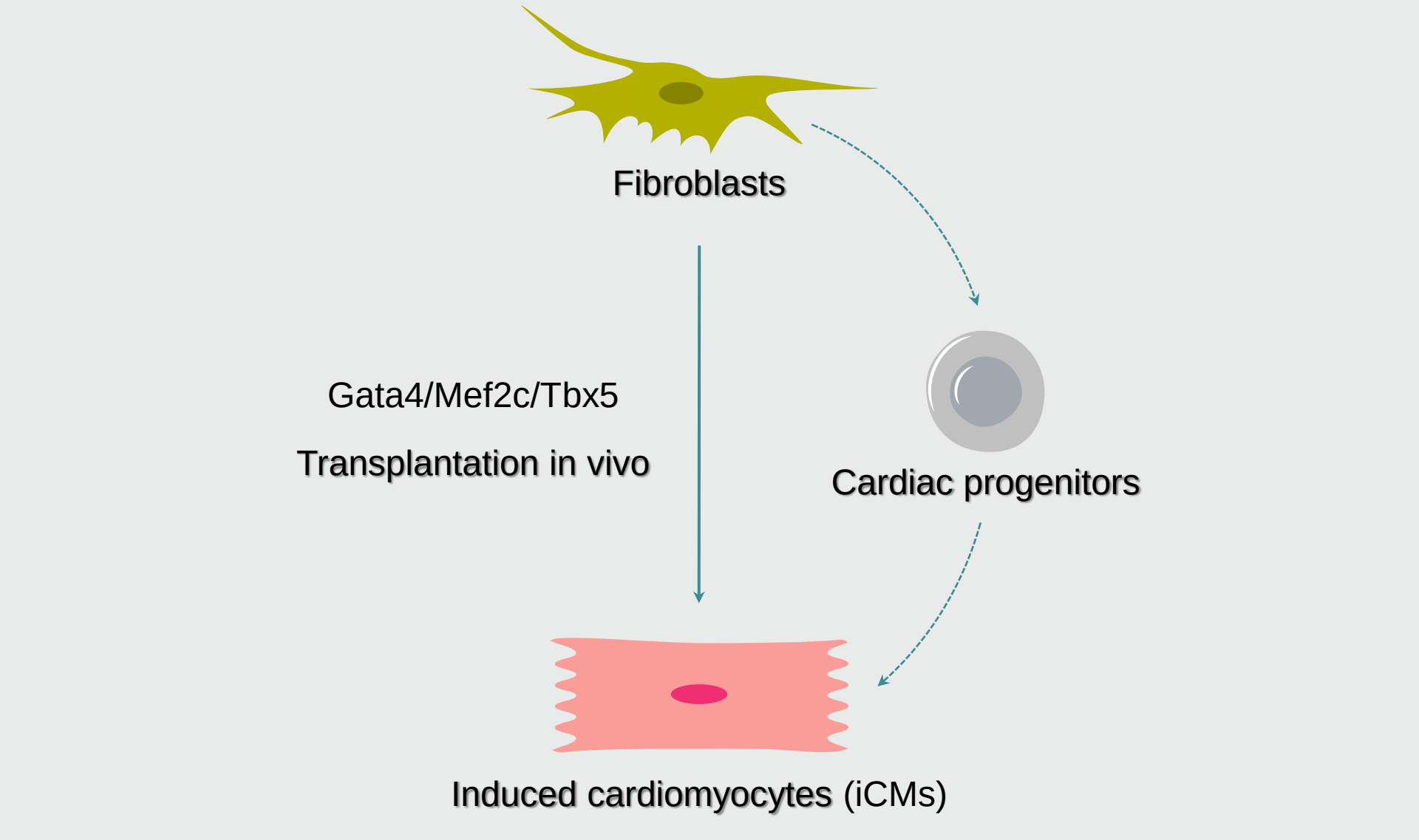
Mesenchymal stem cells (MSCs)

- Early observations: presence of chromosome Y in male patients transplanted with female heart
- Lack of B-7 and MHC Class II molecules
- Present in bone marrow
- May differentiate into myocytes, smooth muscle cells and endothelium

Cellular characteristics of MSCs

- Nkx2.5/Csx, GATA-4, and MEF2C cardiac TF expression
- CXCR4+/Sca-1+/lin–/CD45– mononuclear cell (MNC) fraction in mice and in the
- CXCR4+/CD34+/AC133+/CD45– BMMNC fraction in humans.
- Respond to SDF-1-CXCR4–, HGF-c-Met–, and LIF-LIF-R in migrating to damaged myocardium

iPS reprogramming for myocardial regeneration



Mechanisms of action

- Differentiation vs. Fusion: uncertainties of cellular origin/identity mediating repair
- Paracrine effect: induction of proliferation
- Activation of endogenous repair mechanism

Three-dimensional cardiac regeneration – tissue engineering

- Cardiac tissue matrix
- Electromechanical cell coupling
- Robust and stable contractile function
- Functional vascularization

Regeneration for peripheral vascular disease (PVD)

- Epidemiology: 3-10%
- Pathology: mostly atherosclerosis or some forms of vasculitis
- Clinical forms:
  - Intermittent claudication: an early moderate manifestation
  - Critical limb ischemia: severe muscle tissue loss or ulcers with high risk for limb amputation.

Regenerative approaches in PVD

- Control/reversal of atherosclerosis
- Therapeutic angiogenesis – use of bone marrow-derived progenitors, circulating endothelial progenitors or MSCs
- Local or systemic delivery into recipients

Summary

- Cardiac regeneration requires the simultaneous generation of (1) cardiomyocytes with different specification characteristics (2) vascular endothelial cells and (3) vascular smooth cells, including their capacity to adjust to physical requirements, together with their proper 3D-arrangement.
- This multilineage regeneration capacity may efficiently be manifested by MSCs, although bone marrow-derived hemopoietic/endothelial precursors may also support both cardiac and vascular regeneration.