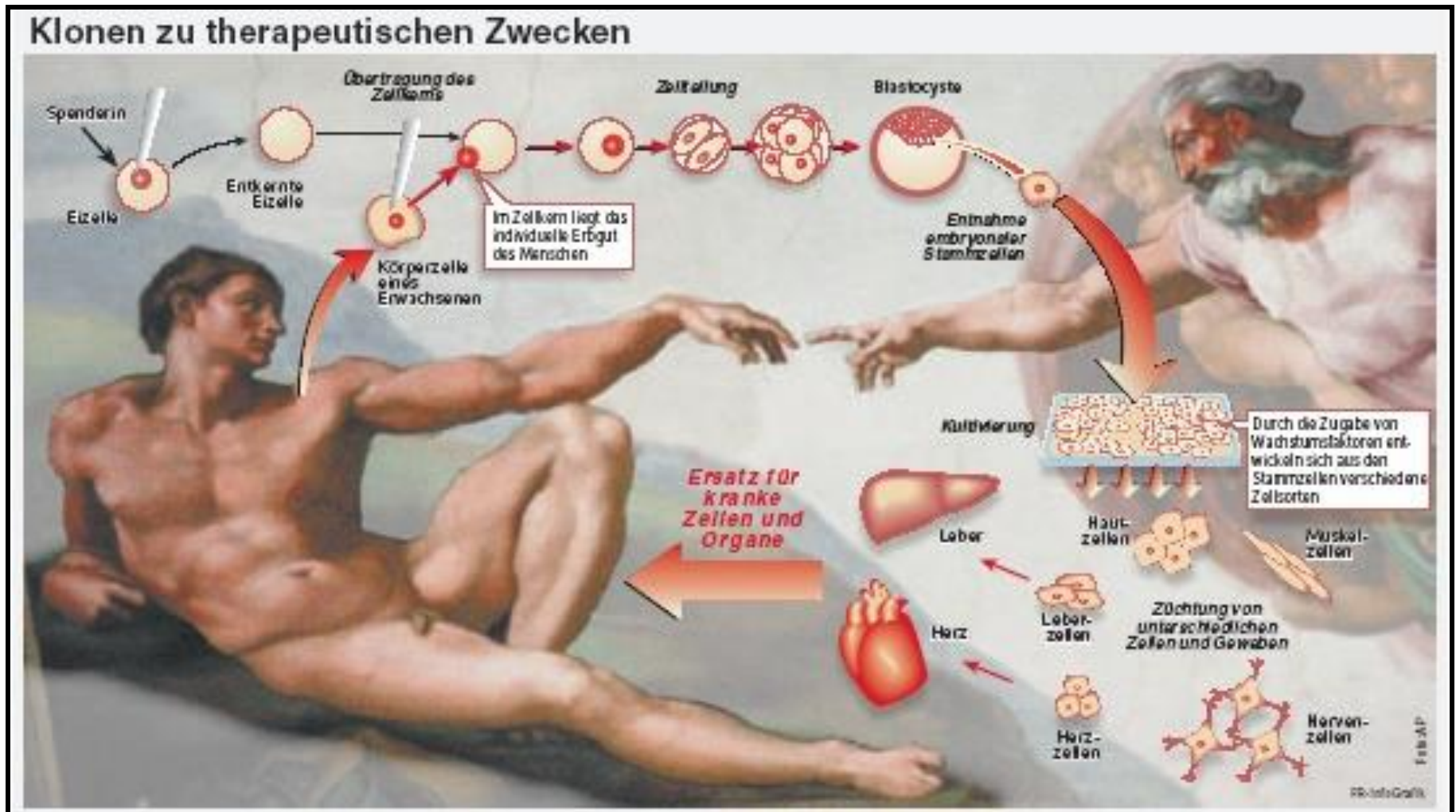


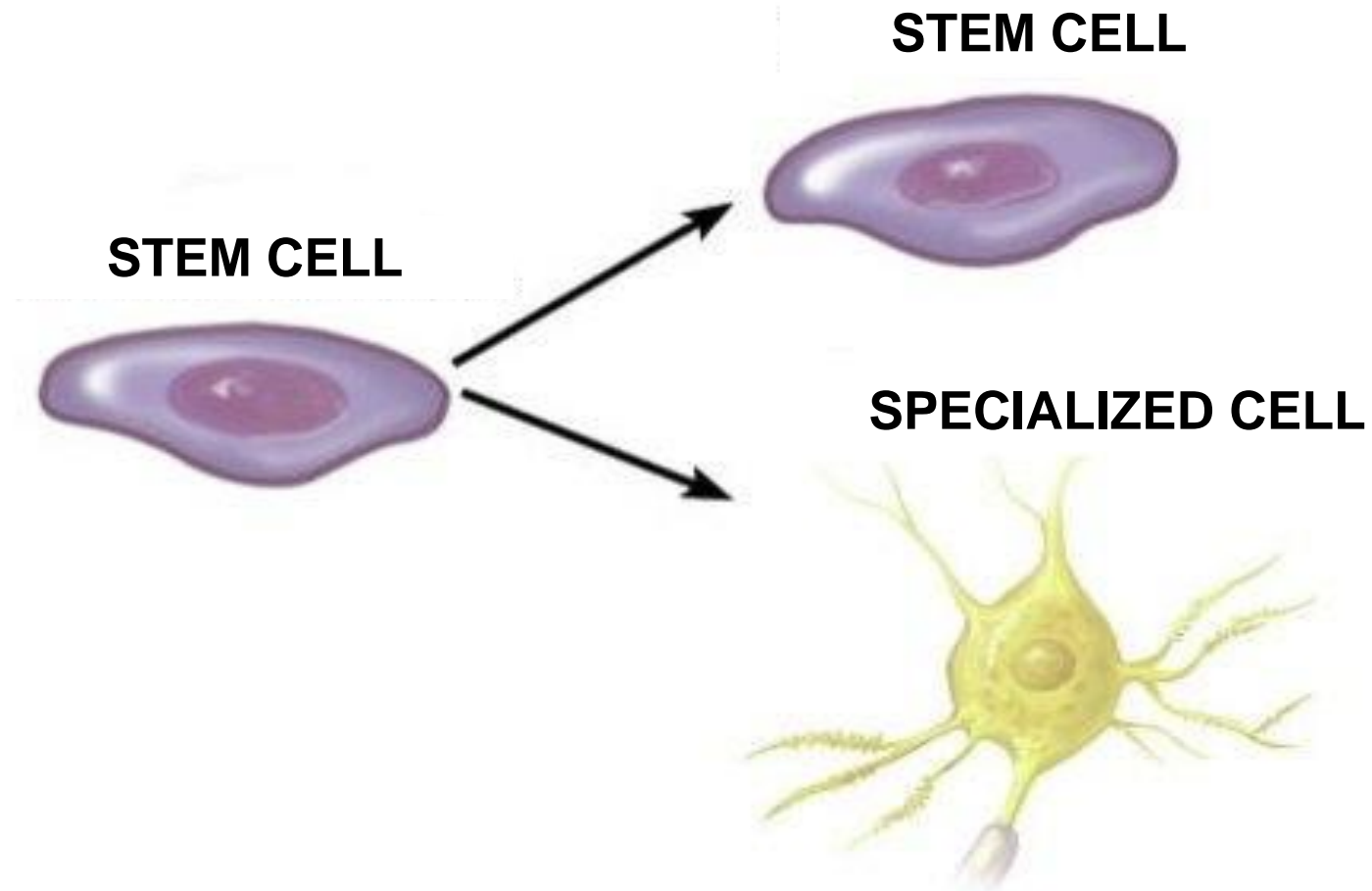
Cancer stem cells

Stem cells

Stem cells are self-renewing, unspecialized cells capable of differentiating into different cell types.

