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 7

REGENERATION AND TRANSDIFFERENTIATION OF SKELETAL MUSCLE

The projects are supported by the European Union.

Conditions requiring skeletal muscle regeneration

Injury leading to extensive muscle damage

Inherited diseases – Duchenne's muscular dystrophy:

- X-linked mutation of dystrophin gene
- 1:3500 males affected
- Dystrophin (2.4 Mb in size) is the largest known mammalian gene
- Onset of the disease: DMD-afflicted patients are diagnosed in childhood. The progressive muscle-wasting disease affects striated muscle including limb muscles, diaphragm, and heart leading to cardiorespiratory failure, and death usually occurs in the teenage years or early 20s.

Experimental models for studying muscle regeneration

- Mdx mice: spontaneous mutation of the distrophin gene (variable severities in different inbred mouse strains)
- Distrophin/utrophin double mutant mouse
- Canine X-linked muscular dystrophy (cxmd) is the best representation of DMD, but the phenotype is variable.

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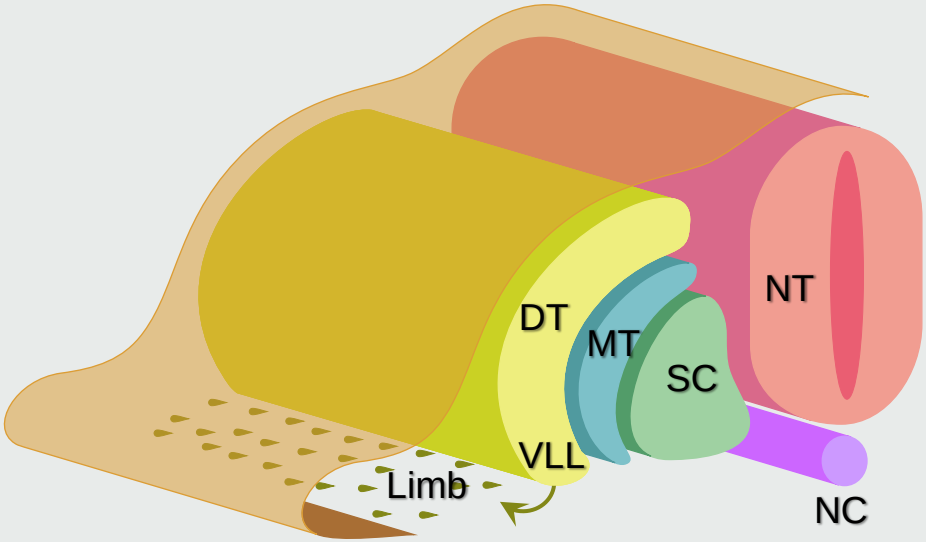
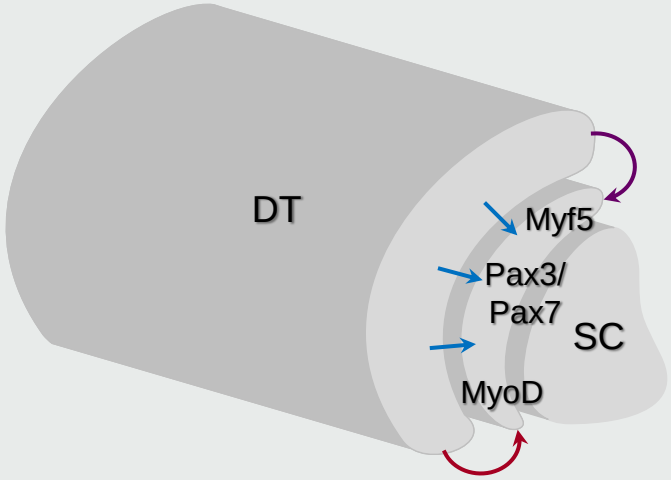
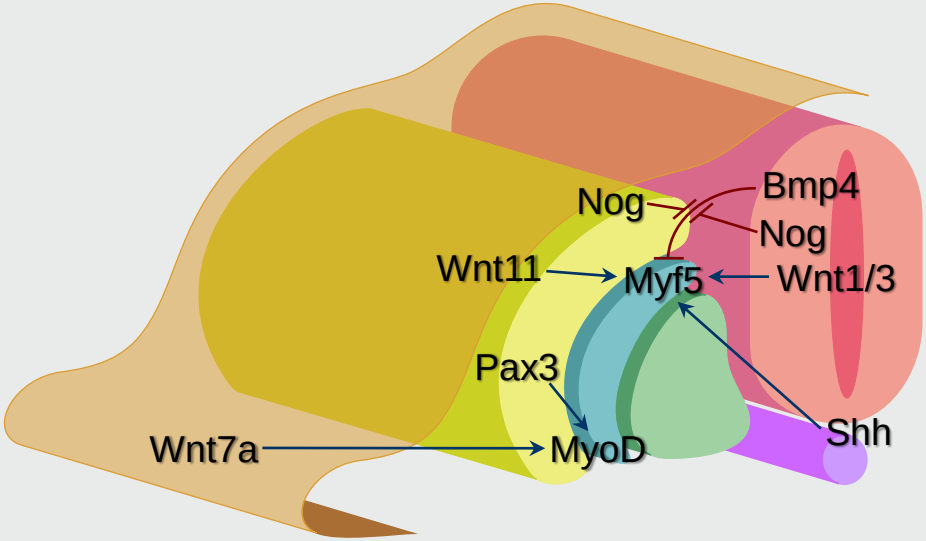
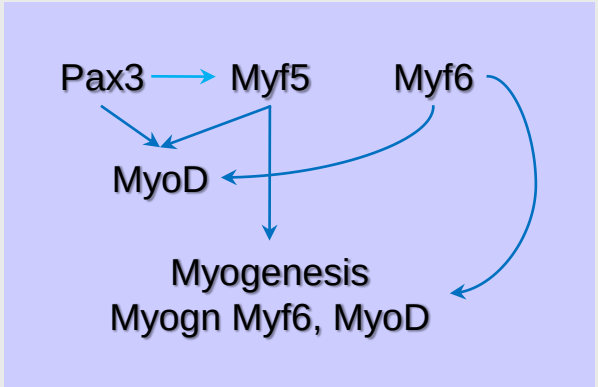
Embyonic development of skeletal muscle









