SUSTech Southern University of Science and Technology

Lecture 20
Stem cells and nerve cells

Outline

- What are stem cells?
- Early metazoan development and embryonic stem cells
- Stem cells and niches in multicellular organisms
- Neurons and glia: building blocks of the nervous system

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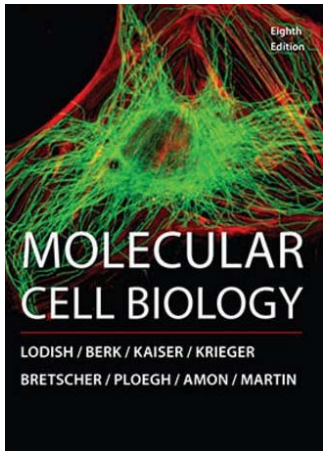
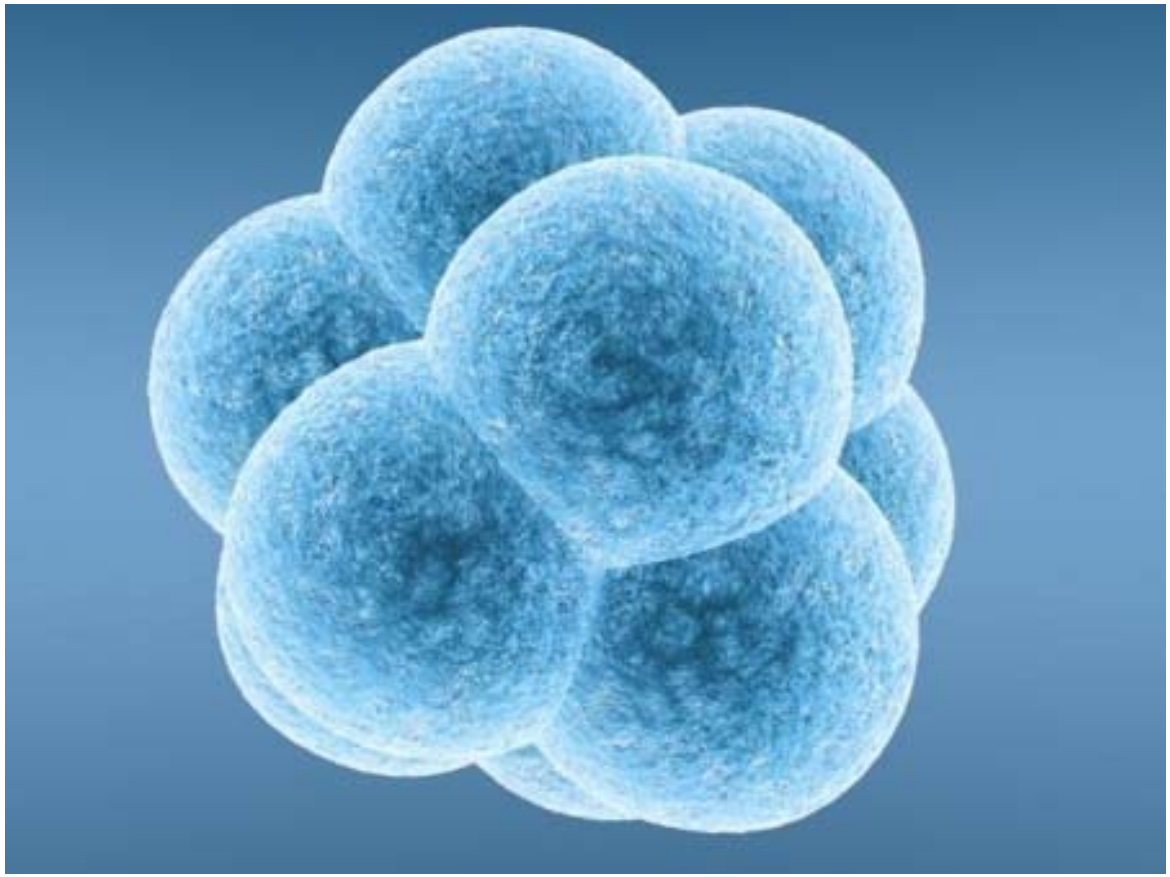


Chapter 21

I. Stem cells

What are stem cells and what is so special about them?



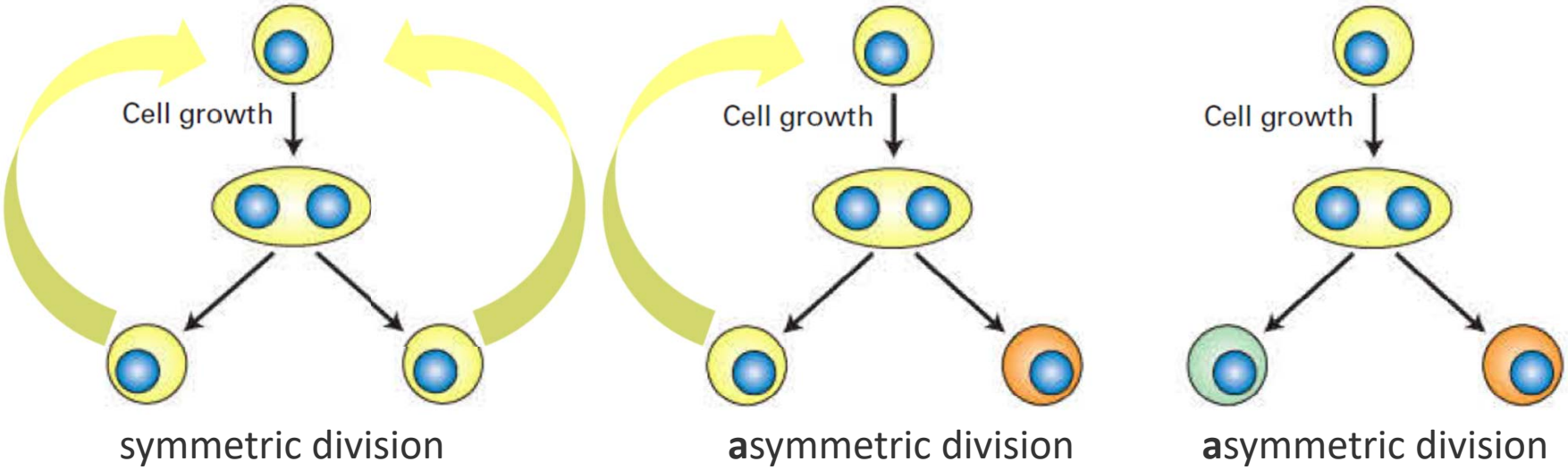
- **Stem cells have unlimited potential for self-renewal and differentiation.**

I. Stem cells

What are stem cells?

- Stem cells are undifferentiated cells that have the potential for **self-renewal** and **differentiation**

What does self-renewal mean?

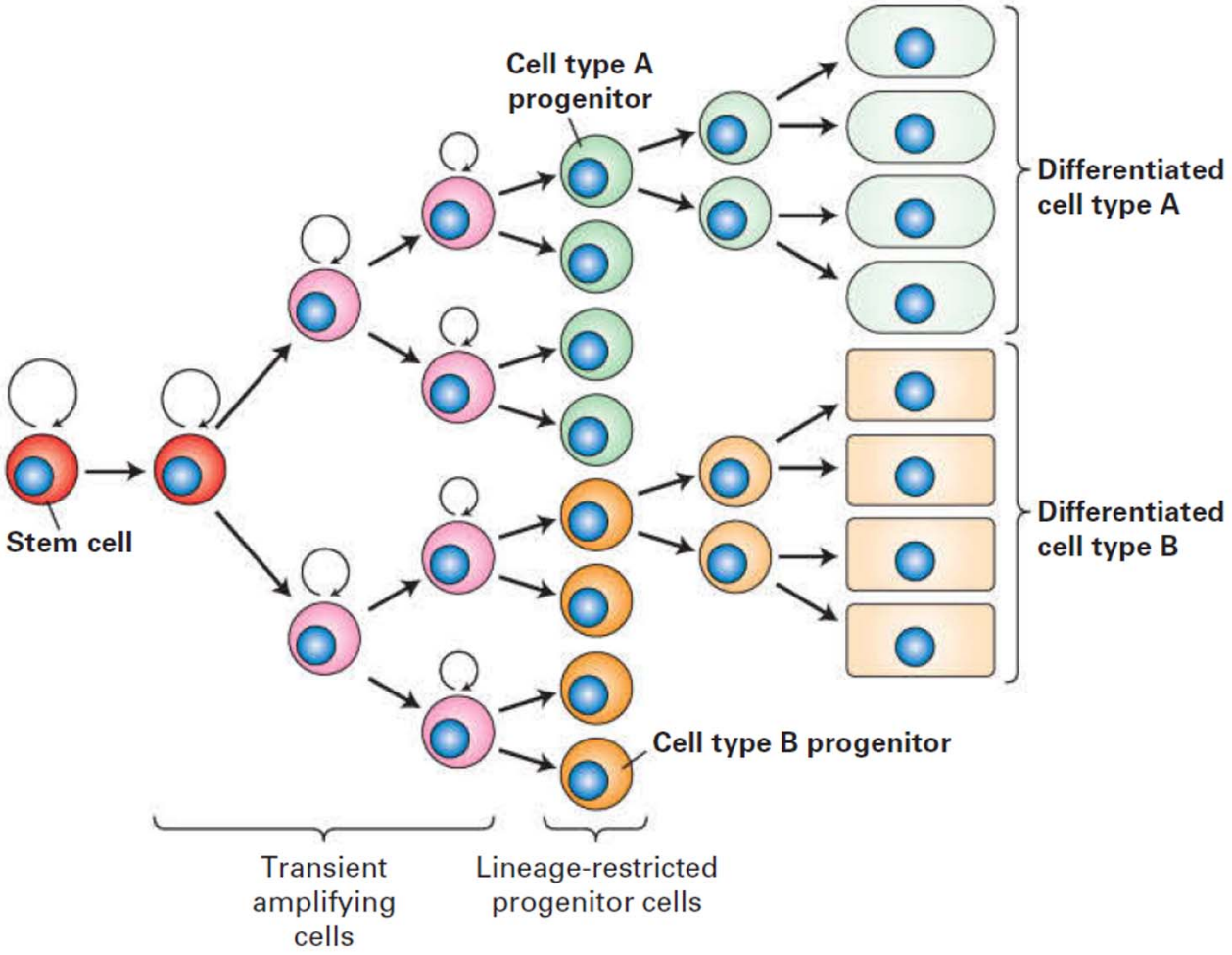


symmetric division | **a**symmetric division | **a**symmetric division

- Self-renewal: at least **one of the daughter cells** is identical to the parent!

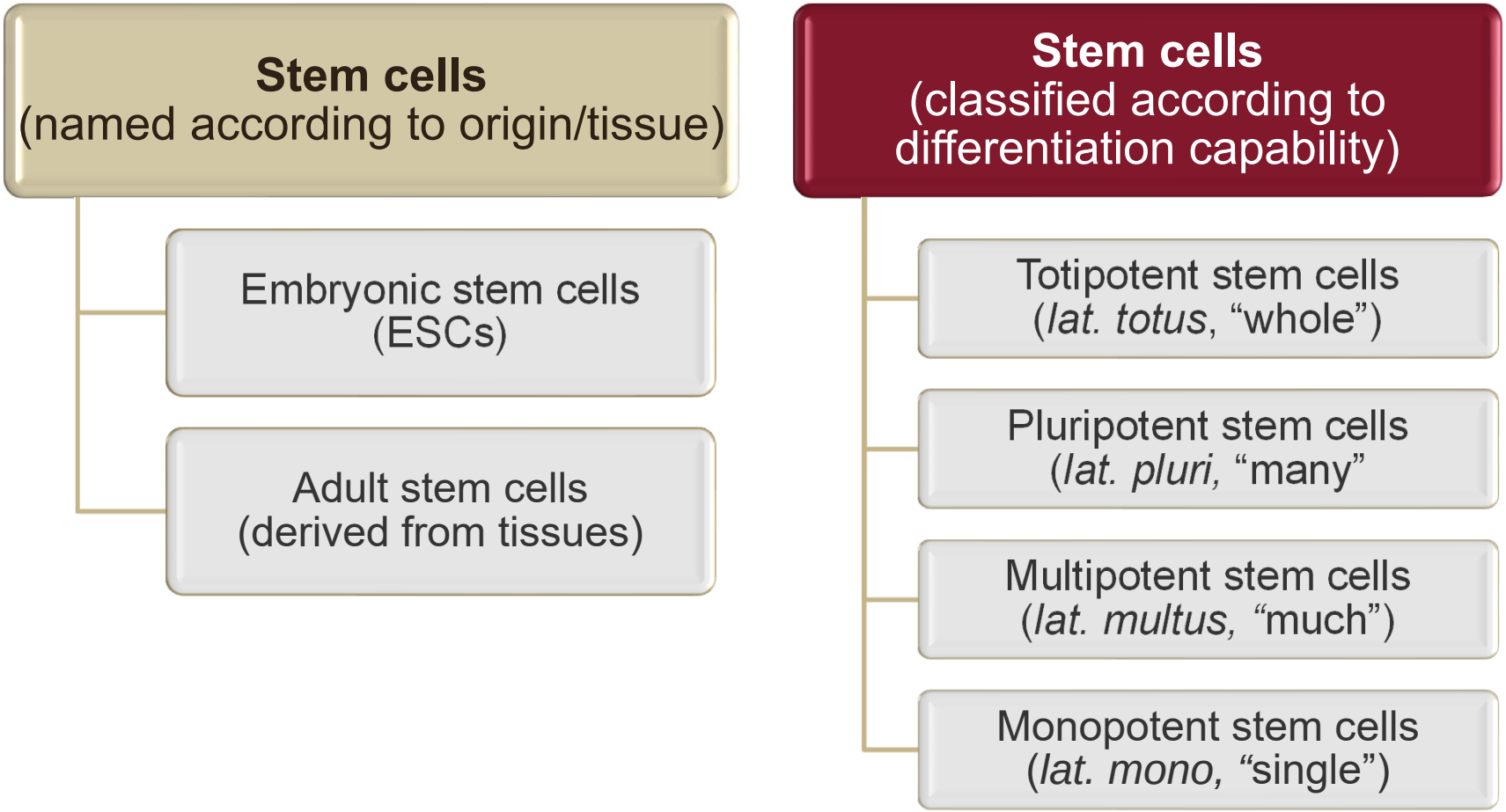
The cell lineage: tracing the origin of a cell

Pathway from stem cells to lineage-restricted progenitors to differentiated cells



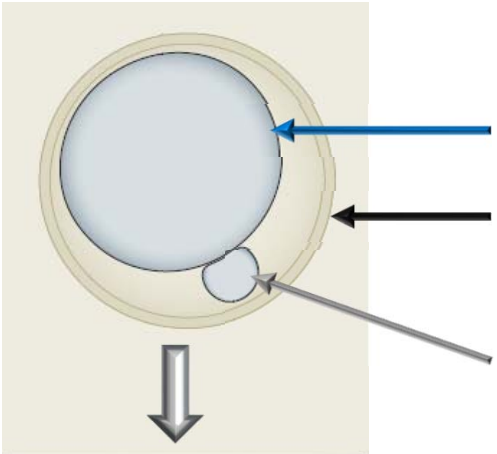
I. Stem cells: Different types of stem cells

Stem cells can be named after their location/fate or according to their differentiation capability