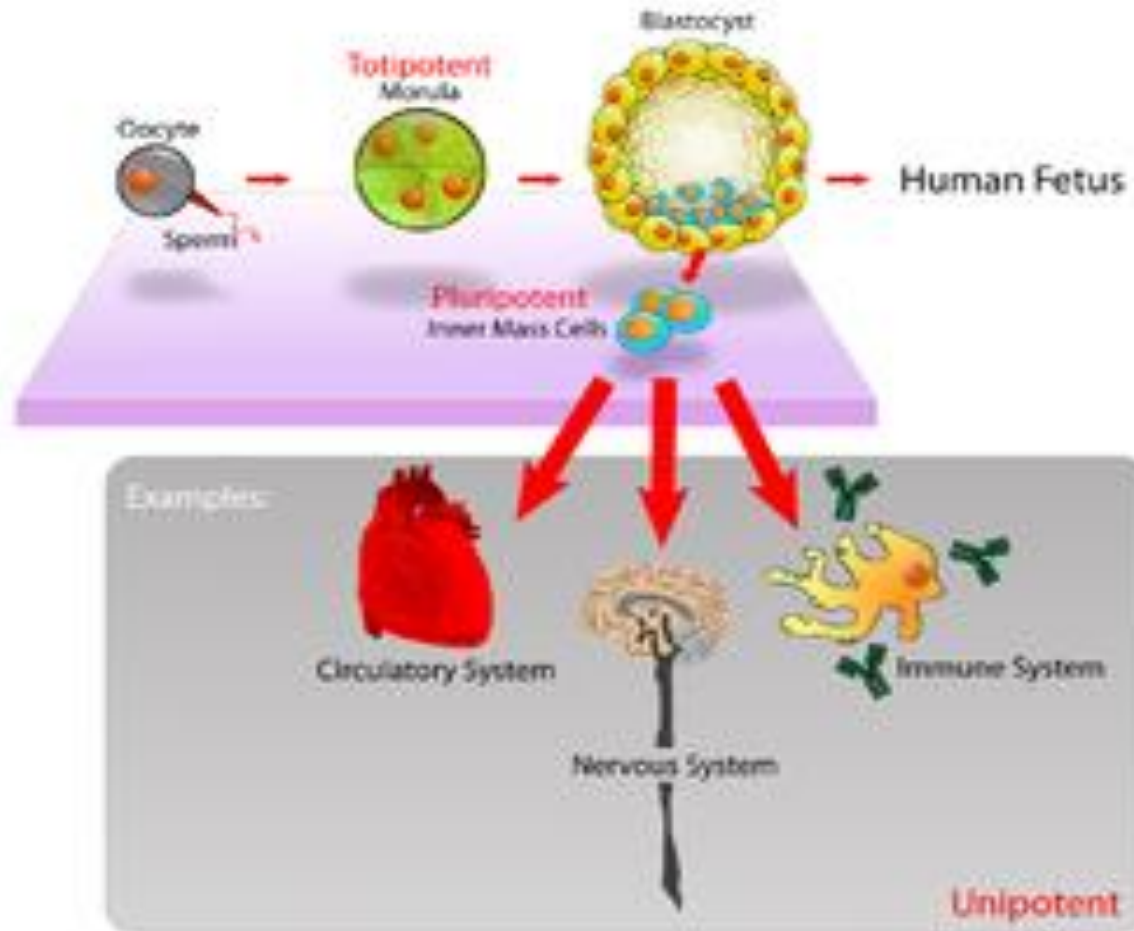


Asymmetric division of stem cells

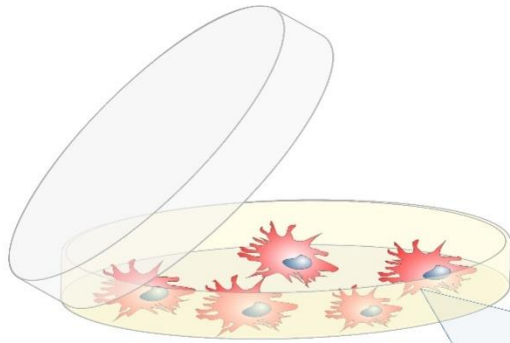


STEM CELLS DISTINCTIONS

- they are not specialized, they do not age, they are shared for a long period of time
- they are characterized by self-renewal, clonogenicity and potency



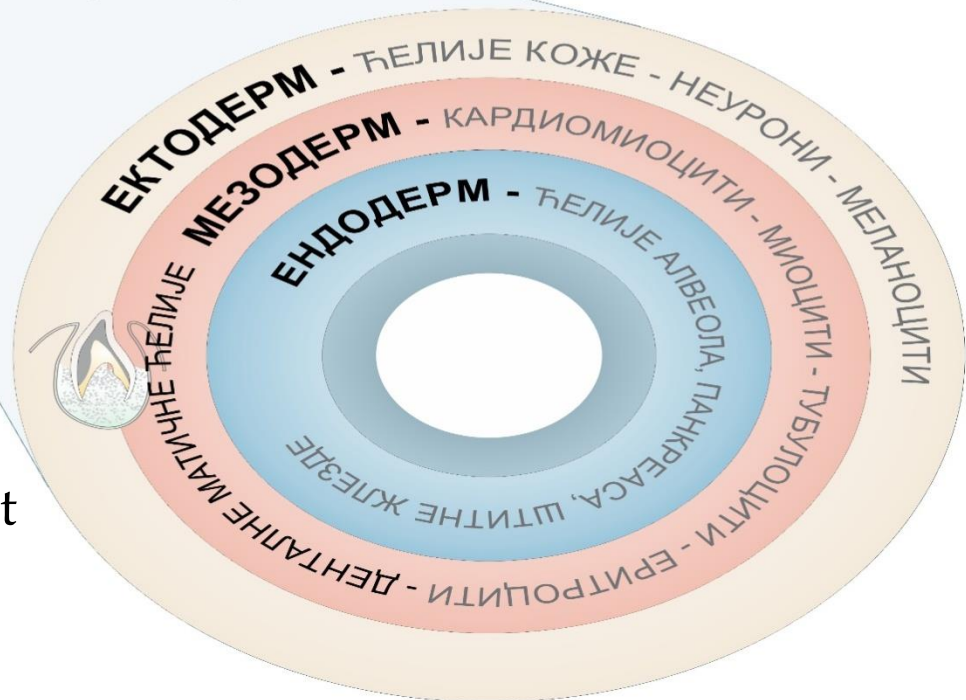
STEM CELLS...



ESCs

...are undifferentiated cells that have a high proliferative capacity and can differentiate into a large number of different cells...

ДИФЕРЕНЦИЈАЦИЈА



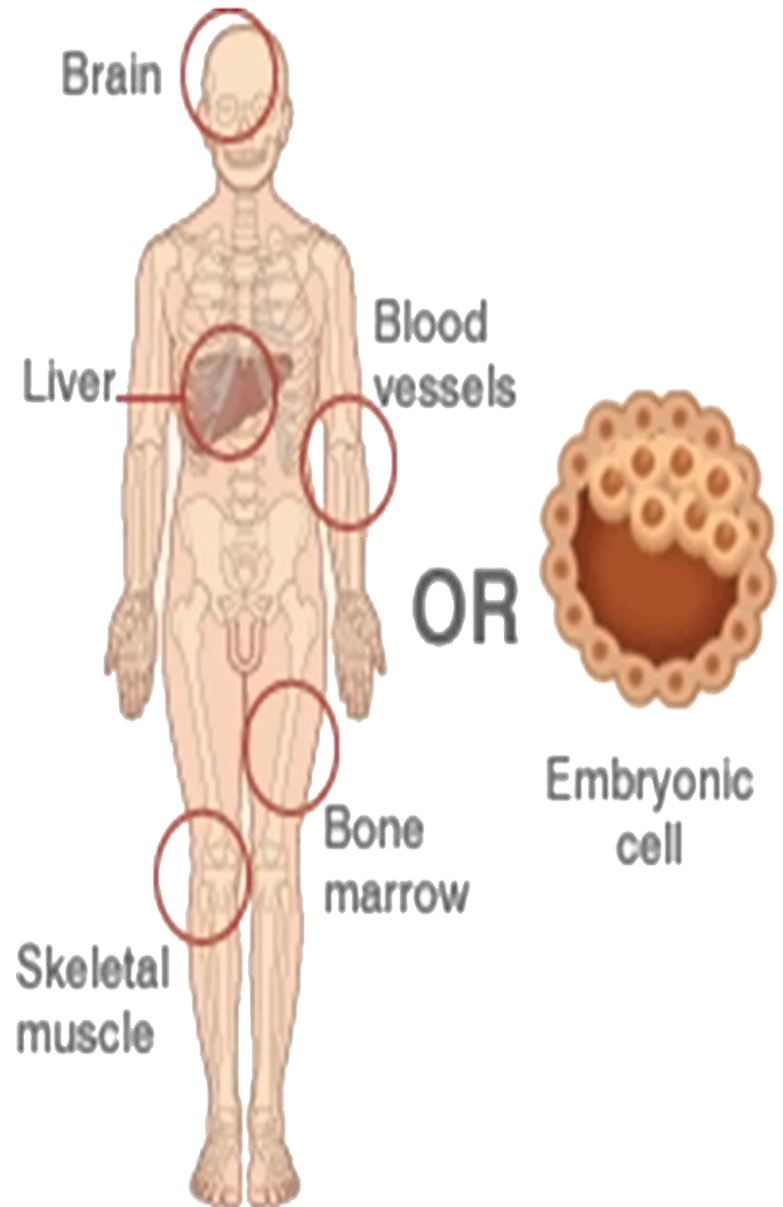
... depending on the tissue from which they are isolated, they are divided into embryonic and adult stem cells that differ from each other in their proliferative capacity and ability to differentiate.