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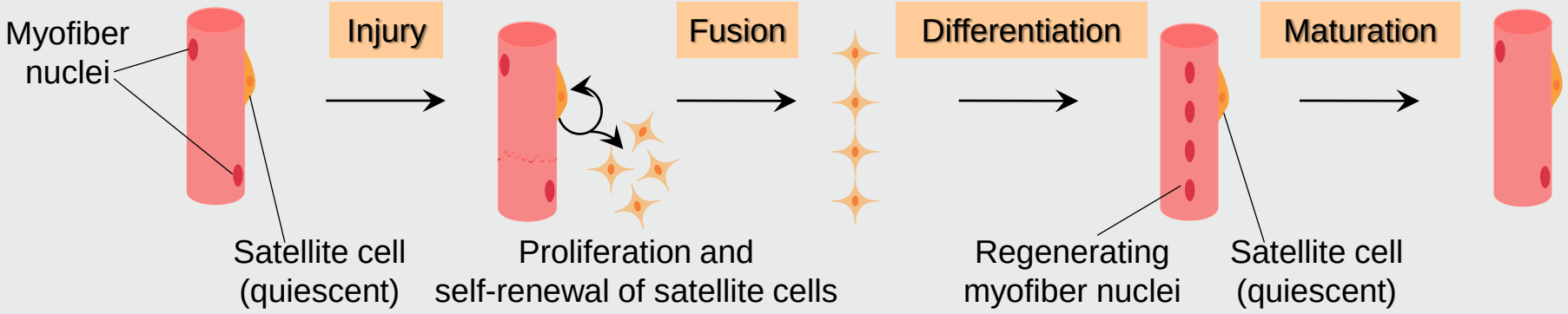
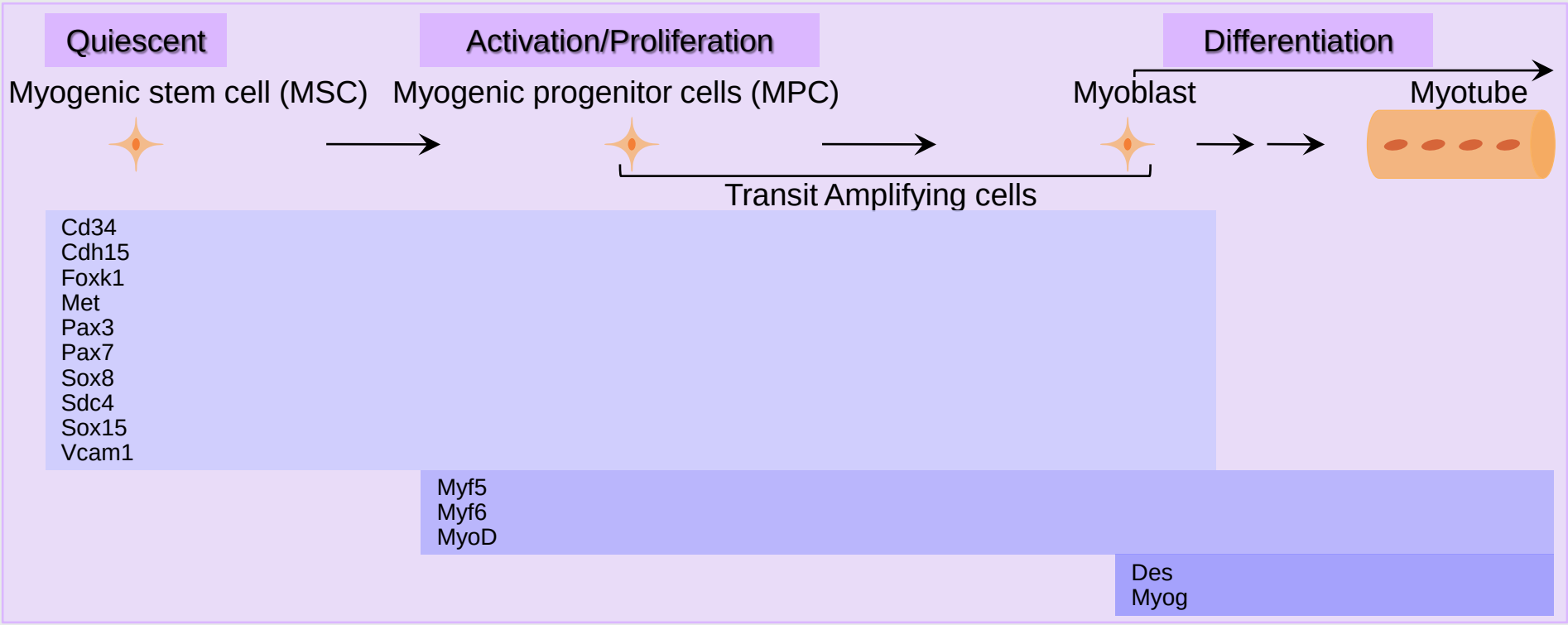
Transcriptional control of myogenic differentiation