Embryogenesis: it starts with the fertilized oocyte…

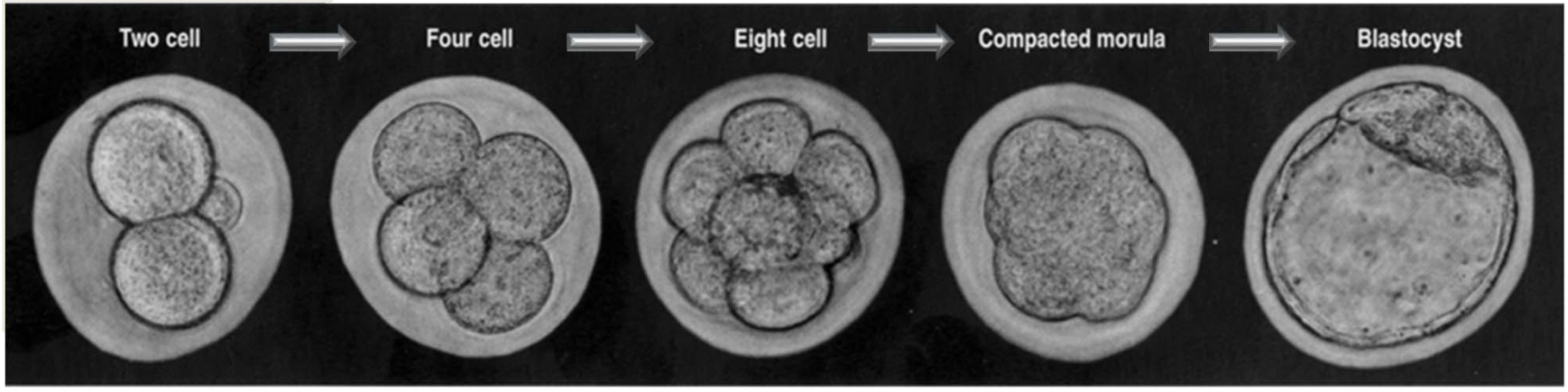
The first 5 days: from the 2-cell stage to the 64 cell stage, the blastocyst



Oocyte

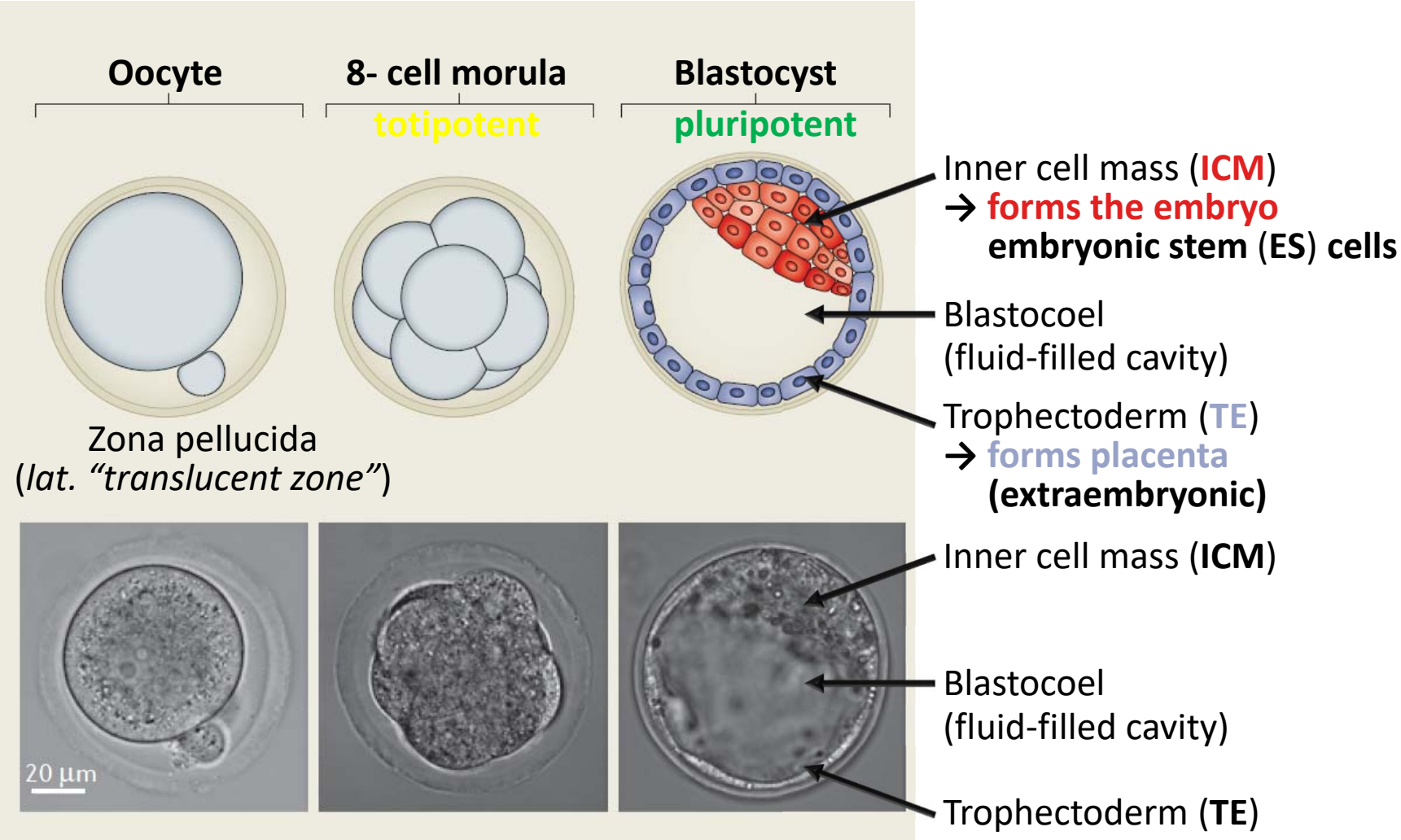
Zona pellucida (*lat. "translucent zone"*)
(glycoprotein matrix, protection)

Polar body
(arises during oogenesis, will undergo apoptosis)



The blastocyst

The first 5 days: from the 2-cell stage to the 64 cell stage, the blastocyst

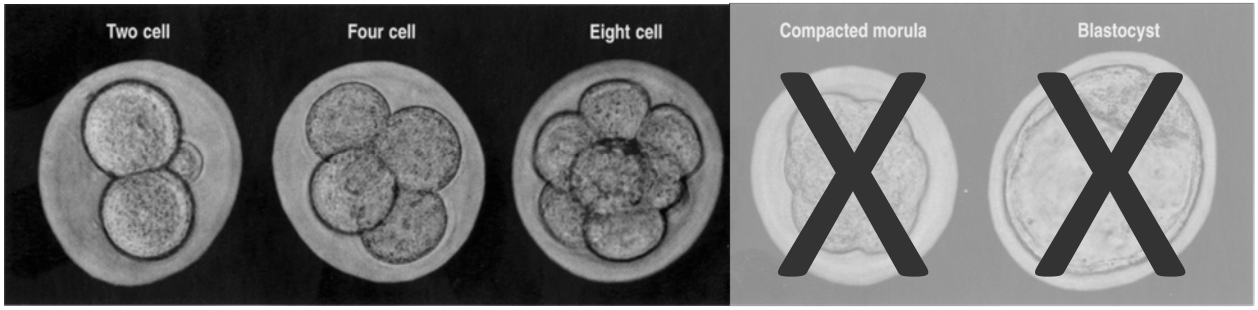


Totipotent cells

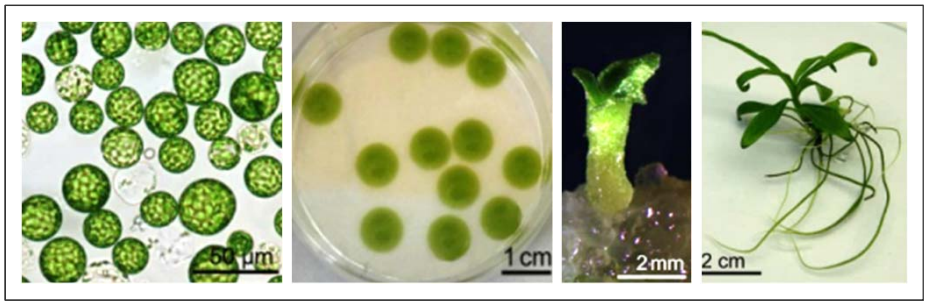
A totipotent cell can differentiate into a whole organism:

Examples:

- fertilized egg
- each cell during the development from the zygote **up to the 8-cell stage**



- **Many cells in a plant are totipotent** and a whole plant can be regenerated from a single cell of e.g. a leaf; suspension cultured cells have eternal growth



Other stem cells: pluri-, multi- & mono-potent stem cells

Pluripotent cells can differentiate into a wide variety of cells, but can not differentiate to form the whole organism

Examples:

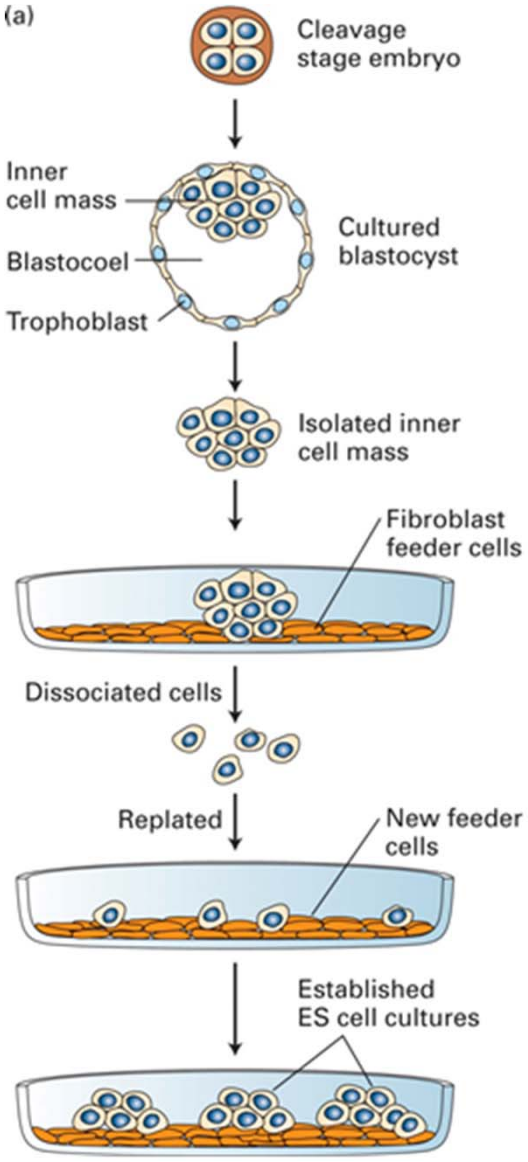
- embryonic stem cells
- bone marrow stromal stem cells
- nerve stem cells
- embryonic germ

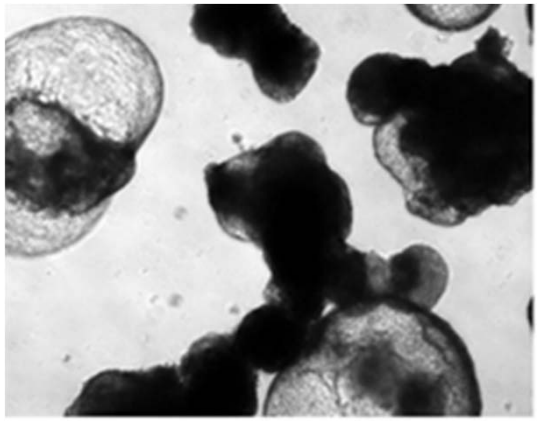
Multi- and **monopotent** stem cells can differentiate into a few types of cells or only in a special type of cells, respectively

Examples:

- neuroglial cells
- nerve stem cells
- satellite cells
- epithelial stem cells
- hematopoietic stem cells

Inner Cell Mass is the source of pluripotent embryonic stem cells

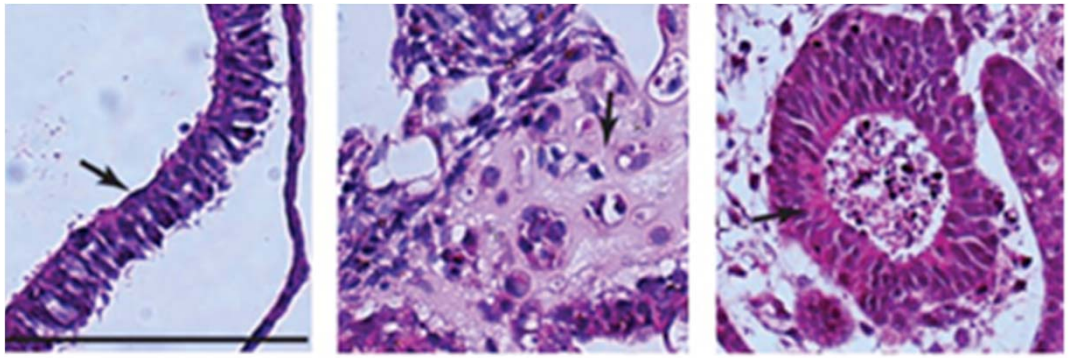




Embryoid bodies

Embryonic stem cells in suspension develop into embryoid bodies upon stimulation with the transcription factor STAT3 (**S**ignal **t**ransducer and **a**ctivator of **t**ranscription **3**)

Tissue staining of embryoid bodies show cell layers resembling that of true embryo.



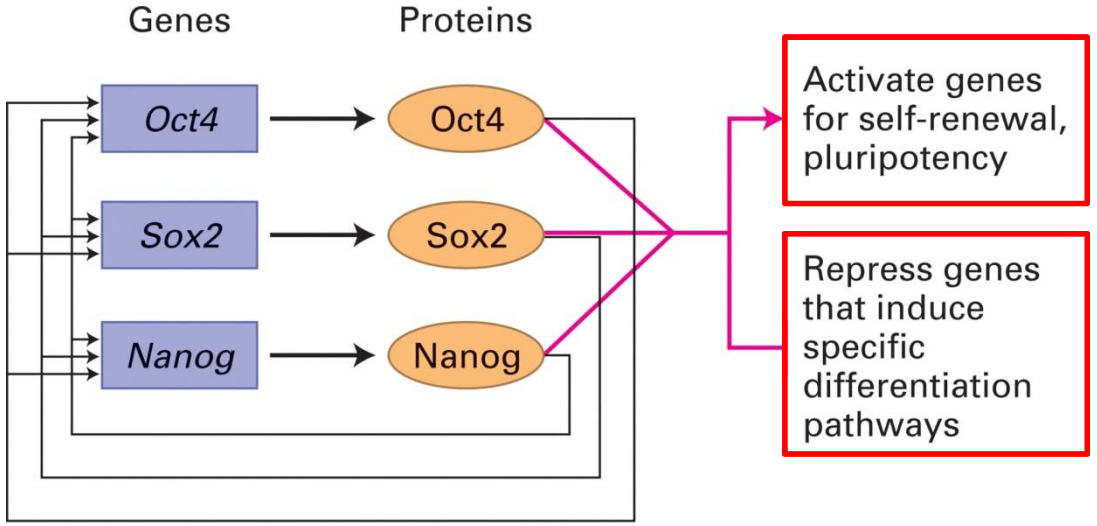
Endoderm Mesoderm Ectoderm

Multiple factors control/maintain the pluripotency of ES cells

Master transcription factors: Oct4, Sox2 & Nanog

- DNA demethylation (at early stage of development, a wide-spread DNA demethylation occurs)
- Transcription factors Oct 4, Sox2, Nanog
- Chromatin regulators
- miRNAs