TYPES OF STEM CELLS

- They were first discovered in 1960 as: hematopoietic stem cells, from which all blood cells arise; stromal stem cells of bone marrow, from which cells of bone, cartilage, fat and connective tissue can arise.

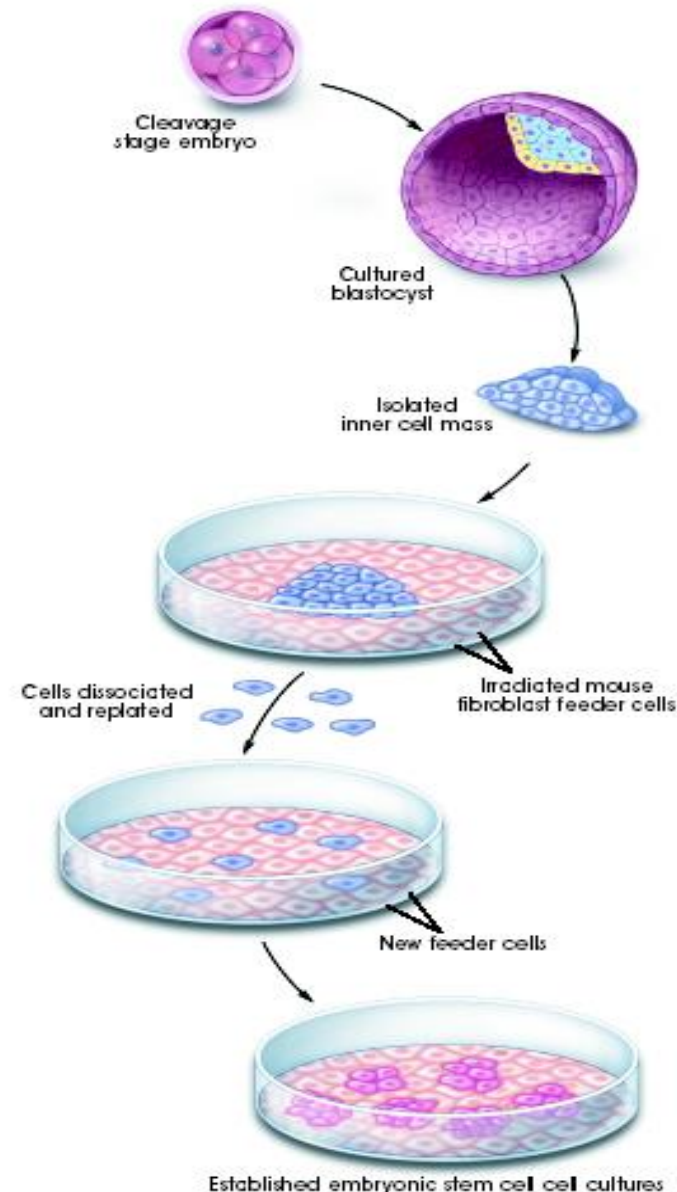
In the 1990s, stem cells were divided into:

- **Embryonic Stem Cells (ESCs)**
- **Adult stem cells: mesenchymal stem cells (MSCs)**
- **induced pluripotent stem cells (iPSCs).**



Embryonic Stem Cells (ESCs)

- Human embryonic stem cells (hESCs) were first isolated in 1998 (Thompson et al).
- They are isolated from the intracellular mass of the blastocyst.
- Undifferentiated, pluripotent cells from which all cells of the organism can arise.



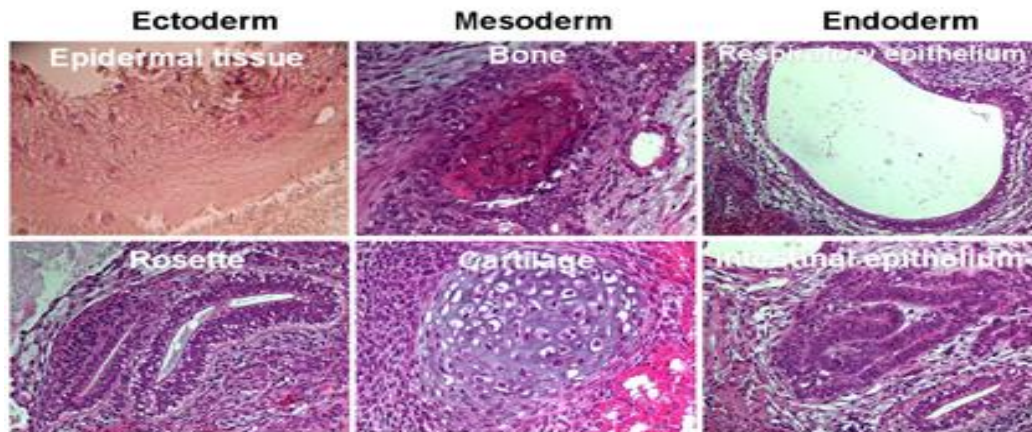
hESCs identification

Membrane markers: TRA1-60, TRA1-81, SSEA3, SSEA4, CD9, CD90, MHC class I molecule

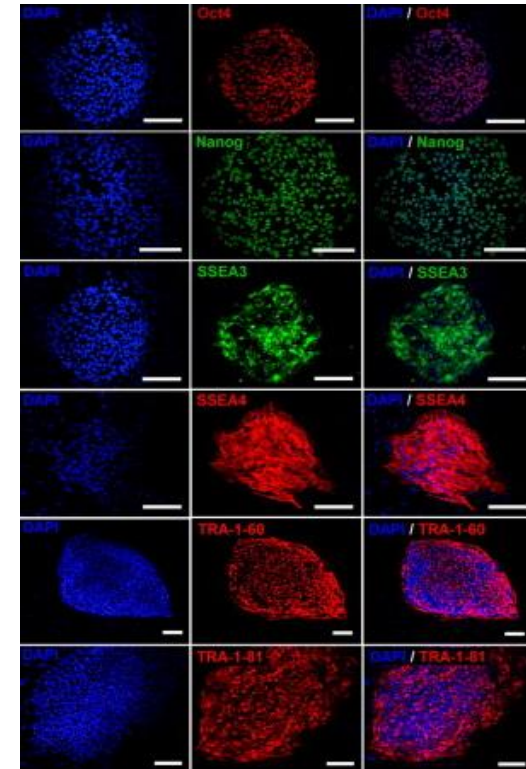
Intracellular markers : NANOG, OCT4, REX1, SOX

In vitro: pluripotency

(differentiation into all 3 leaf germs)



In vivo: formation of teratoma after injection in SCID (*severe combined immunodeficiency*) mice