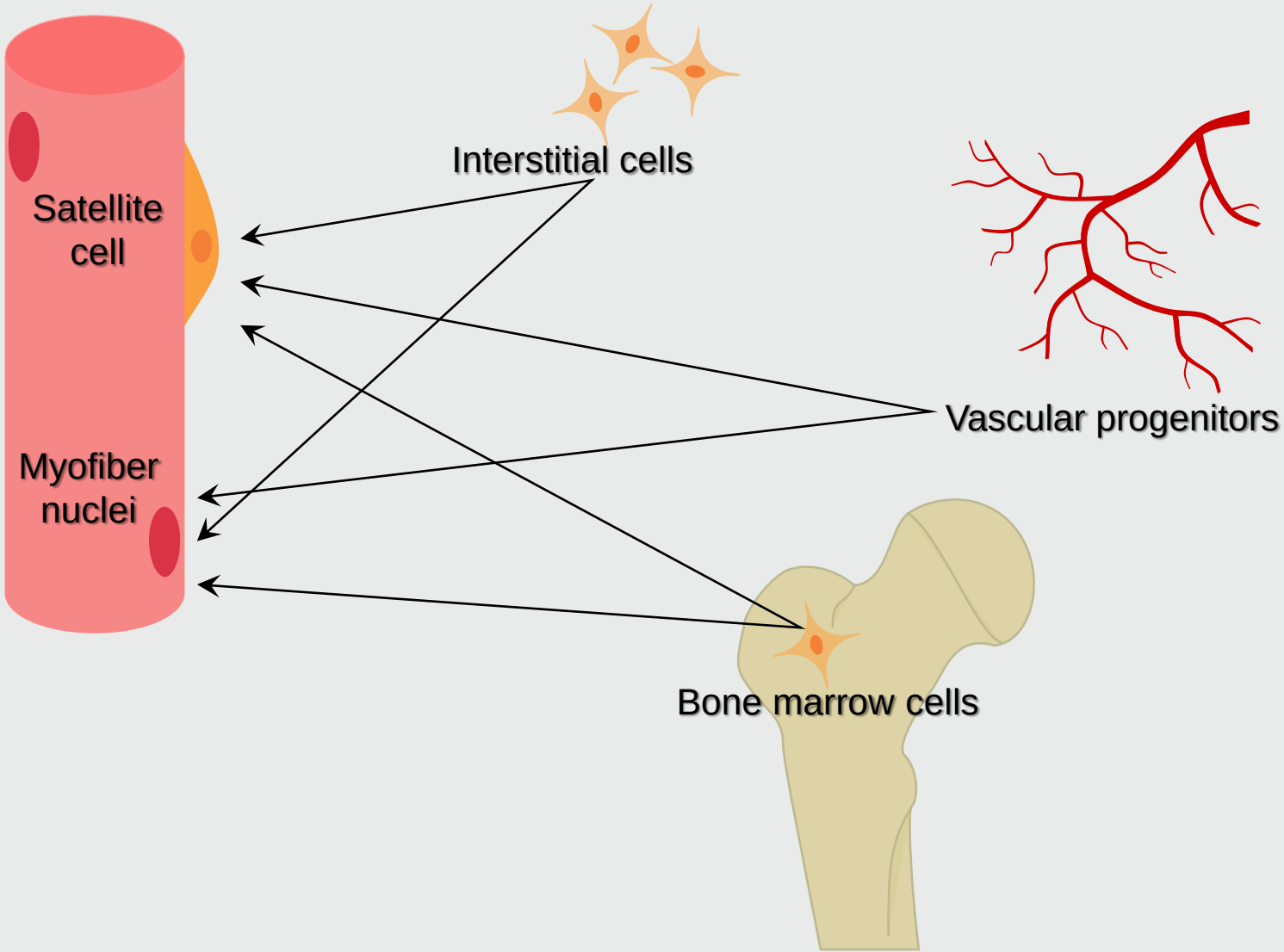




Cellular sources for muscle regeneration

- Satellite cells and their precursors
- Endothelial cells associated with embryonic limb muscles
- Mesangioblasts
- Bone marow-derived stem cells
- Pluripotent cells found within muscle-derived side population (SP) cells
- Highly active Mdr-dependent expulsion of Hoechst 33342 dye

Tissue sources for muscle regeneration



Muscle stem cells – satellite cells

- The satellite cells reside beneath the basal lamina of muscle, closely juxtaposed to muscle fibers
- Approximately up 2–7% of the nuclei associated with a particular fiber
- Heterogeneous composition: fusing/non-fusing subsets
- Ontogeny: somite/perivascular cells expressing Pax3/Pax7
- Surface markers
  - Mouse: M-cadherin, CD34, VCAM, CD56, c-*met* (HGF-receptor)
  - Human: CD56