Positive autoregulative loop

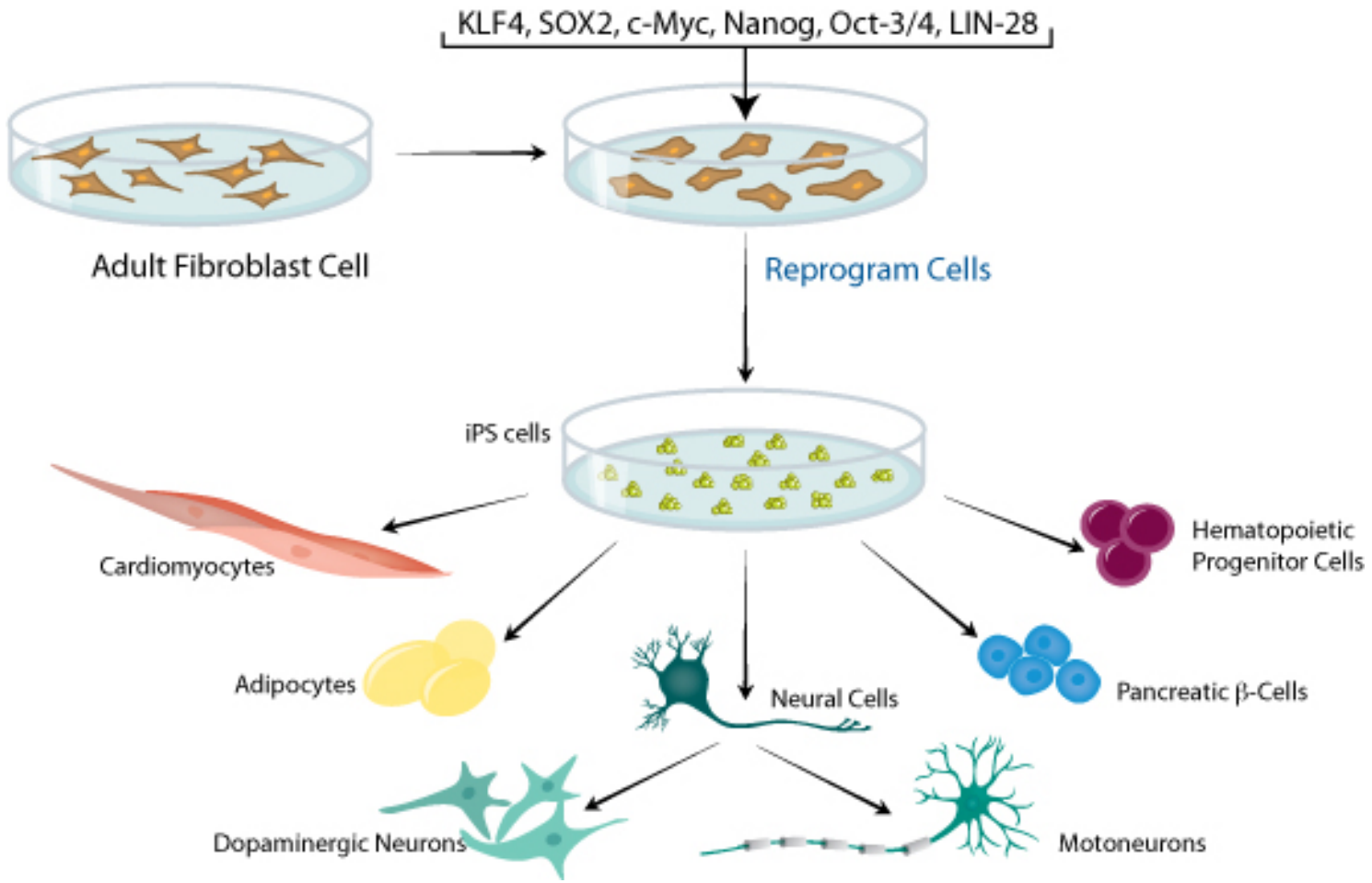


Each of these transcription factors has been found to regulate **over 1000 different genes**

OCT 4 (octamer binding transcription factor **4)**
Sox2 (sex determining region Y- b**ox** 2)
Nanog (*Irish,* Tír **na nÓg** , "land of eternal youth")

Pluripotency can be regained: induced pluripotent stem cells (**iPS**)

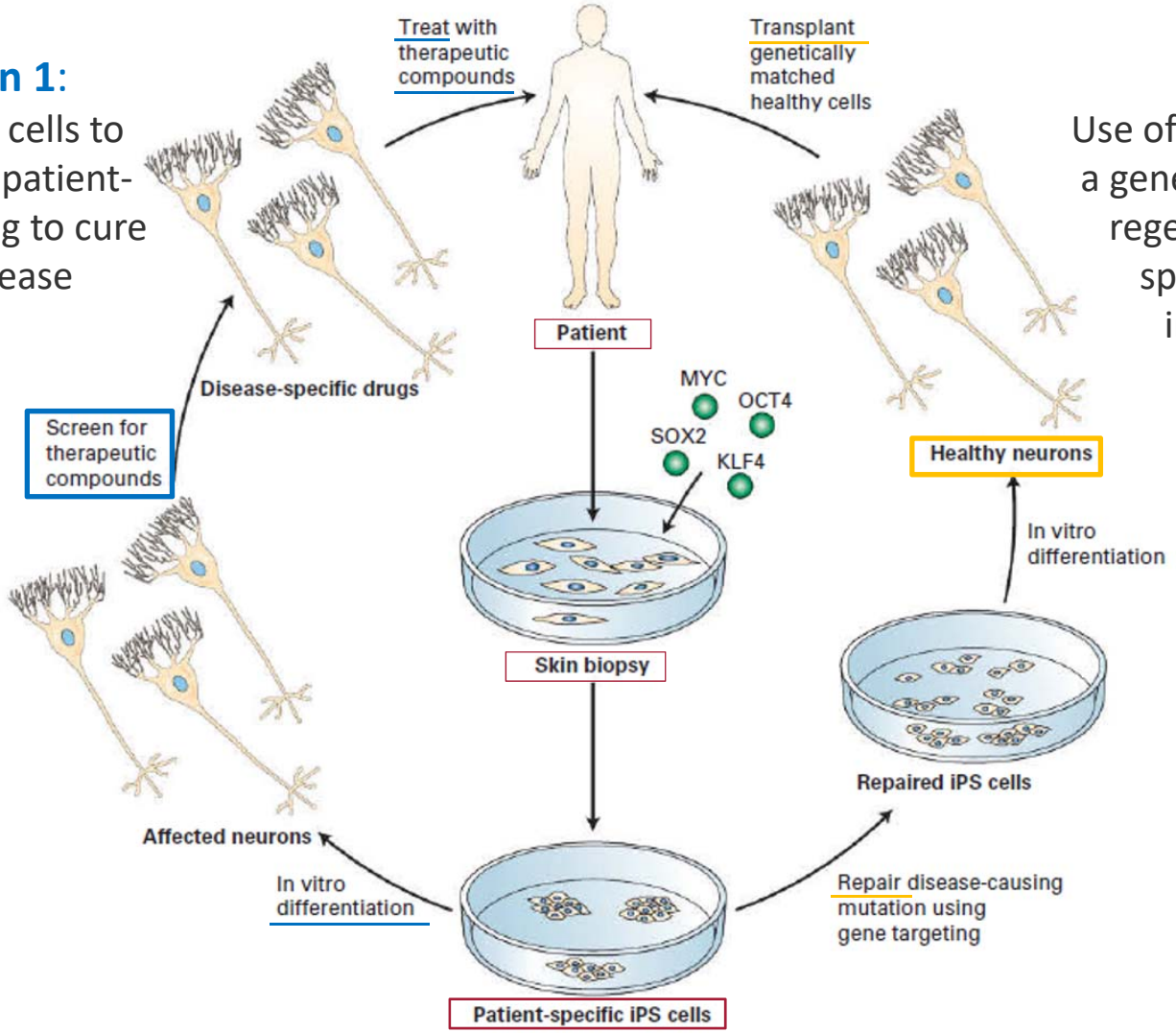
By introducing four different transcription factors, Klf4, Sox2, Oct4, c-myc (they are also called Yamanaka transcription factors)



Medical applications for induced pluripotent stem cells (**iPS**)

Two strategies for using patient-specific iPS cells:

Option 1:
Use of iPS cells to produce a patient-specific drug to cure the disease



Option 2:
Use of iPS cells to repair a genetic defect and to regenerate patient-specific cells for implantation

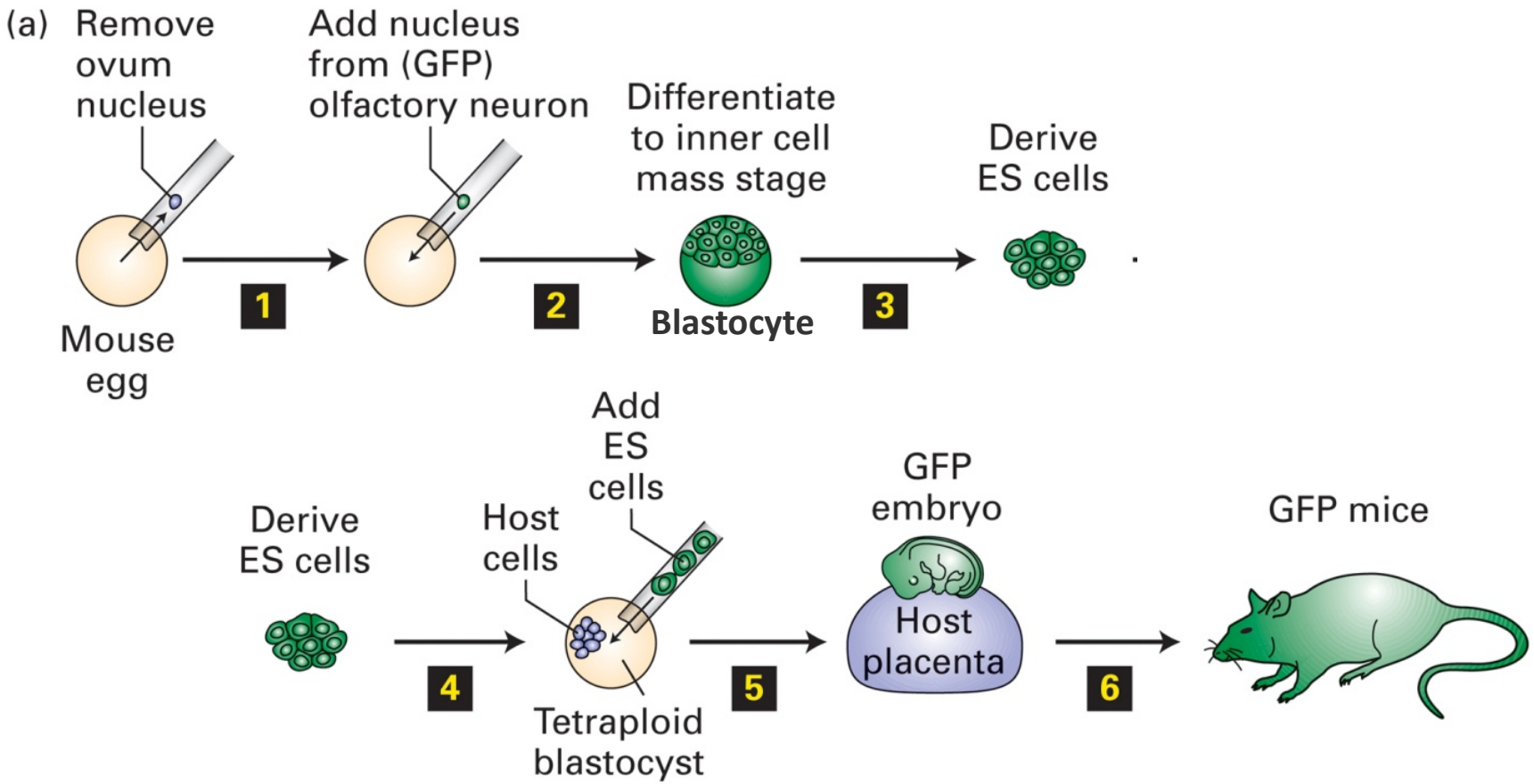
Embryonic stem cells to restore and replace damaged tissue

The use of embryonic stem cells to cure diabetes

- Embryonic stem cells were **induced to differentiate into pancreatic endoderm**, which were then transplanted into mice.
- These mice will produce functional beta islet cells to produce insulin.
- Danger in introducing **undifferentiated embryonic stem cells**, because they will **produce tumor like mass,** containing large amounts of poorly differentiated cells

Animal cell differentiation can be reversed

Cloned animal by the transfer of a nucleus of a differentiated somatic cell into an induced pluripotent stem cell (iPS):
- Generation of iPS cells based on the nucleus of a differentiated olfactory neuron -



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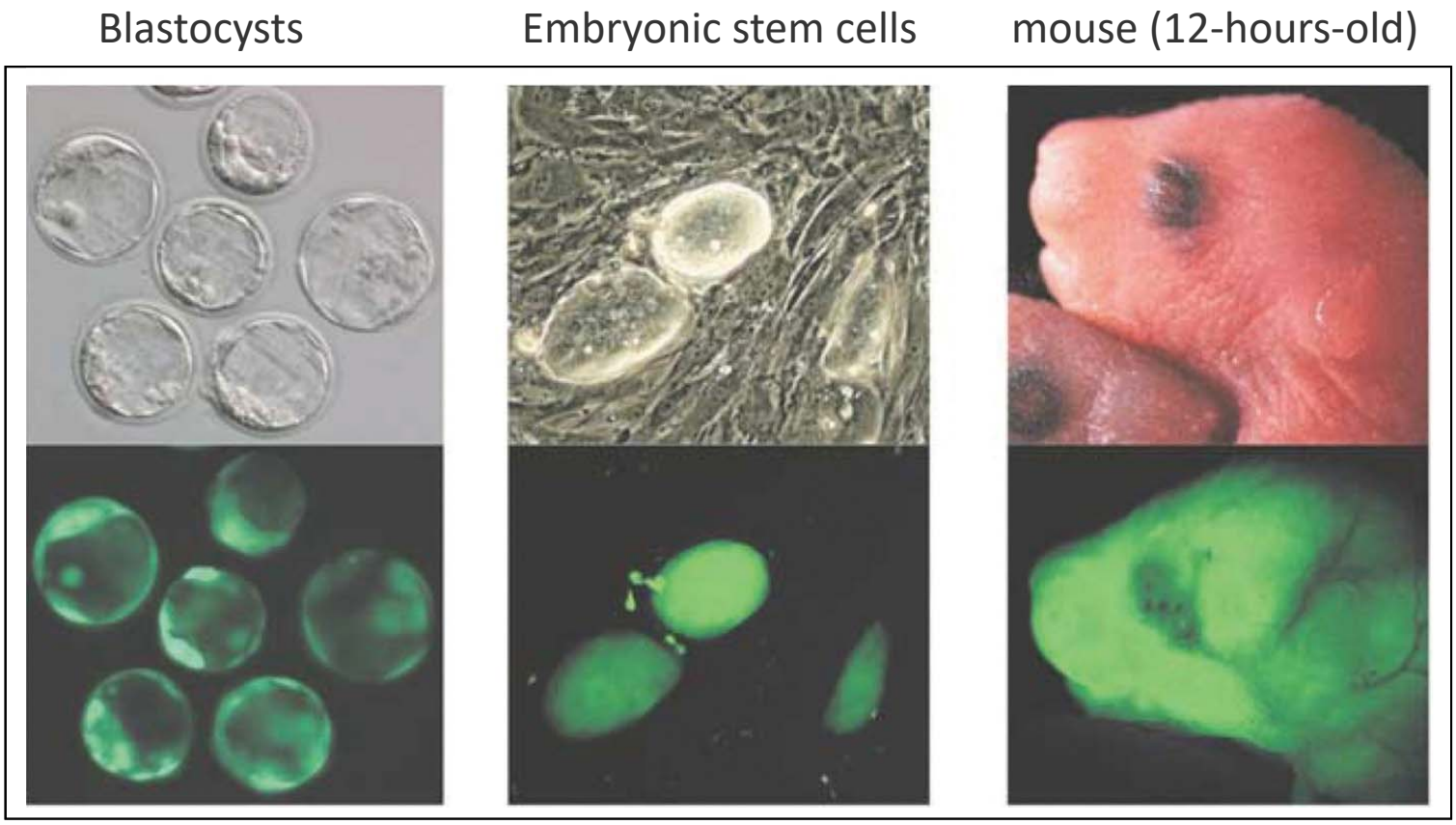


III. Stem cell and Niches in multicellular organisms

Stem cells occur in many tissues:

- blood
- intestine
- skin
- muscles
- ovaries and testes

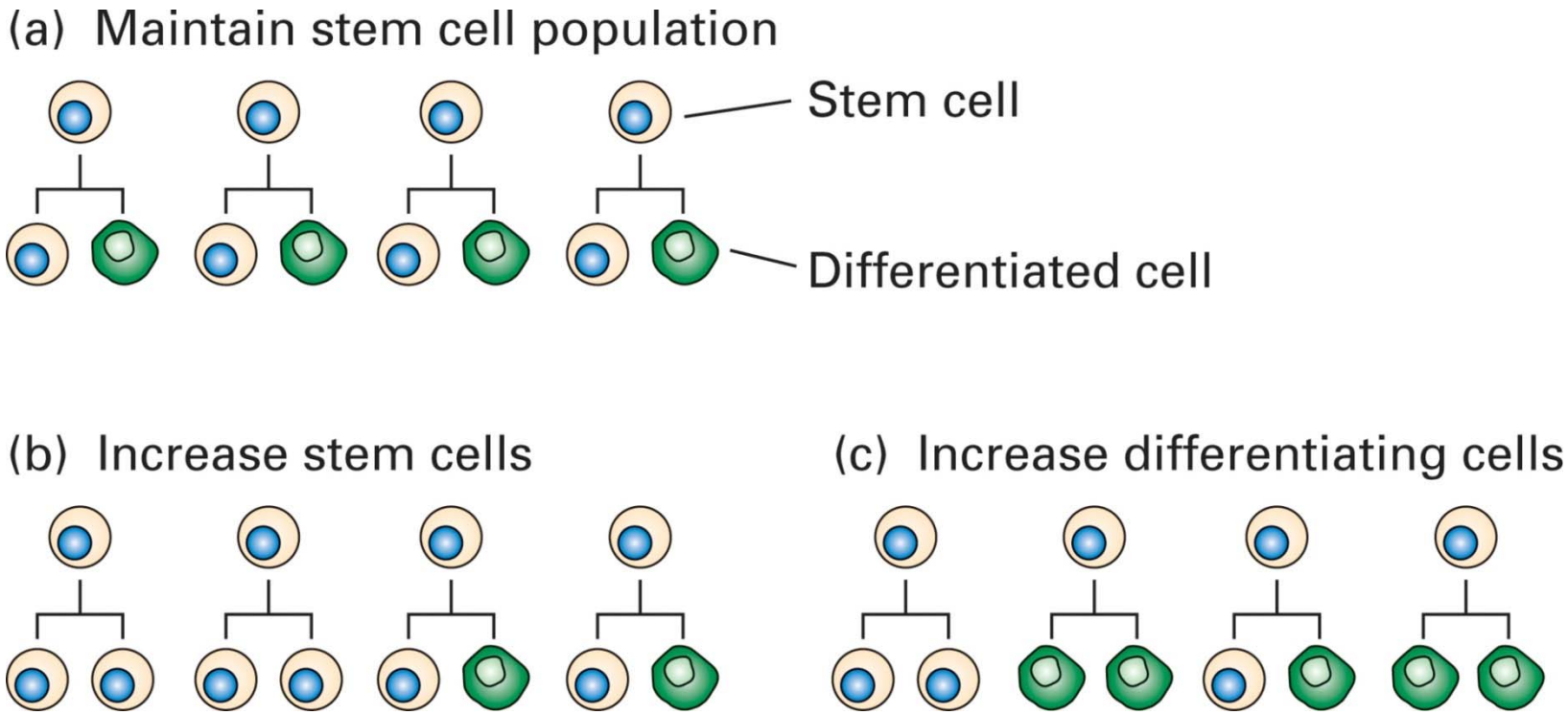
Reason:

- to replace old differentiated cells or tissue regeneration
  (while for liver and pancreatic beta-islet, cells renewal maybe from existing differentiated cells)

1. germ-line stem cells
2. intestinal stem cells
3. neural stem cells
4. hematopoietic cells

Regulation of stem-cell population

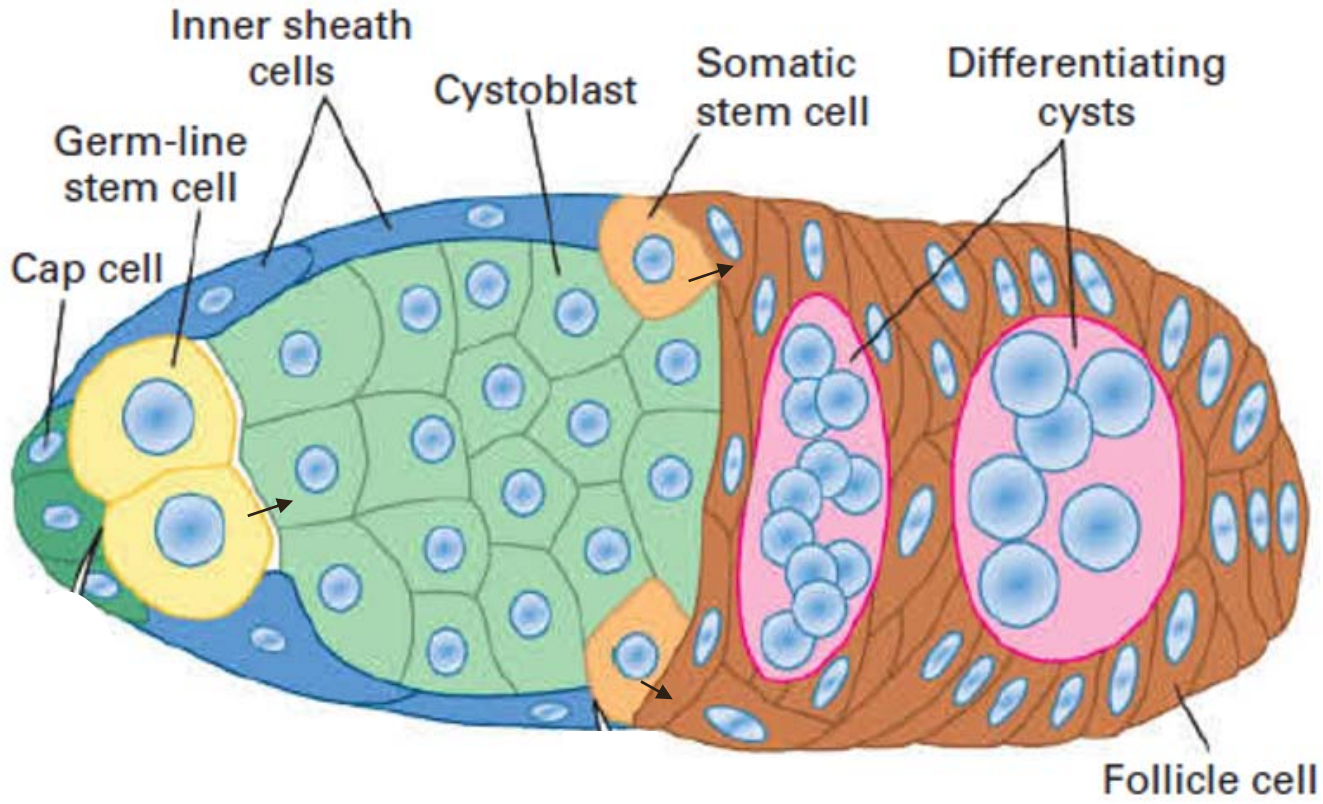
Homeostasis, increase or decrease of the stem cell population



Both, intrinsic and extrinsic factors control stem cell status. Extrinsic factors refer to hormonal and regulatory signals from surrounding cells

1. Germ-line stem cells: cell lineage that produce sperm and oocyte

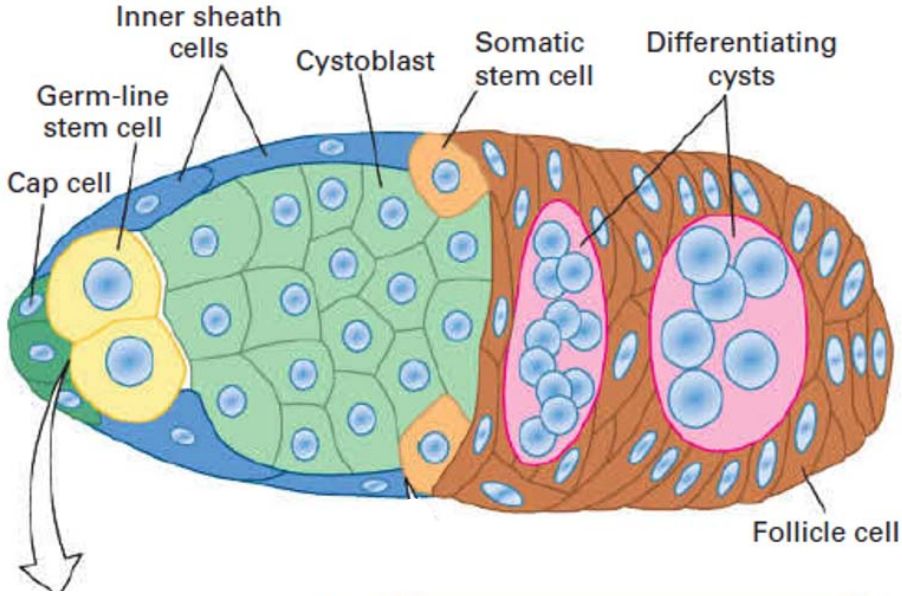
Stem cells and niches in fly germarium



The **germ-line stem cells** produce cystoblasts (green),
which undergo four rounds of mitotic division to produce 16 interconnected cells, one of which becomes the oocyte.
The **somatic stem cells** produce follicle cells (brown), which will make the eggshell

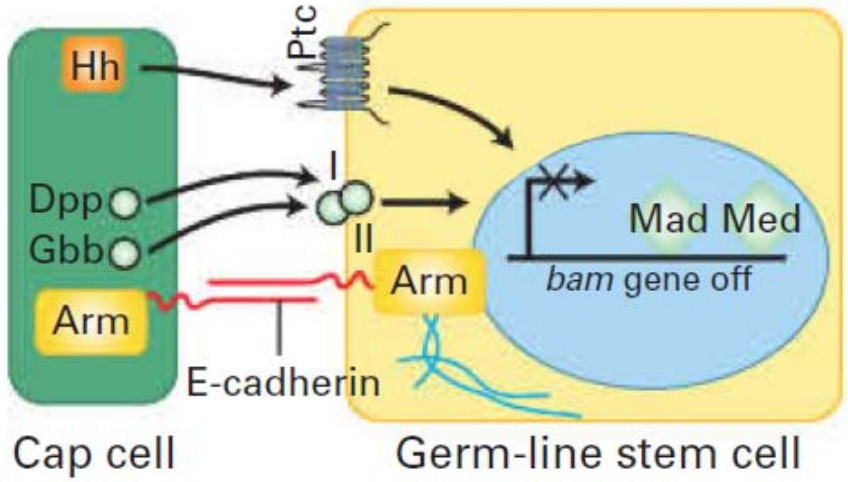
1. Germ-line stem cells: cell lineage that produce sperm and oocyte

Stem cells and niches in fly germarium



Control of germline stem cells:

- TGF-ß family proteins Dpp & Gbb bind to the TGF-ß receptors I/II
  →repression of *bam* genes by the transcription factors Mad & Med
- Repression of *bam* triggers self-renewal; expression of bam triggers differentiation
- E-Cadherin forms homotypic adherens junction, Armadillo (Arm)/catenin links actin



1. Germ-line stem cells: cell lineage that produce sperm and oocyte

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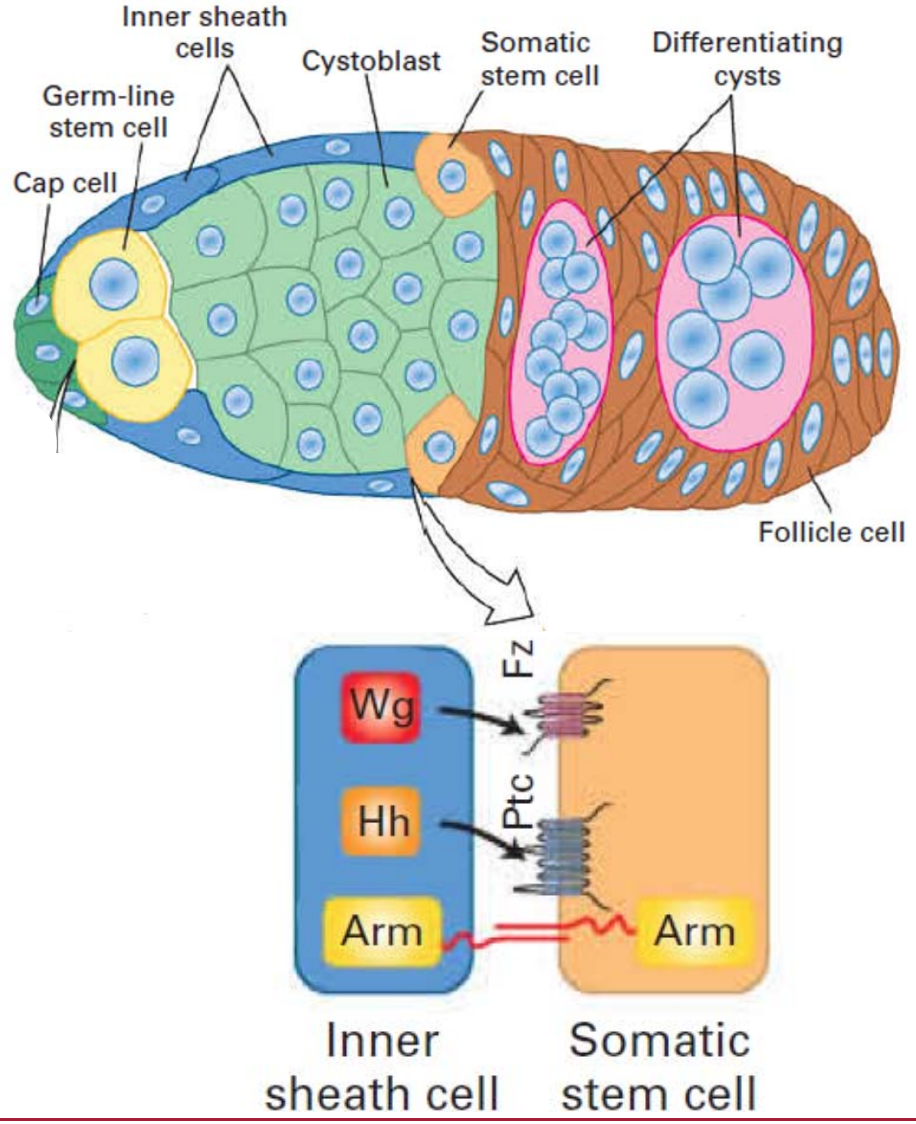
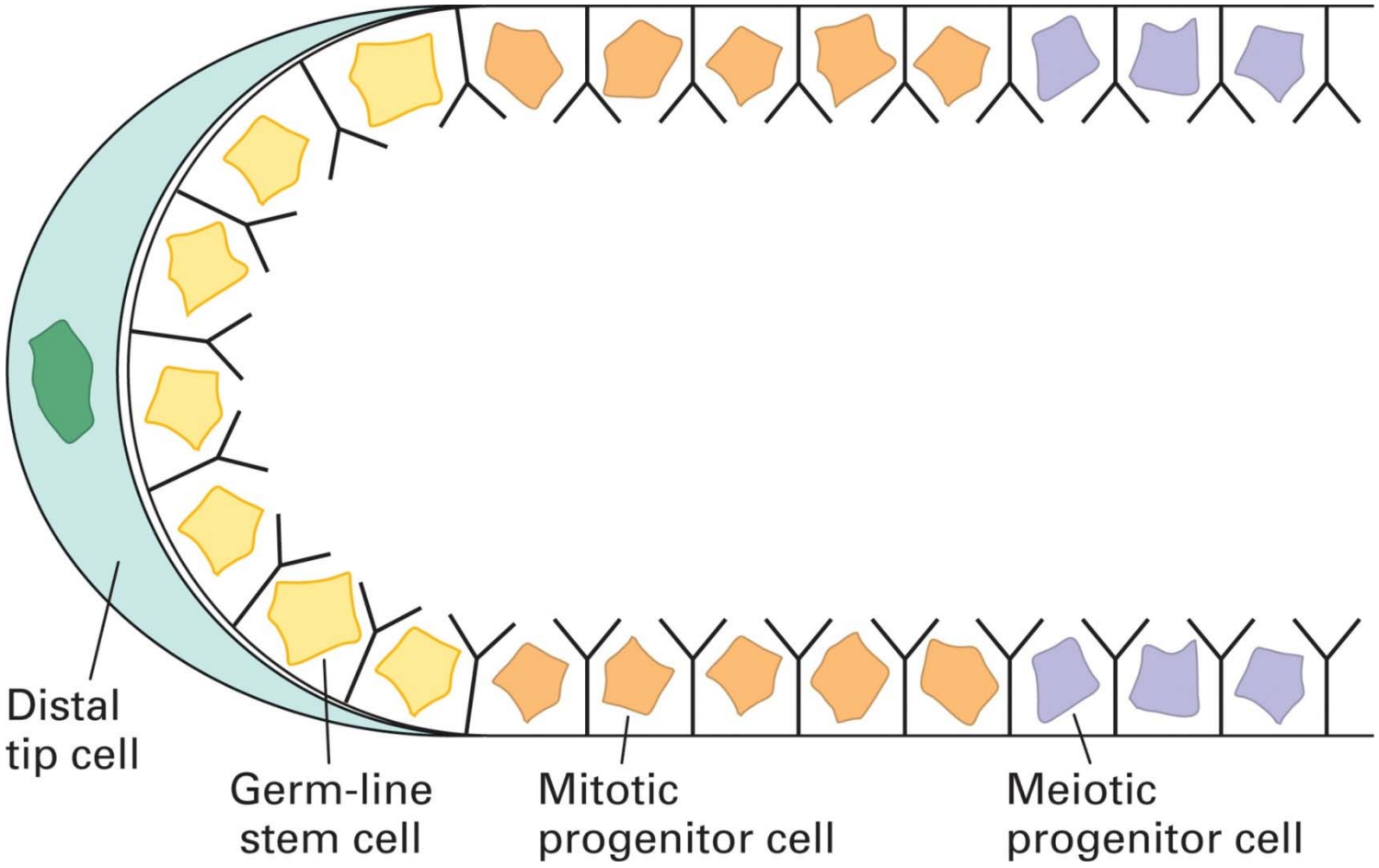