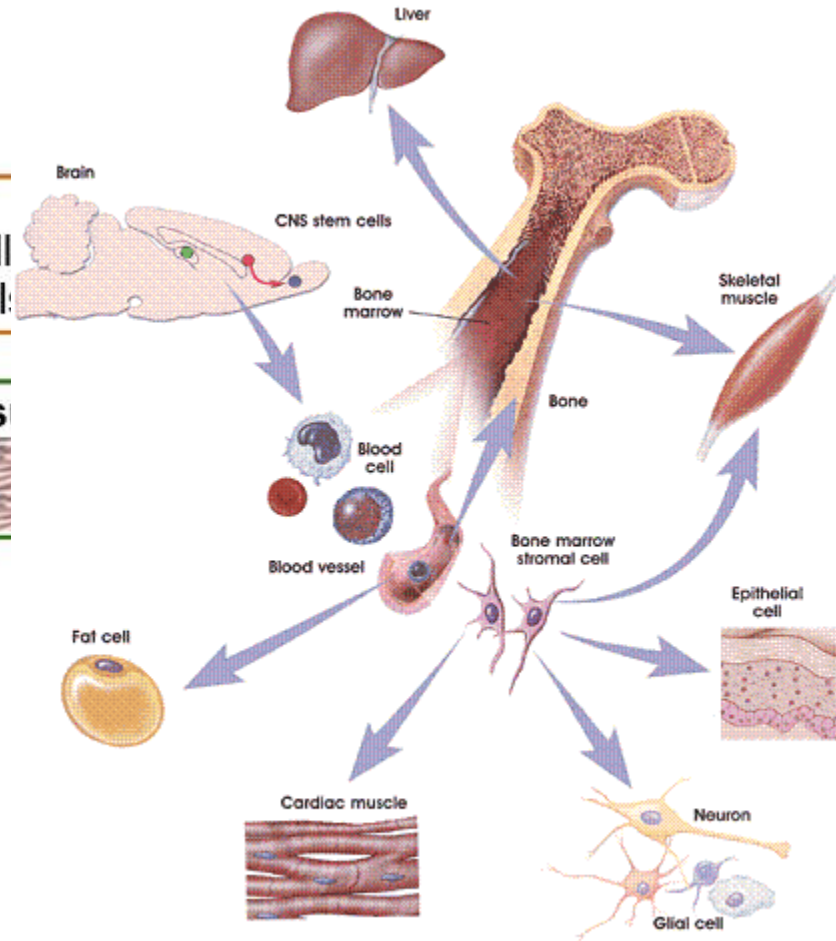
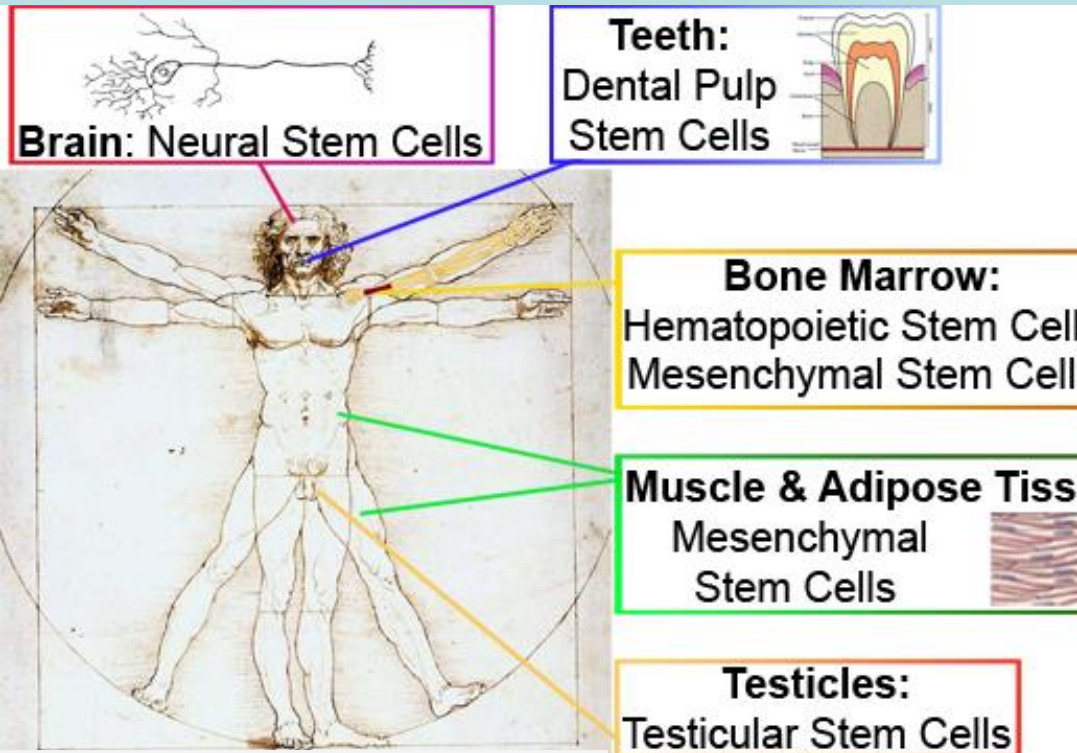


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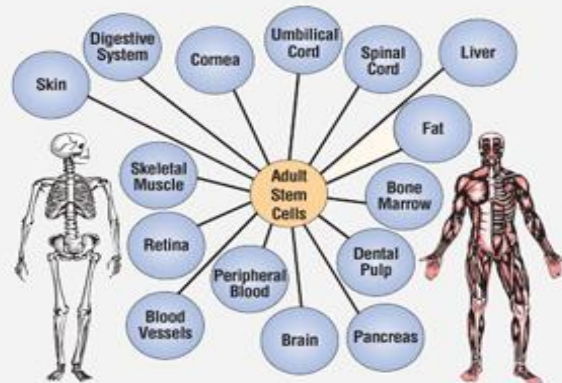
B

Adult stem cells in the body



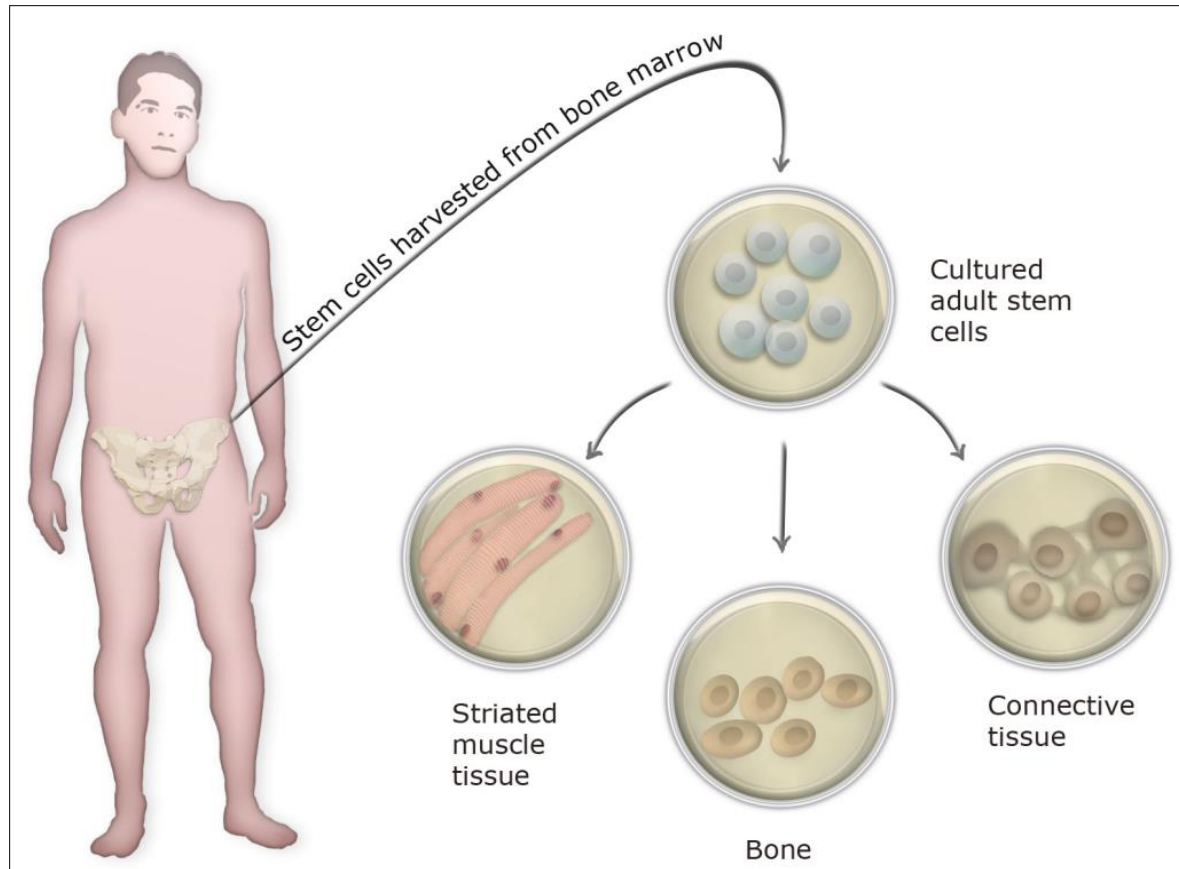
© 2001 Terese Winslow, Lydia Kibiuk, Caitlin Duckwall

Where are adult stem cells found?