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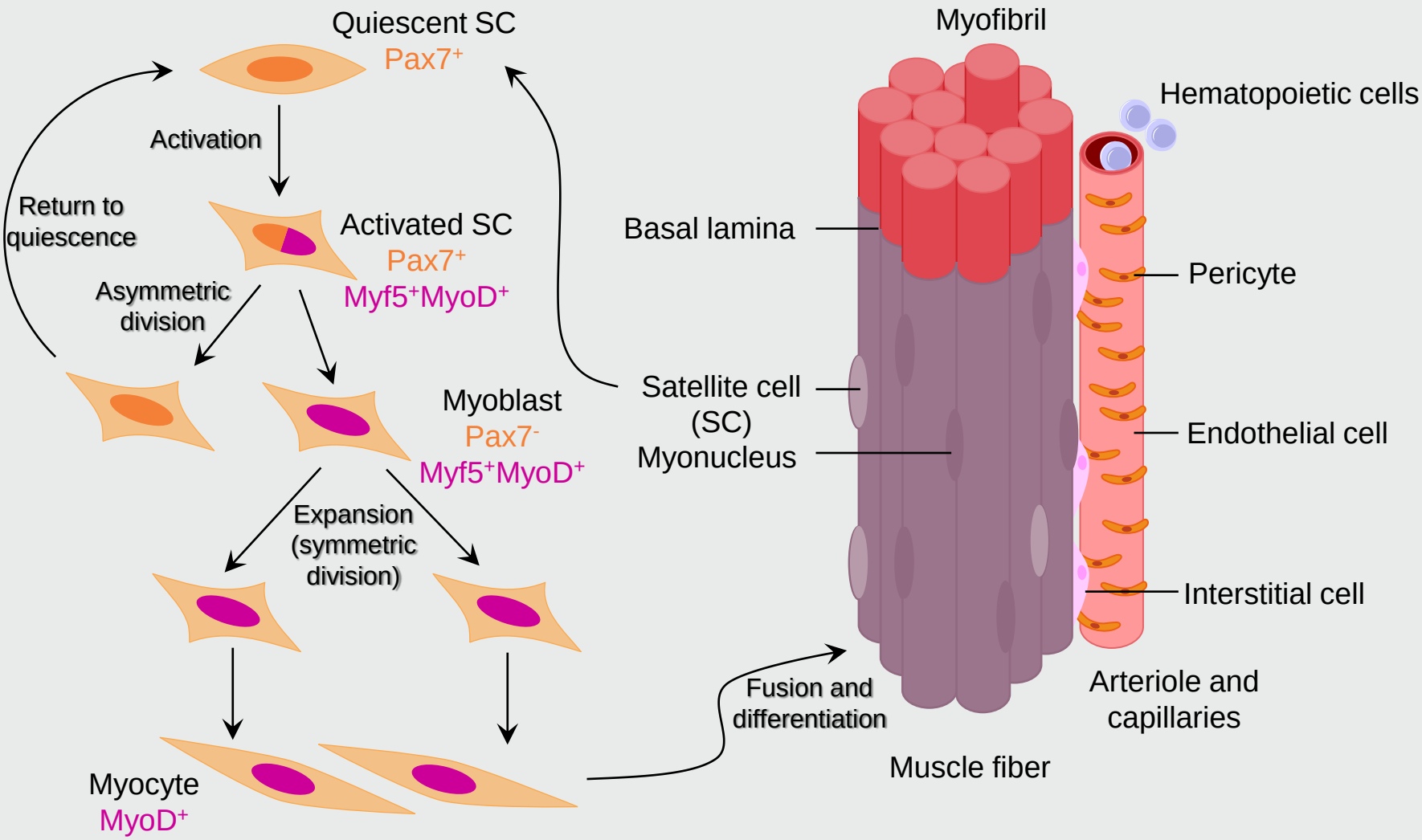