Control of somatic stem cells:

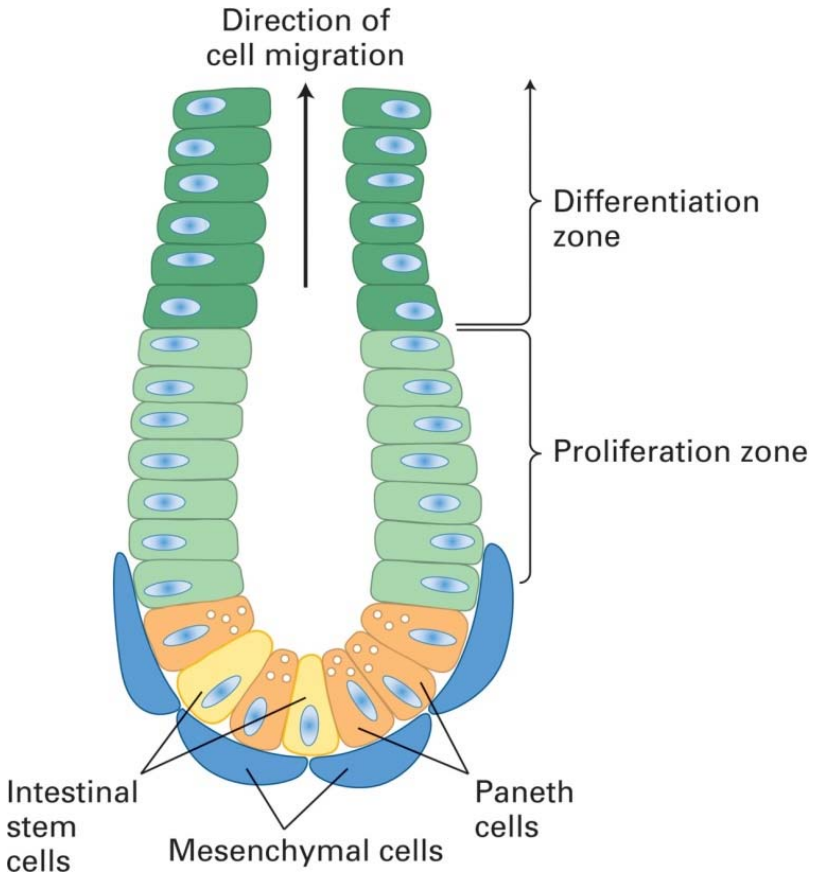
- The Wnt signal Wingless (Wg) is produced by the inner sheath cells and is received by the Frizzled receptor (Fz) on a somatic stem cell.
- Hh is similarly produced and is received by the Ptc receptor.
- Both of these signals result in self-renewal of somatic stem cells
- E-Cadherin forms homotypic adherens junction, Armadillo (Arm)/catenin links actin

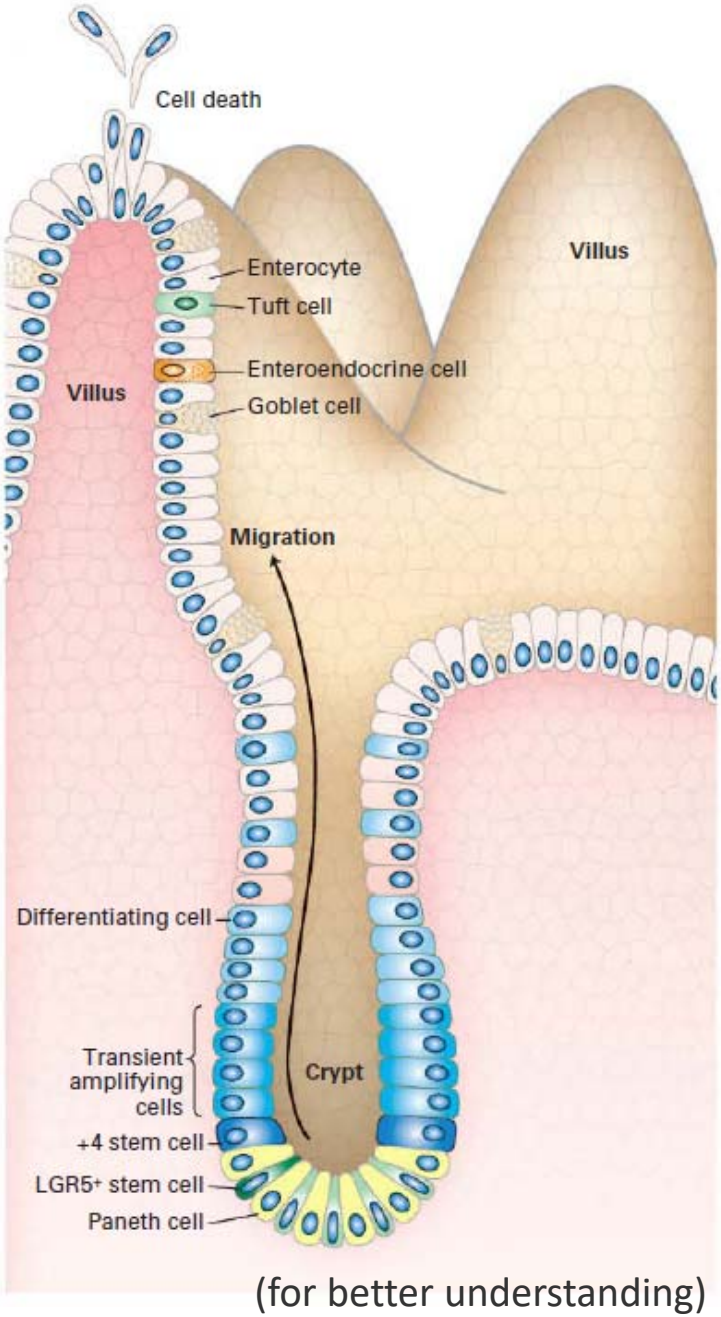
Germ-line stem cells in C. elegans



2. Intestinal stem cells

Intestinal epithelial cells renew every 5 days, through stem cells beneath the crypts: movement of cells

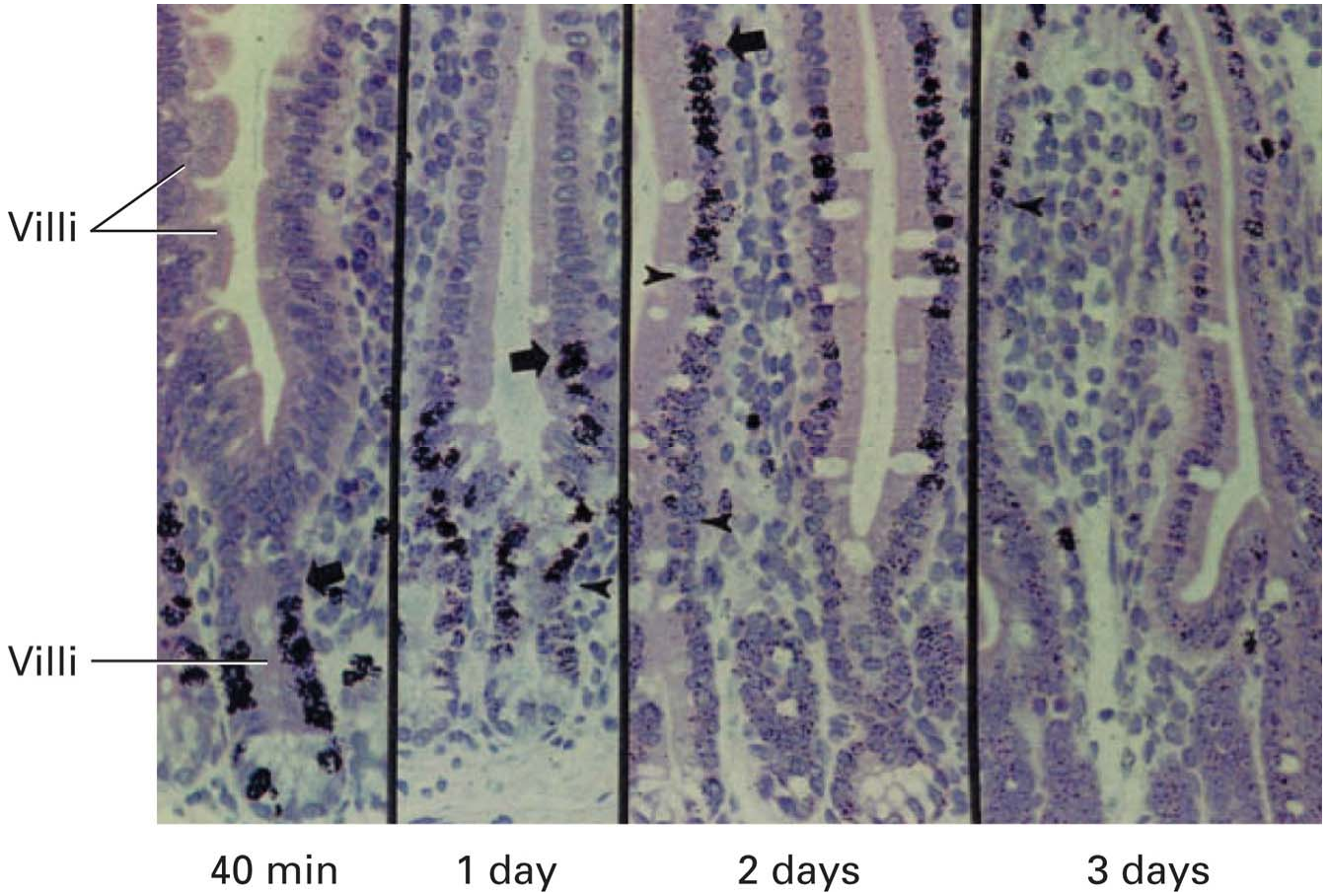




(for better understanding)

How to prove the movement of the epithelial cells?

Pulse-chase experiments using radiolabeled thymidine

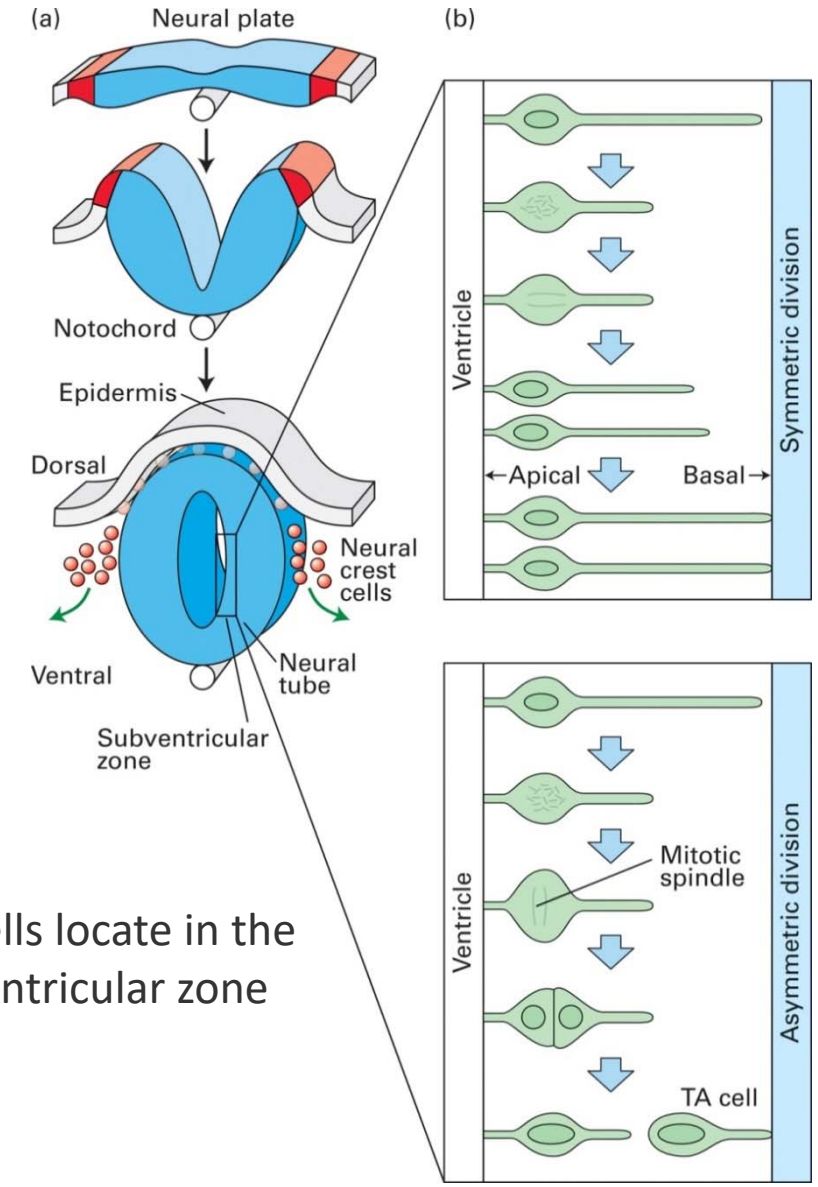


3. Neural stem cells

Neural stem cells form nerve and glial cells in the central nervous system

It is promising to use neural stem cells to find a cure for neurodegenerative disease.