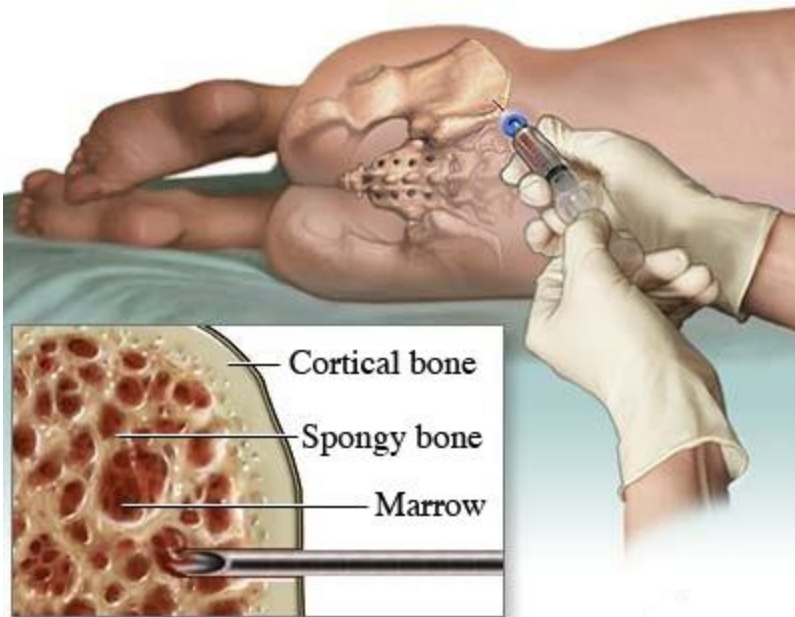
Adult stem cells in the body

- Mesenchymal stem cells (MSCs)
- Induced pluripotent stem (iPSCs)



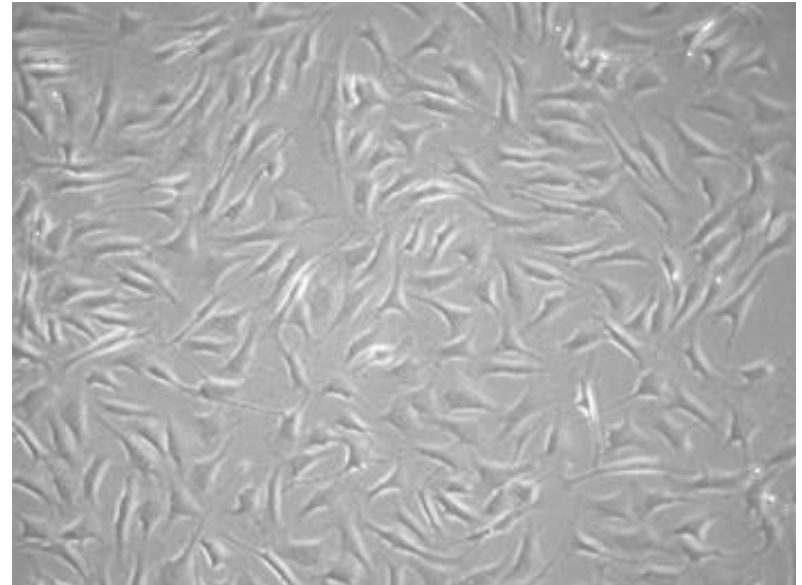
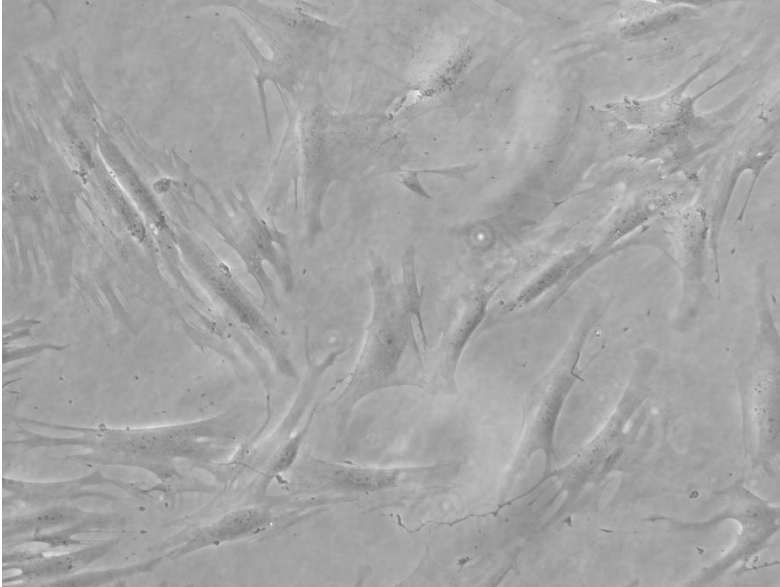
Mesenchymal stem cells (MSC)

- Bone marrow, adipose tissue, peripheral blood, umbilical cord, amniotic fluid,...



Mesenchymal stem cells (MSCs)

- Spindle-like appearance, adheres well to plastic
- Growth medium (DMEM, FBS, L-glutamine, penicillin/streptomycin)
- Problem: possible presence of heterogeneous cell colonies after isolation

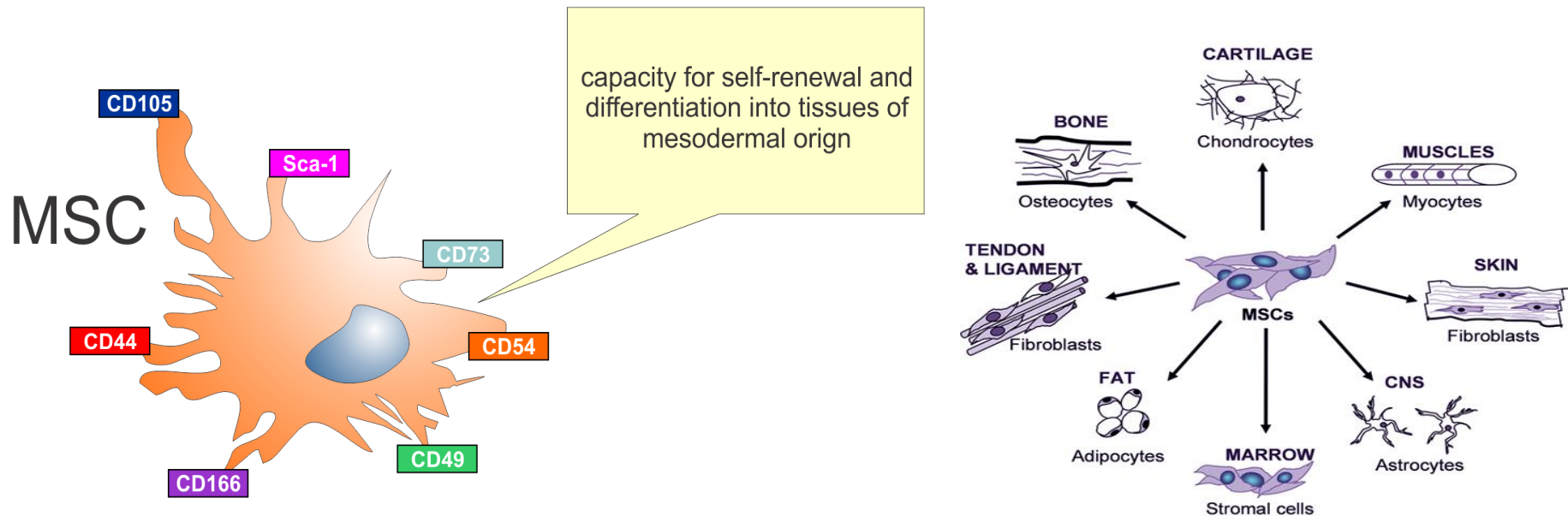


MSCs identification

MSCs have the ability to self-renew and differentiate into mesodermal cells.