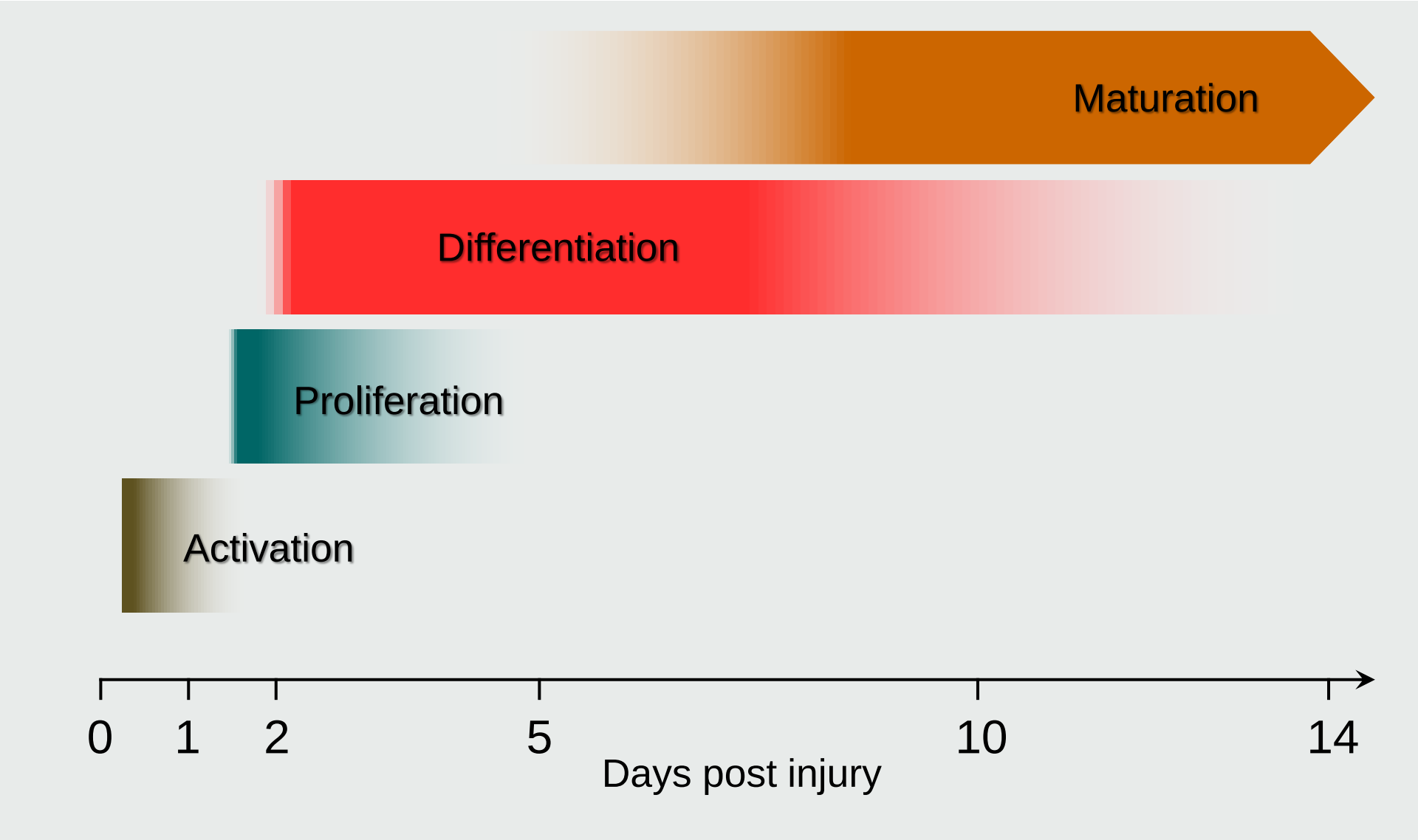
Structure and regeneration of skeletal muscle