Formation of the neural tube and division of the neural stem cells

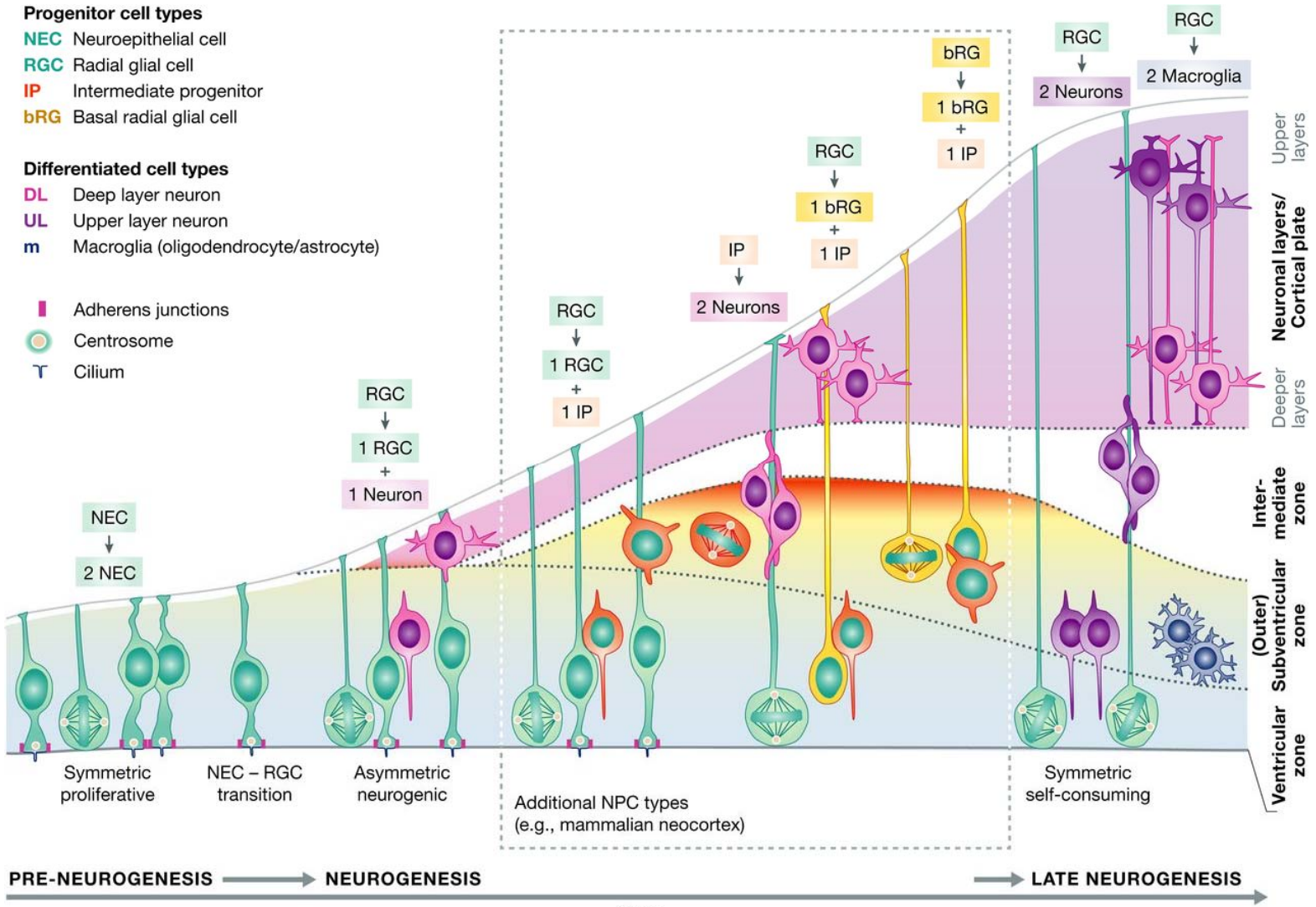


Stem cells locate in the subventricular zone

Spindle poles orient differently

For further reading:

Neurogenesis during development of the vertebrate



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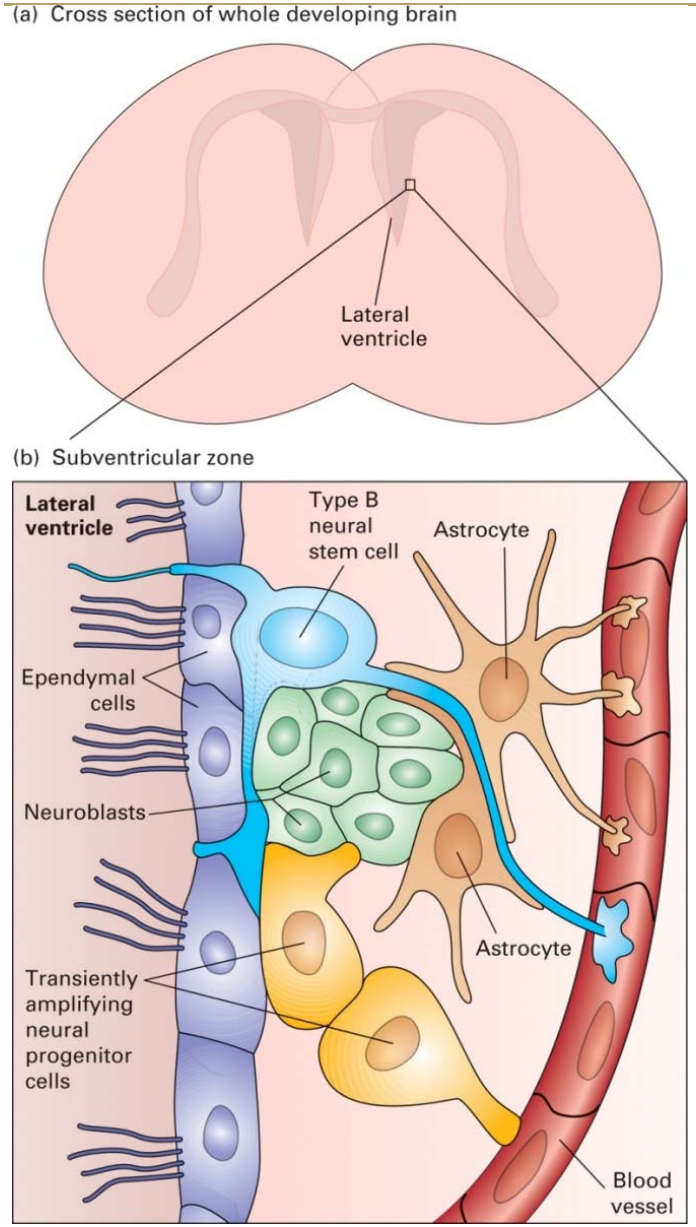
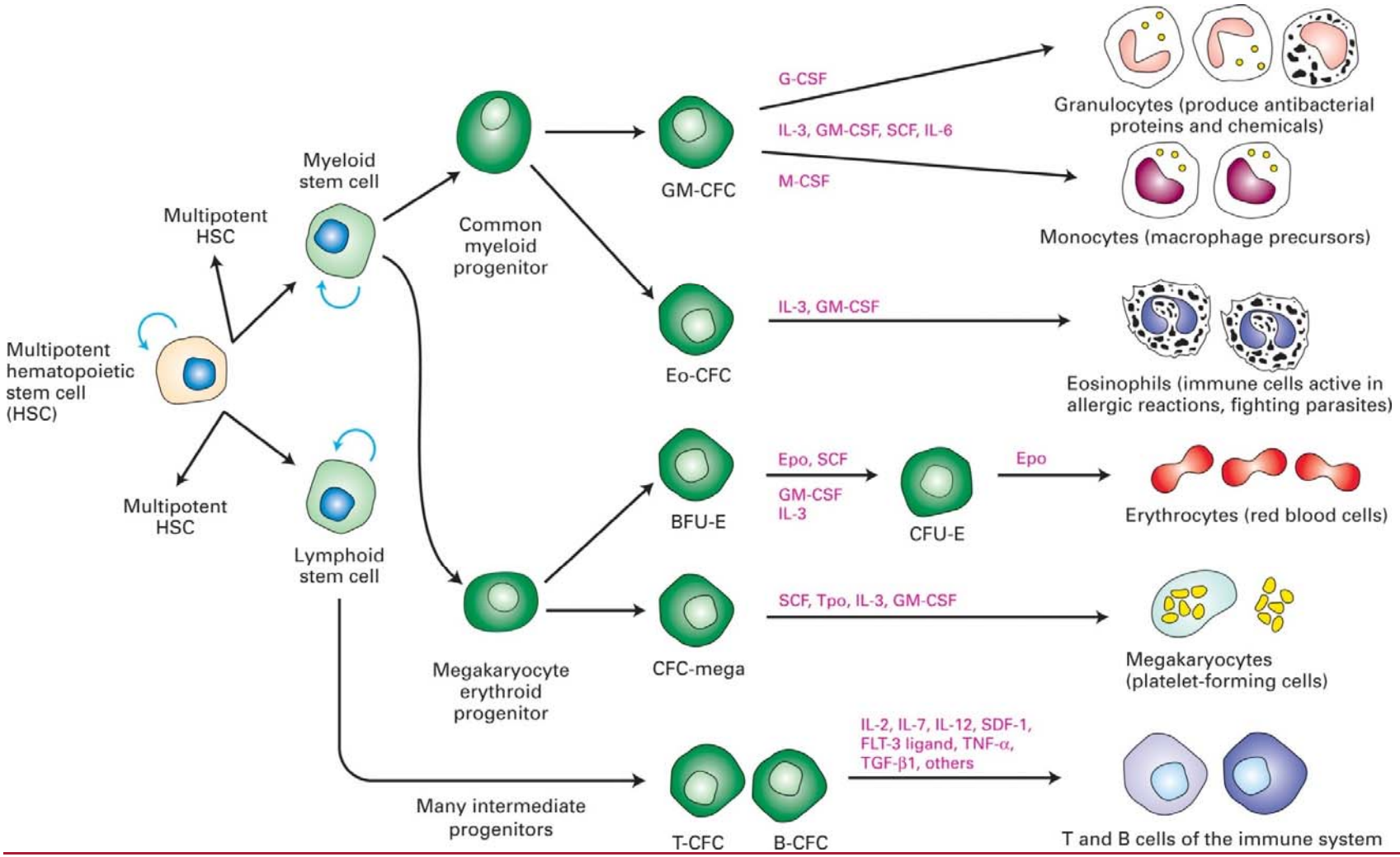
Does adult brain produce new nerve cells?



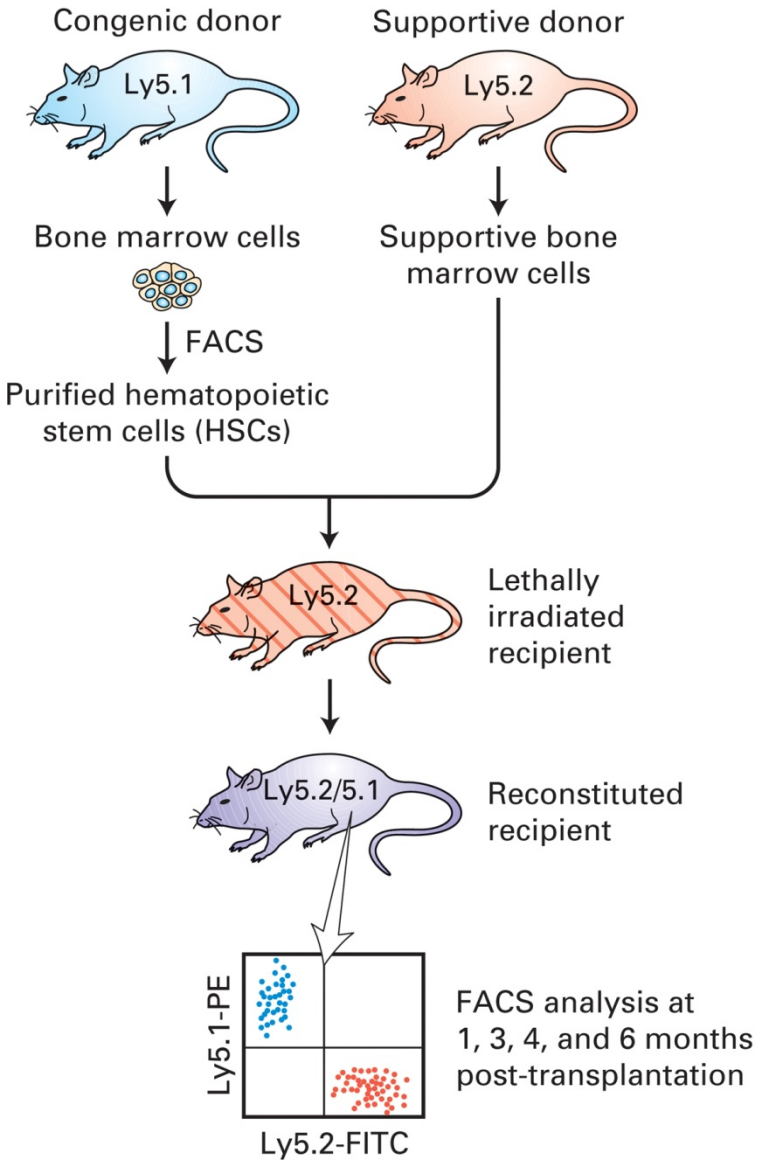
Yes: nerve stem cells exist in
Hippocampus zone, subventricular region

4. Hematopoietic stem cells (HSCs)

Hematopoietic stem cells in embryonic liver and adult bone marrow.
form all blood cells



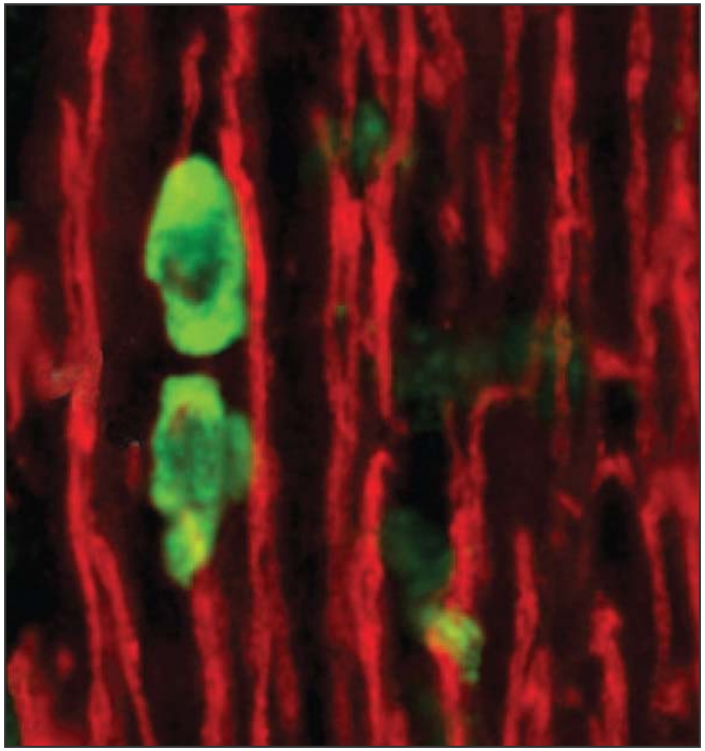
Bone marrow transplantation has been effective to treat many blood disease including leukemia



IV. Neurons and glia

Human brain has 10^{11} neurons and about 10^{14} synapses.

Glial cells occupy the space between neurons and modulate neuron function.