They express membrane markers : CD105, Sca-1, CD73, CD44, CD49, CD54, CD166,

And they not express CD14, CD34, LFA-1, CD45 (characteristic of hematopoietic cells), glycophorin A (erythrocytes), CD31 (platelets and endothelial cells).



Therapeutic potential of mesenchymal stem cells

- **Regenerative potentiation**

MSCs can differentiate to :

adipocytes

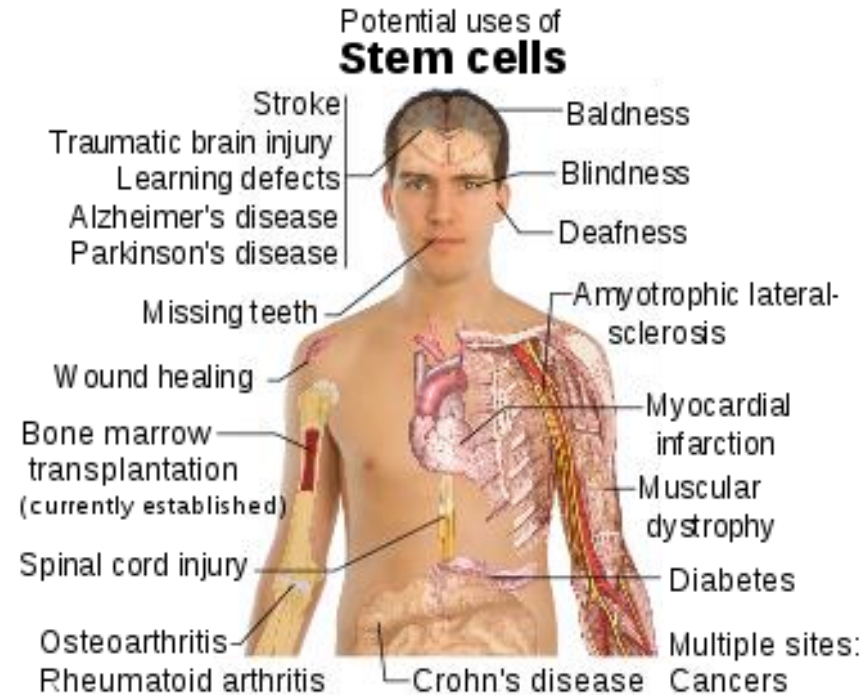
chondrocytes

osteoblasts

β pancreatic cells

Endothelial cells

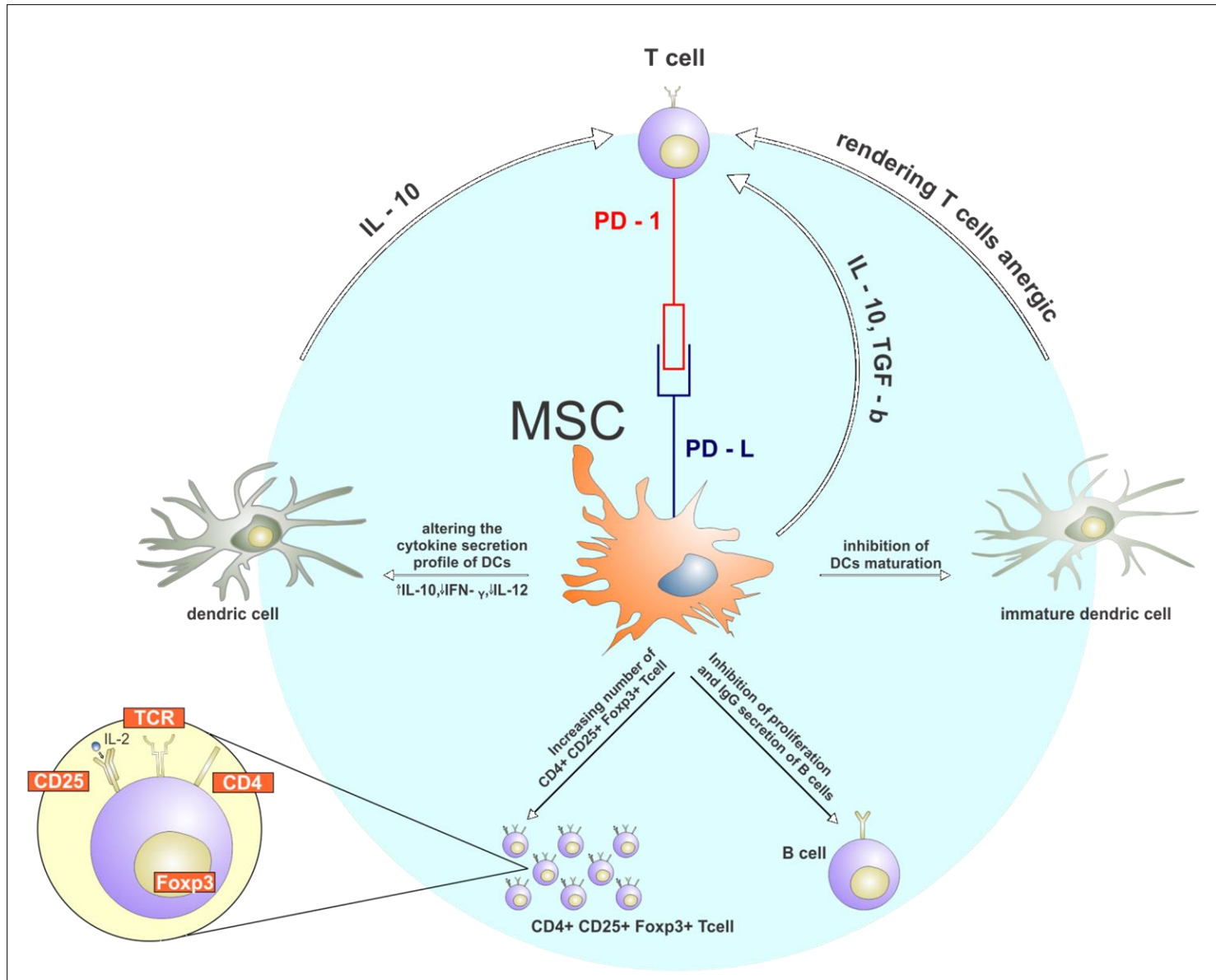
Myocyte, cardiomyocyte, ...