Kinetics of muscle repair



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Problems with myoblast regeneration in Duchenne's muscular distrophy

- Necessity for immunosuppression
- Immunosuppressant drugs cause myoblast apoptosis
- Short migratory distance following intramuscular injection – 100 injections/cm^2 (totalling up to 4,000 injections in a single patient!)

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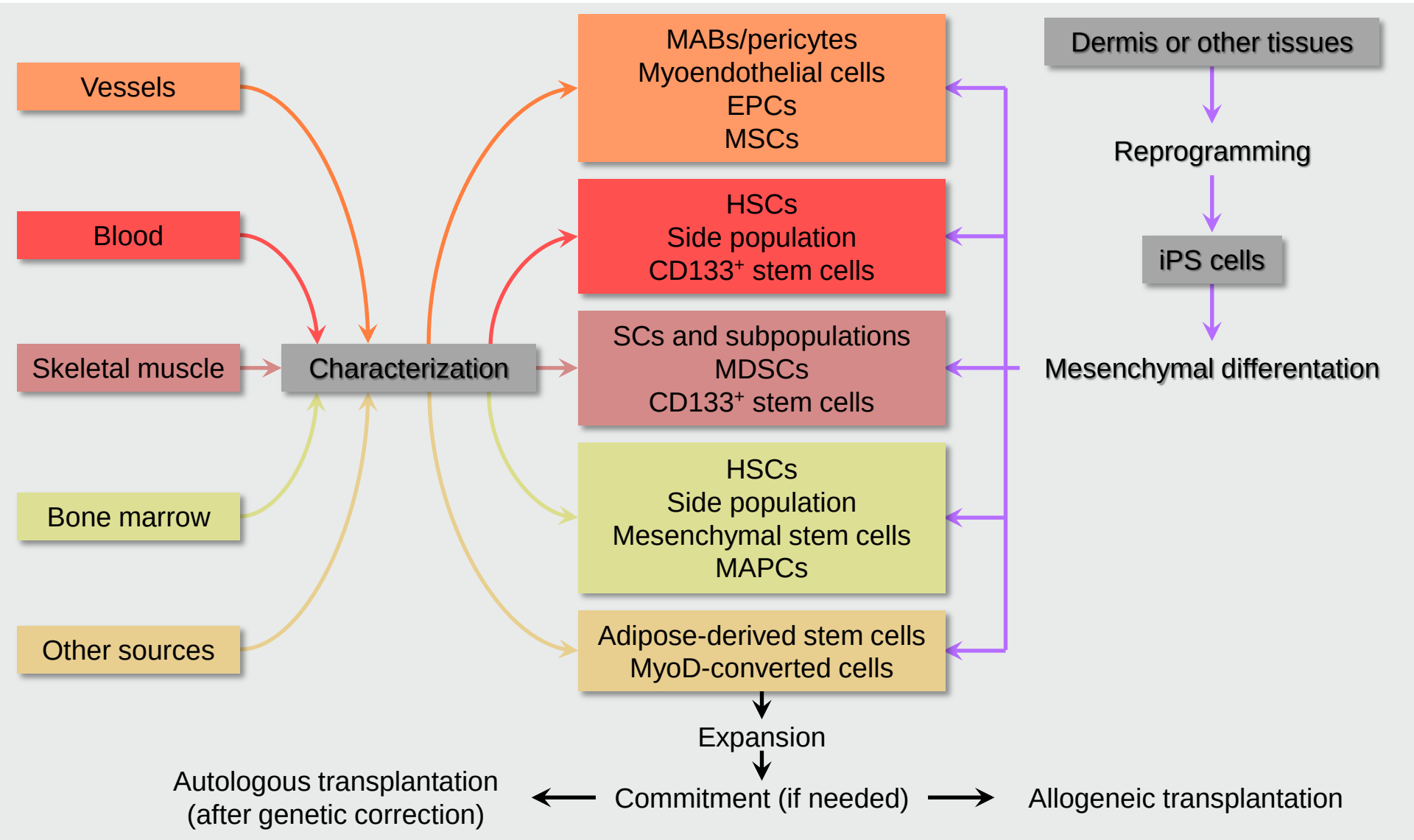
Non-SCs contributing to muscle regeneration



Summary

- The prime candidates for skeletal muscle regeneration are the satellite cells, but cells from other sources (embryonic as well as non-embryonic) may also associate/promote the process.

- Muscle regeneration is accomplished through (a) promoting vascular repair, (b) cellular differentiation from muscle stem cells and (c) possible transdifferentiation.