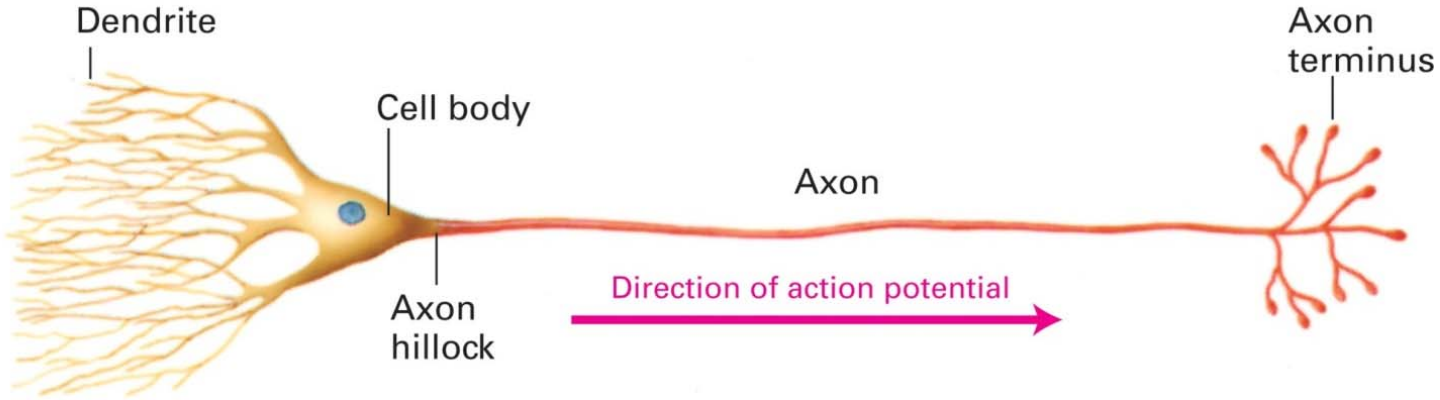


Red: neuron axon

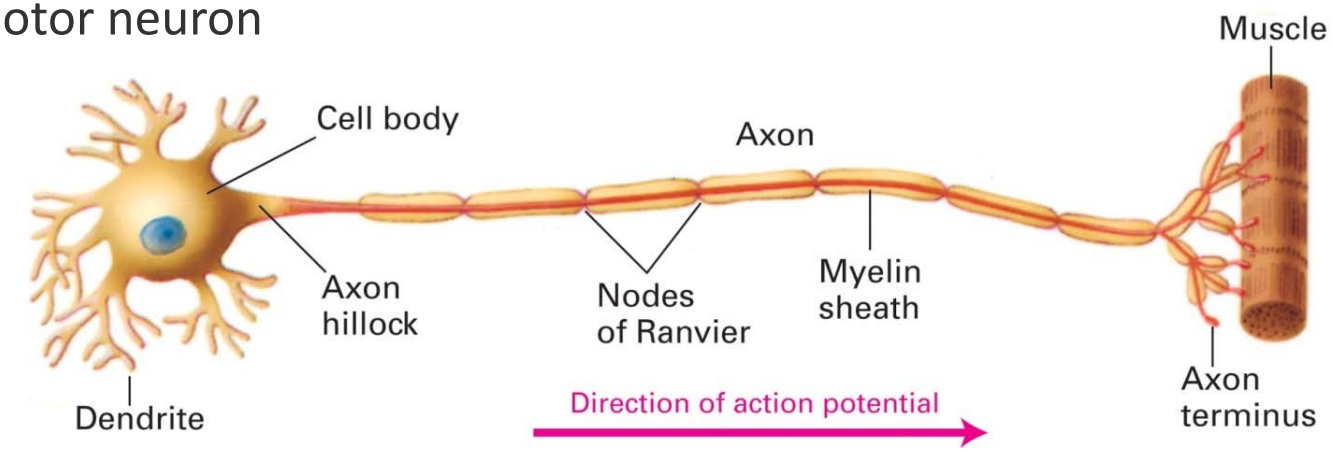
Green: glial cells

Two types of neurons: multipolar interneuron and motor neuron

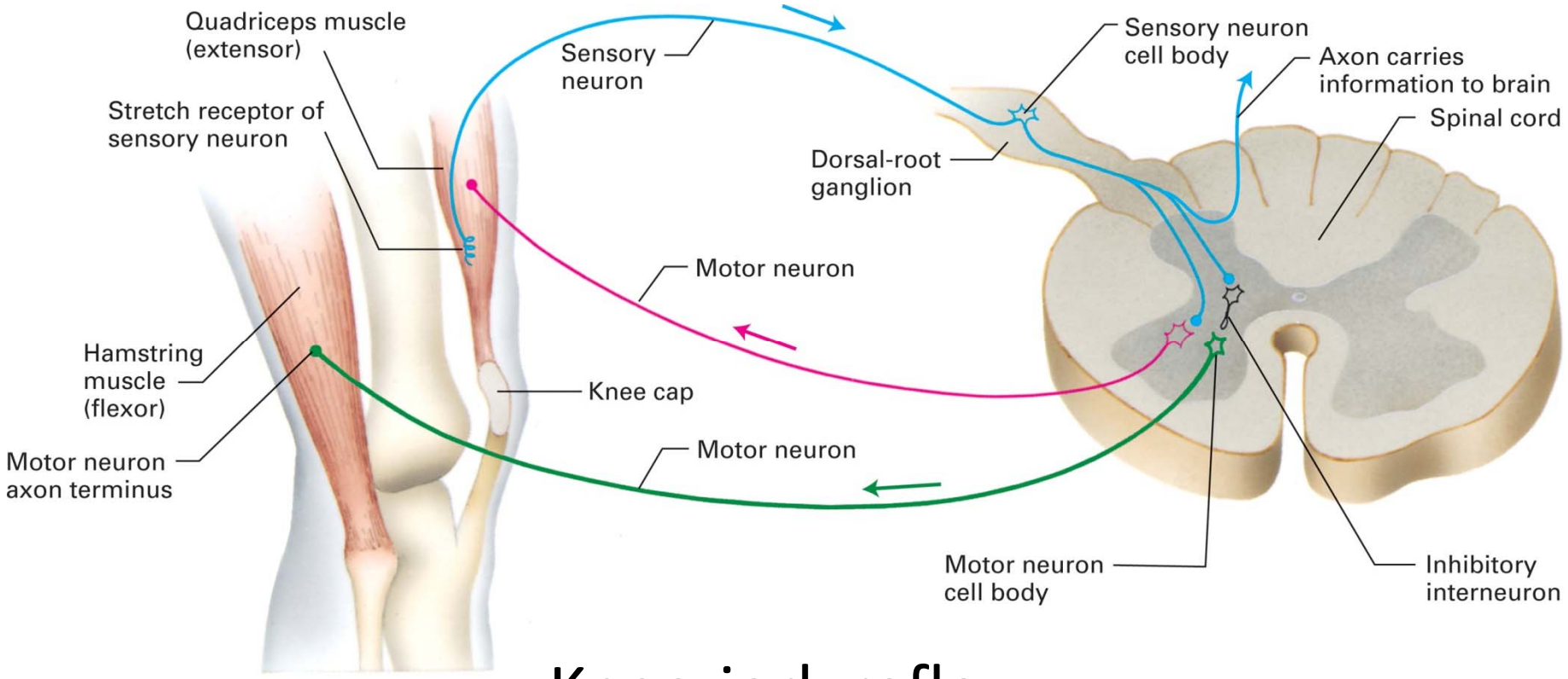
Multipolar interneuron



Motor neuron



Multiple neurons in signaling circuits



Knee-jerk reflex

Sensory neurons

Effector neurons

Interneurons: the largest group

Glia cells

Glia cells form myelin sheaths and support neurons

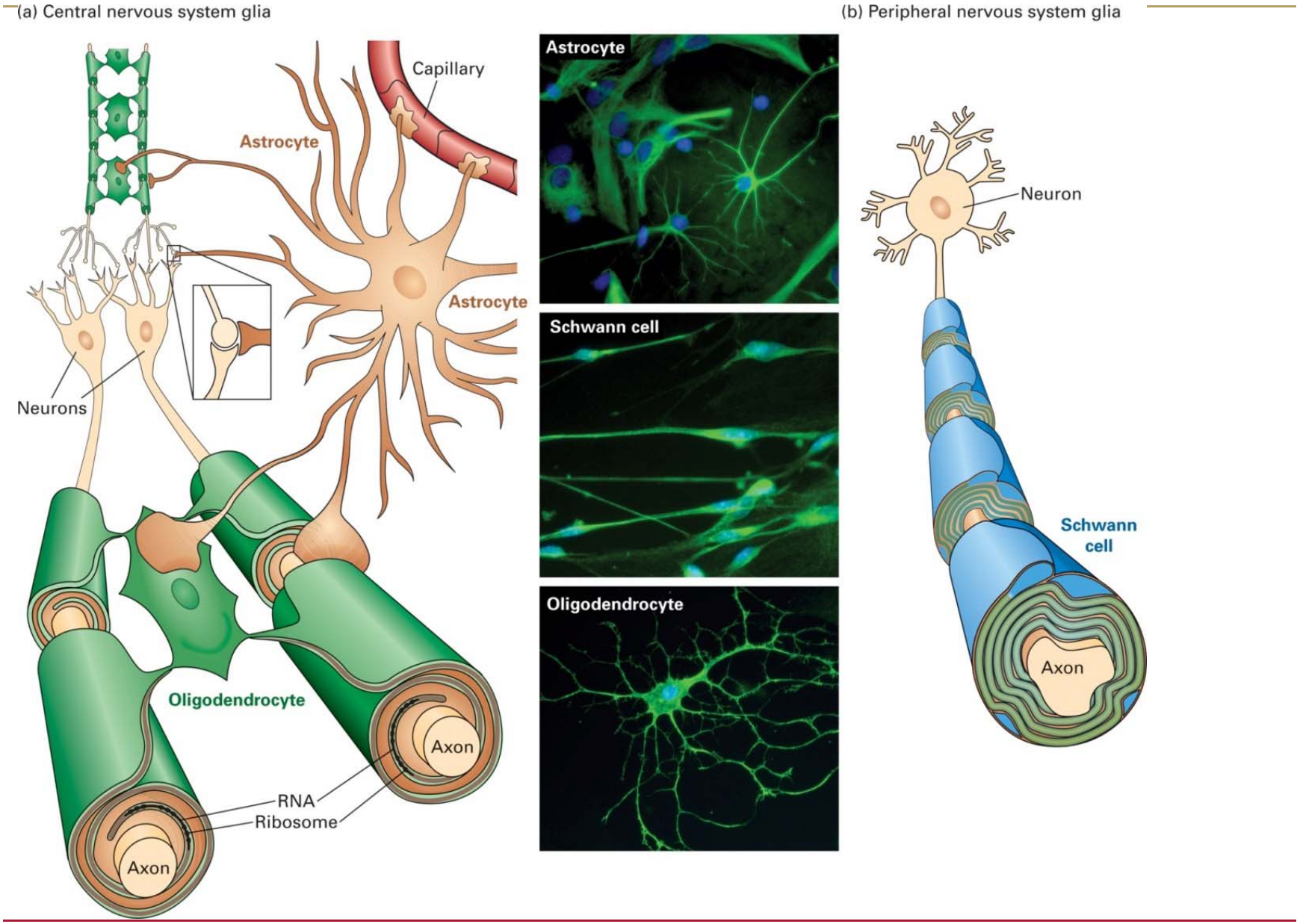
Glia cells can be divided into three categories:

1. Oligodendrocytes:
    - make sheaths for the **central nervous system**

2. Schwann cells:
    - make sheaths for the **peripheral nervous system**

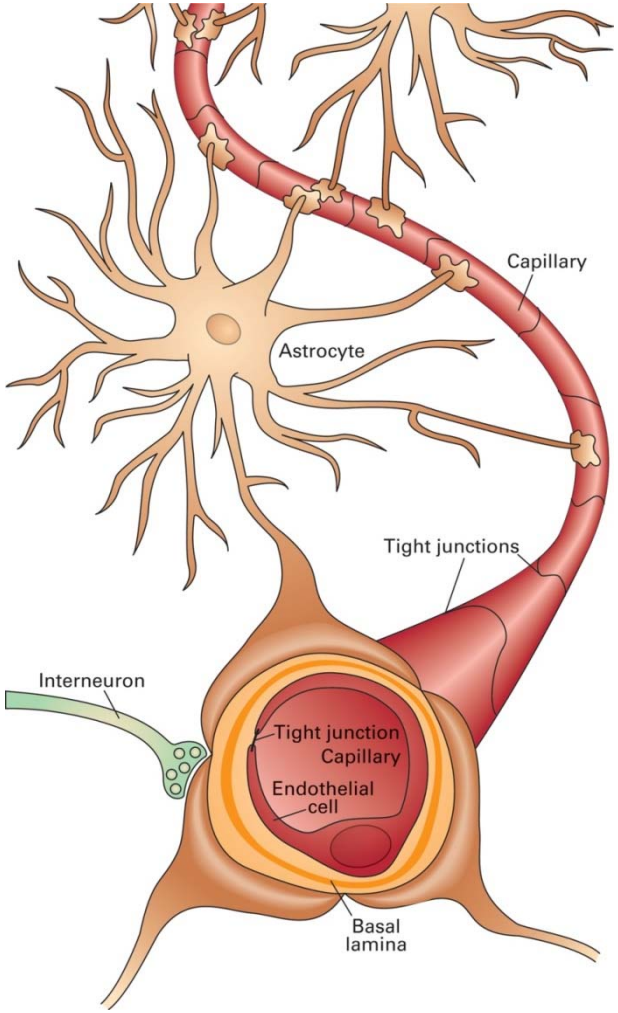
3. Astrocytes:
    - star-like shape,
    - provide growth factors and other signals to neurons
    - receive signals from neurons and induce synapse formation between neurons.

The three types of glia cells



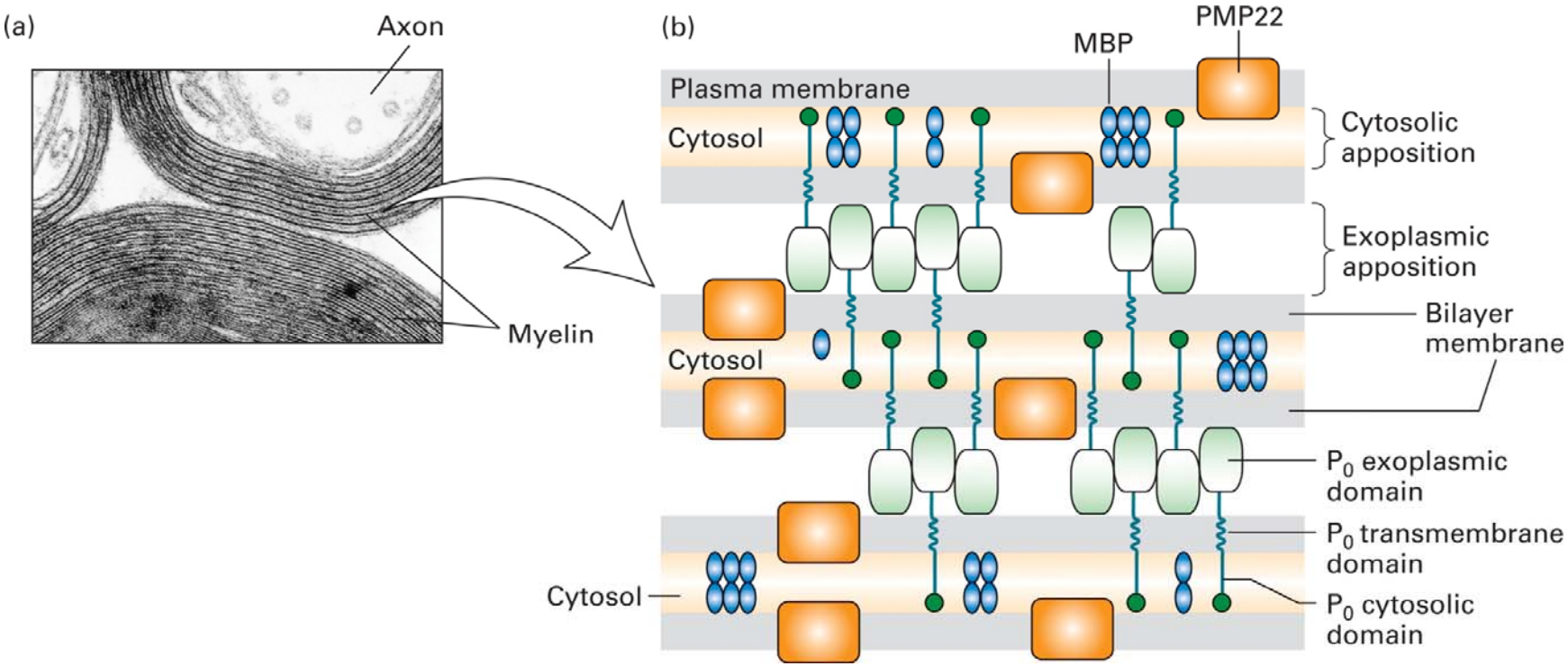
Astrocytes

Astrocytes interact with endothelial cells at the blood-brain barrier



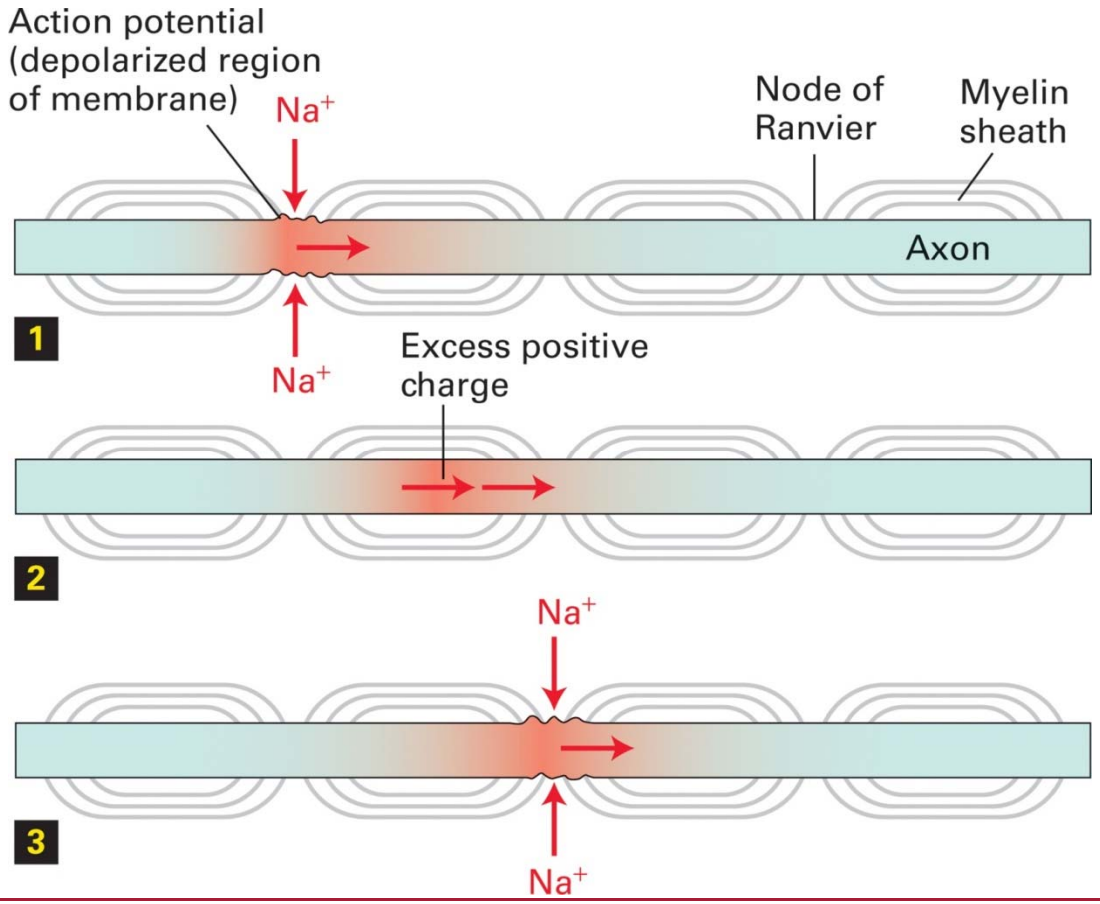
- Approximately 1/3 of the brain mass and about 1/2 of the total brain cells are astrocytes.
- Produce ECM proteins.
- Joined together by gap junctions