- **Immunomodulatory characteristic**

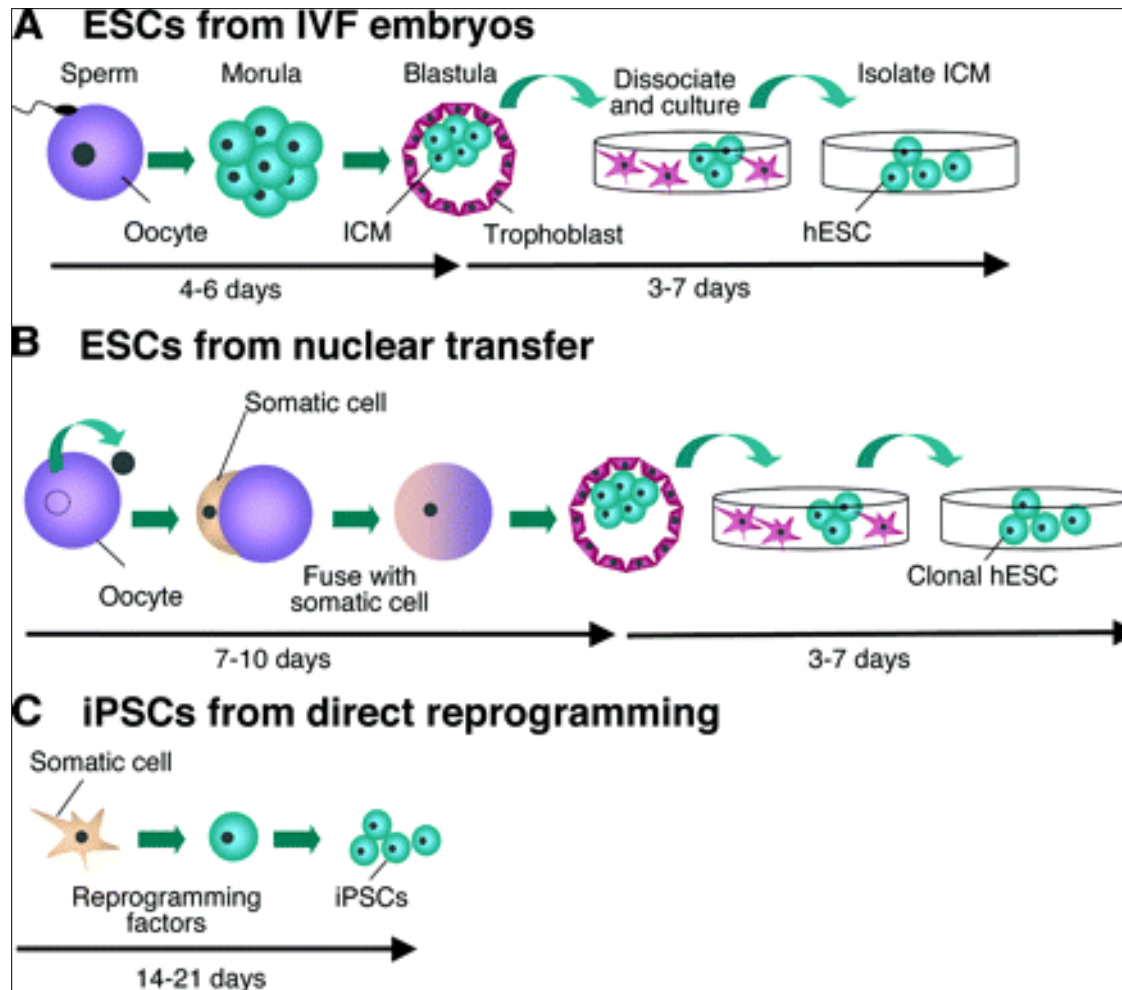
Effects on dendritic cells, T and B lymphocytes, and T regulatory cells

Immunomodulatory potential of MSCs



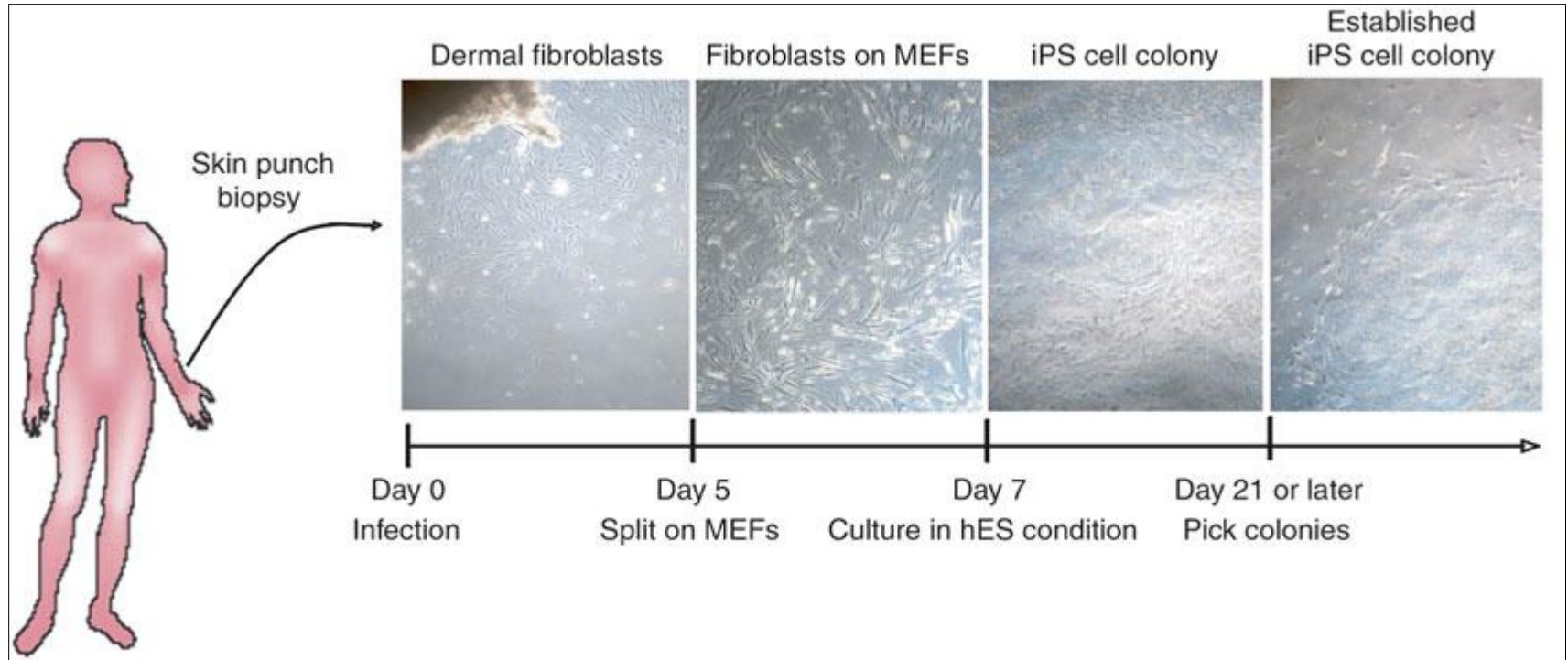
Induced pluripotent stem cells (iPSCs)