The structure of myelin sheath



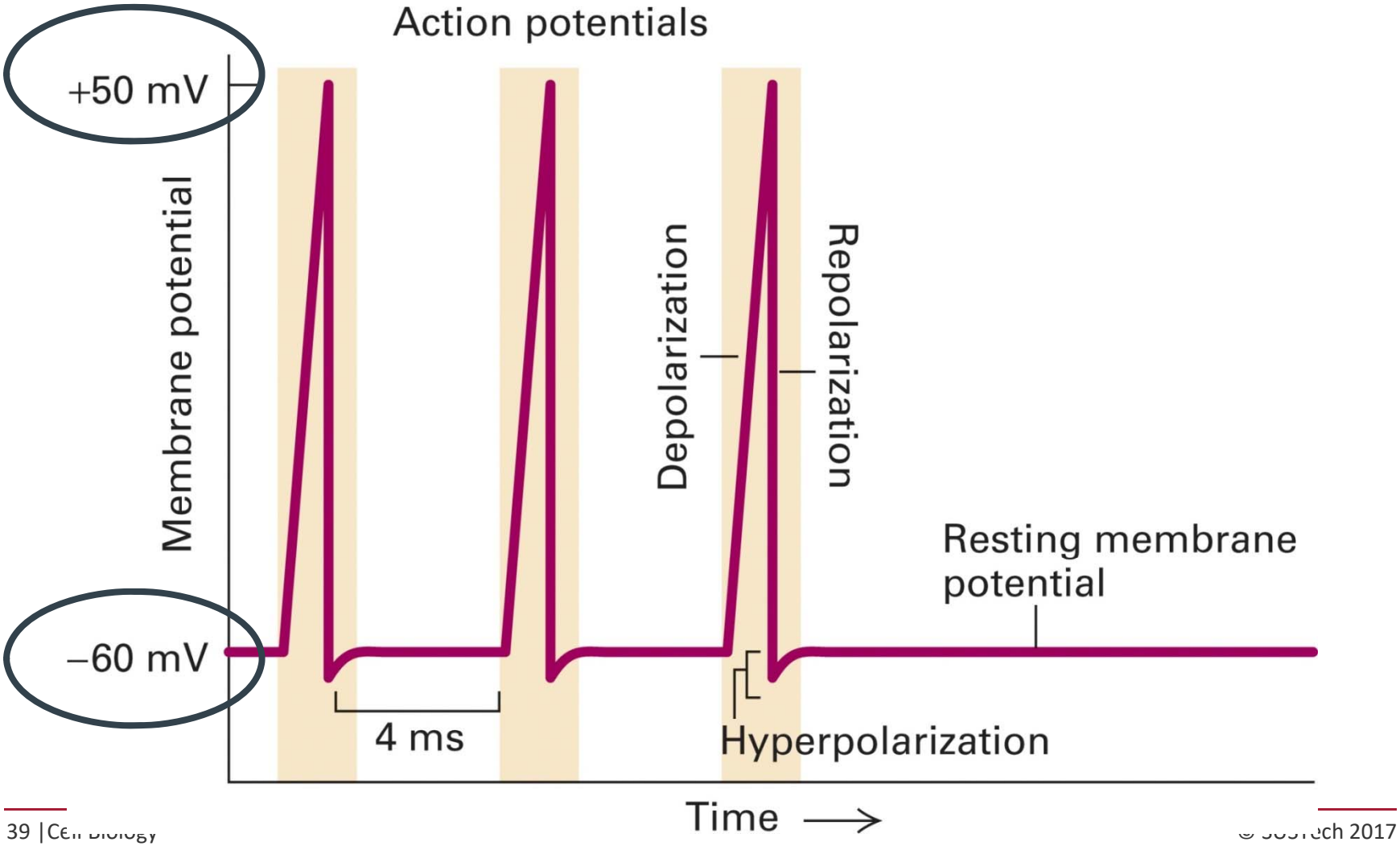
Functions of myelin sheath

Increases the velocity of impulse conduction

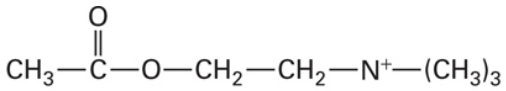


Action potential
Jumps from node
To node

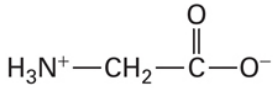
Nerve resting potential and action potential



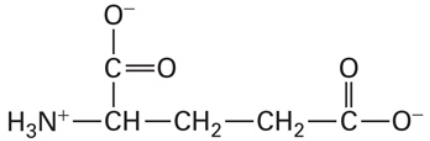
Several neurotransmitters



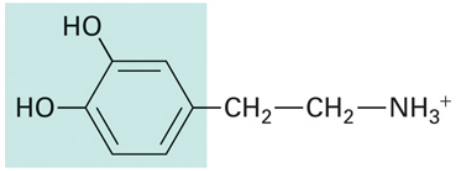
Acetylcholine



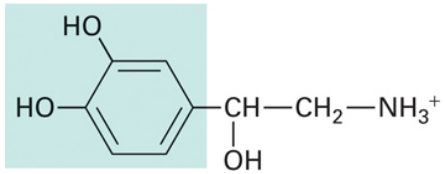
Glycine



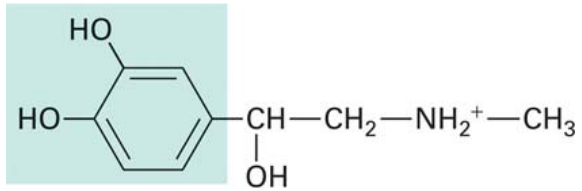
Glutamate



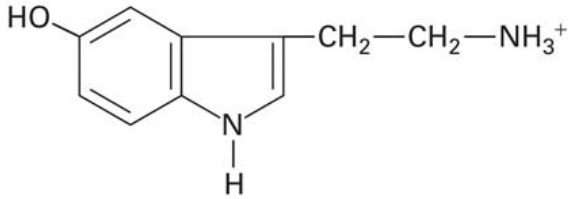
Dopamine
(derived from tyrosine)



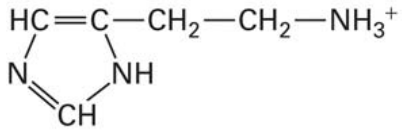
Norepinephrine
(derived from tyrosine)



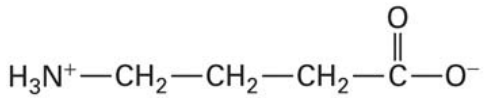
Epinephrine
(derived from tyrosine)



Serotonin, or **5-hydroxytryptamine**
(derived from tryptophan)



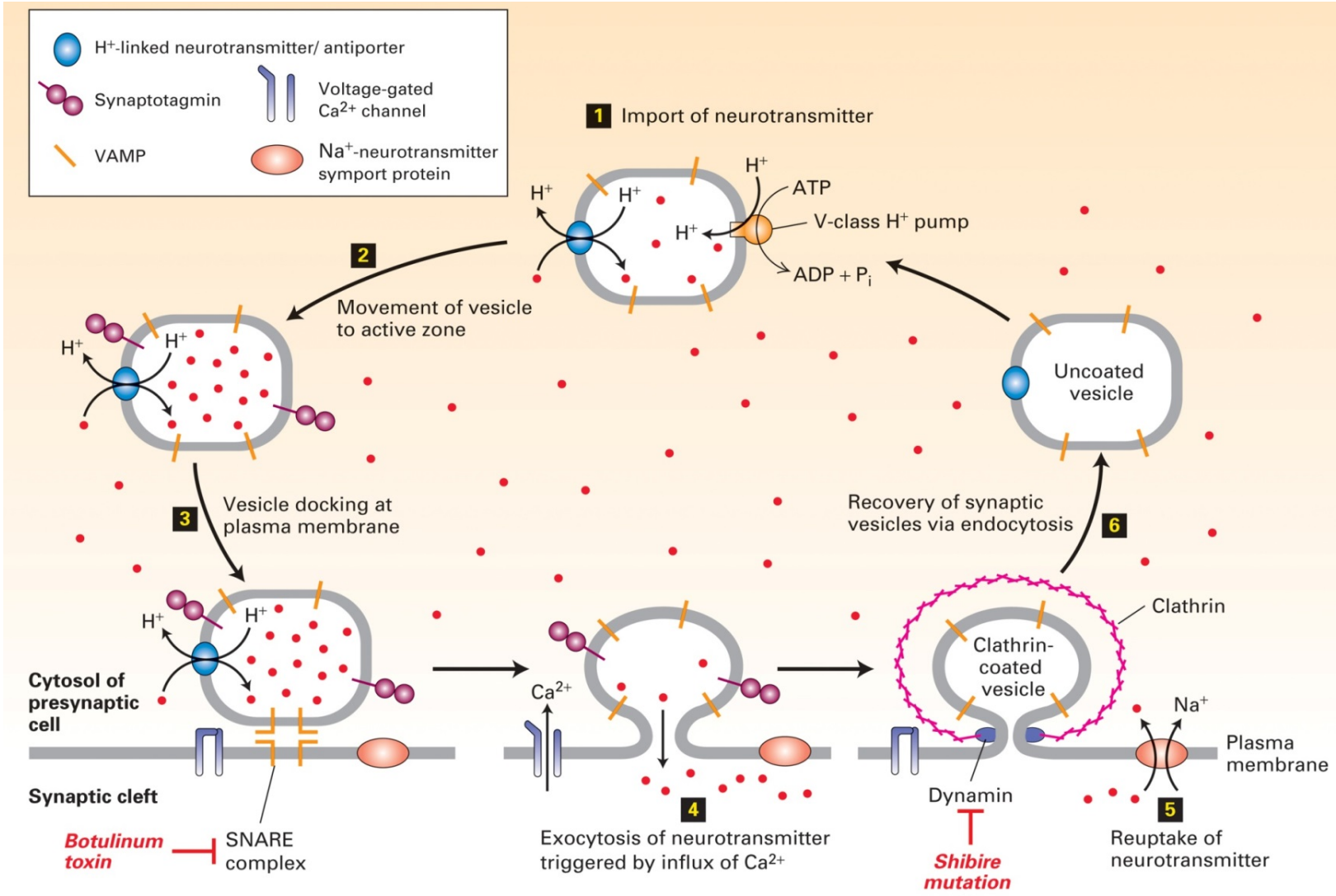
Histamine
(derived from histidine)



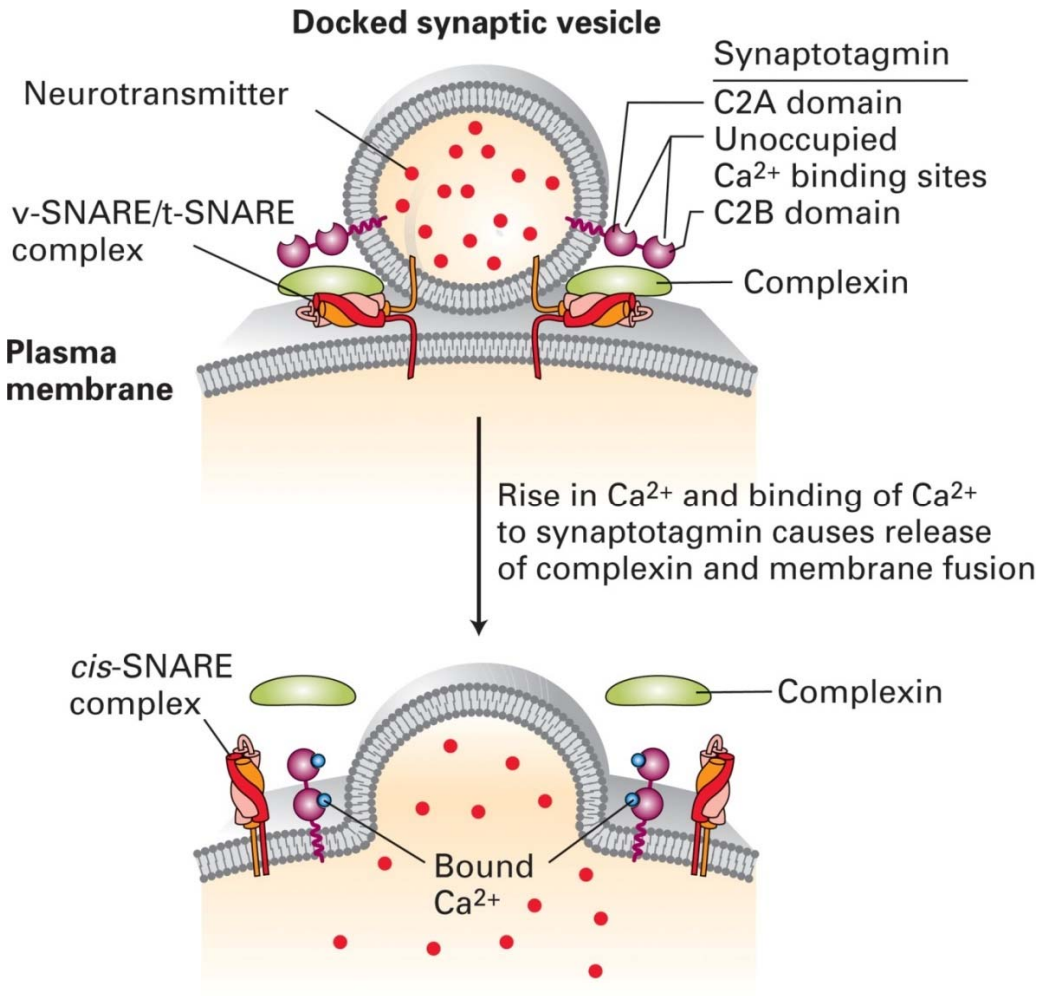
γ-Aminobutyric acid, or **GABA**
(derived from glutamate)

The cycling of neurotransmitters and of synaptic vesicles in axon termini

All neurotransmitters are synthesized in the cytosol and are imported into vesicles



Fusion of synaptic vesicles with the plasma membrane



Signaling at synapses is terminated by degradation or reuptake of neurotransmitters

And this lecture series is terminated with this slide

Thank you for your attention !!!