Reprogrammed adult somatic cells

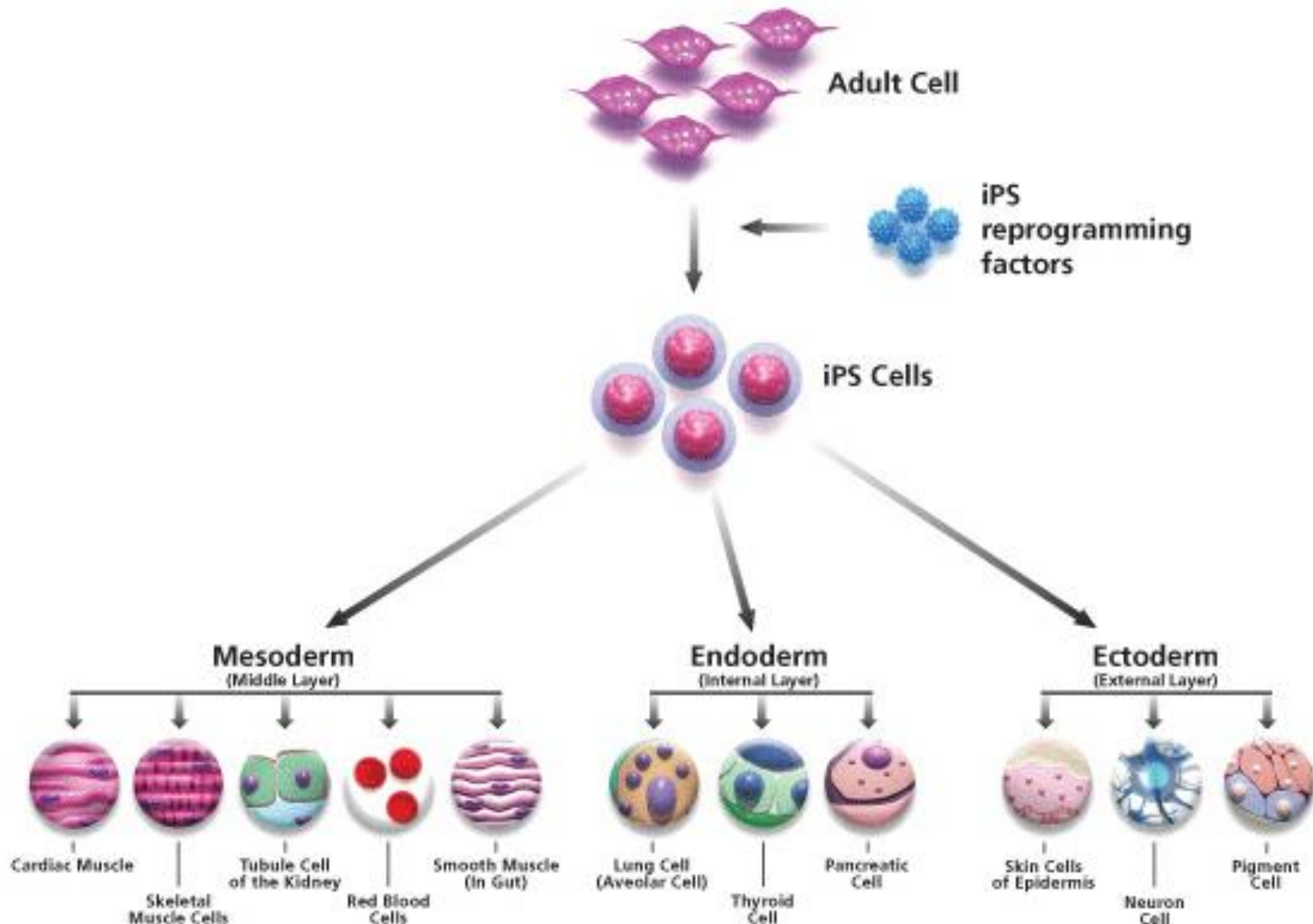


Induced pluripotent stem cells (iPSCs)

Reprogramming of somatic cells into iPSCs induced by gene expression Oct3/4, Sox2, c-Myc, Klf4 .

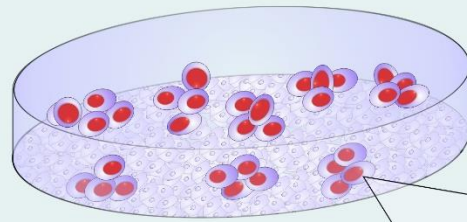


Induced pluripotent stem cells (iPSCs): pluripotency



iPS

hESC



ECTODERM

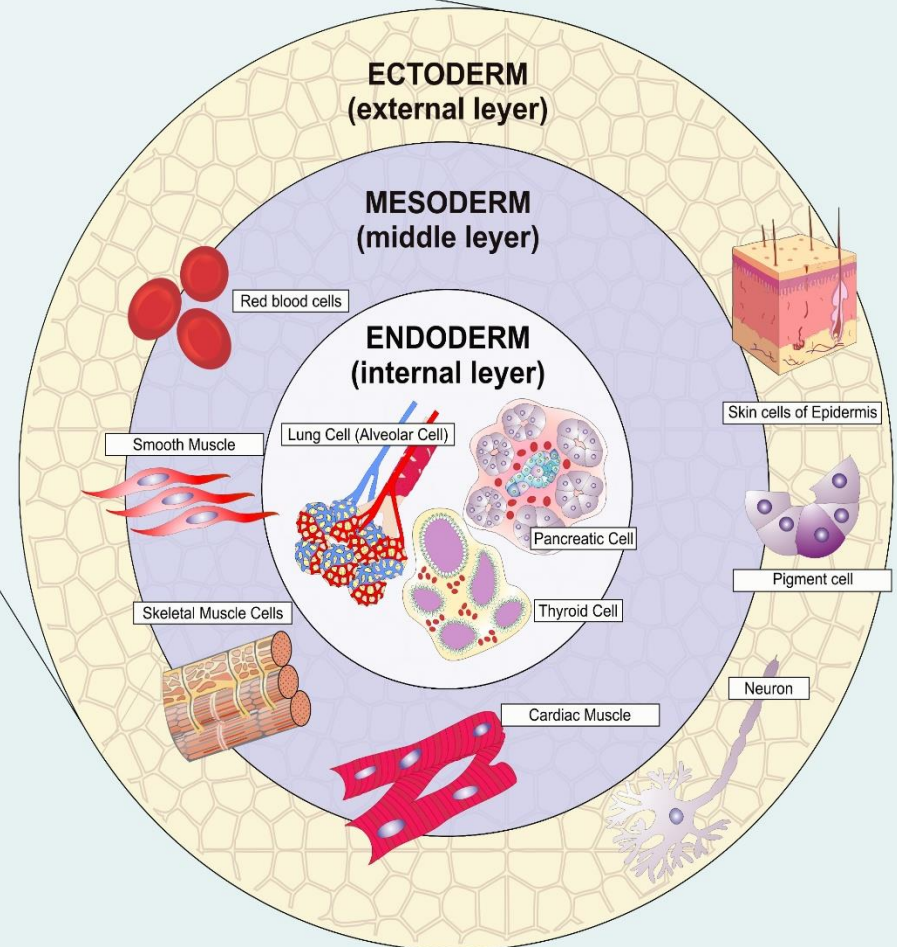
Skin Cells of Epidermis
Neuron of Brain
Pigment Cell

MESODERM

Cardiac Muscle
Skeletal Muscle Cells
Tubule Cell of the Kidney
Red Blood Cells
Smooth Muscle (in Gut)

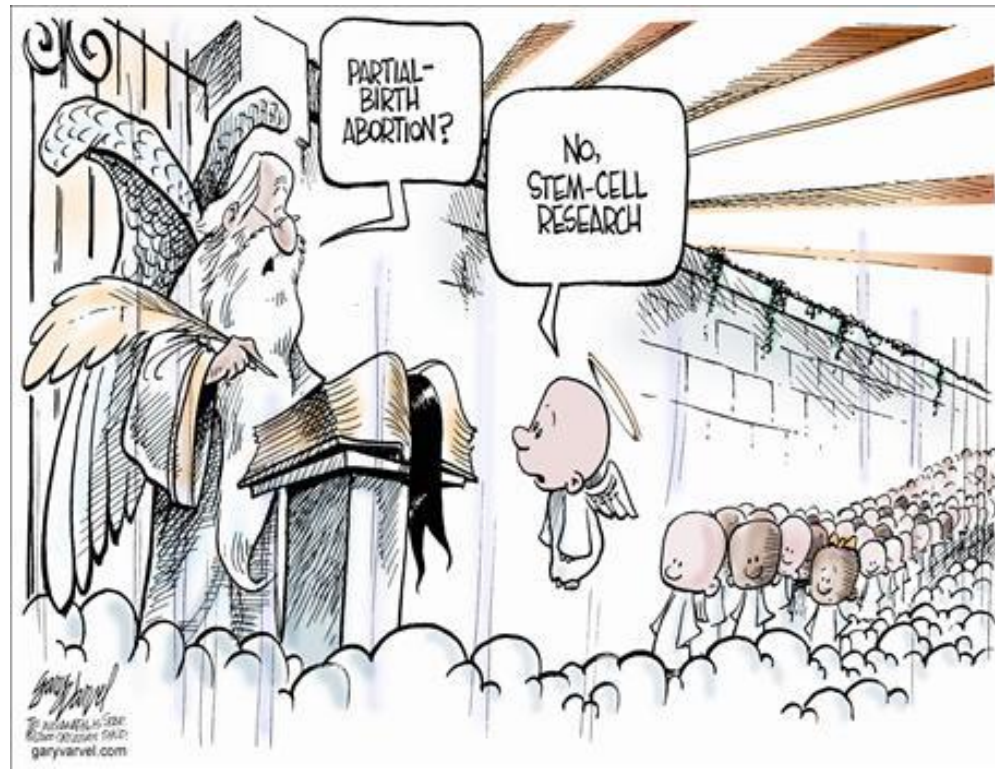
ECTODERM

Skin Cells of Epidermis
Neuron of Brain
Pigment Cell



Problems for therapeutic application of ESCs and iPSCs

- Unstable karyotype and malignant potential (ESCs and iPSCs)
- Immune Response Cell Rejection (ESCs)
- Difficulties in propagation, early entry into "*senescence*" (iPSCs)
- Ethical Reasons (ESCs)



Classification of stem cells in relation to function and source of isolation

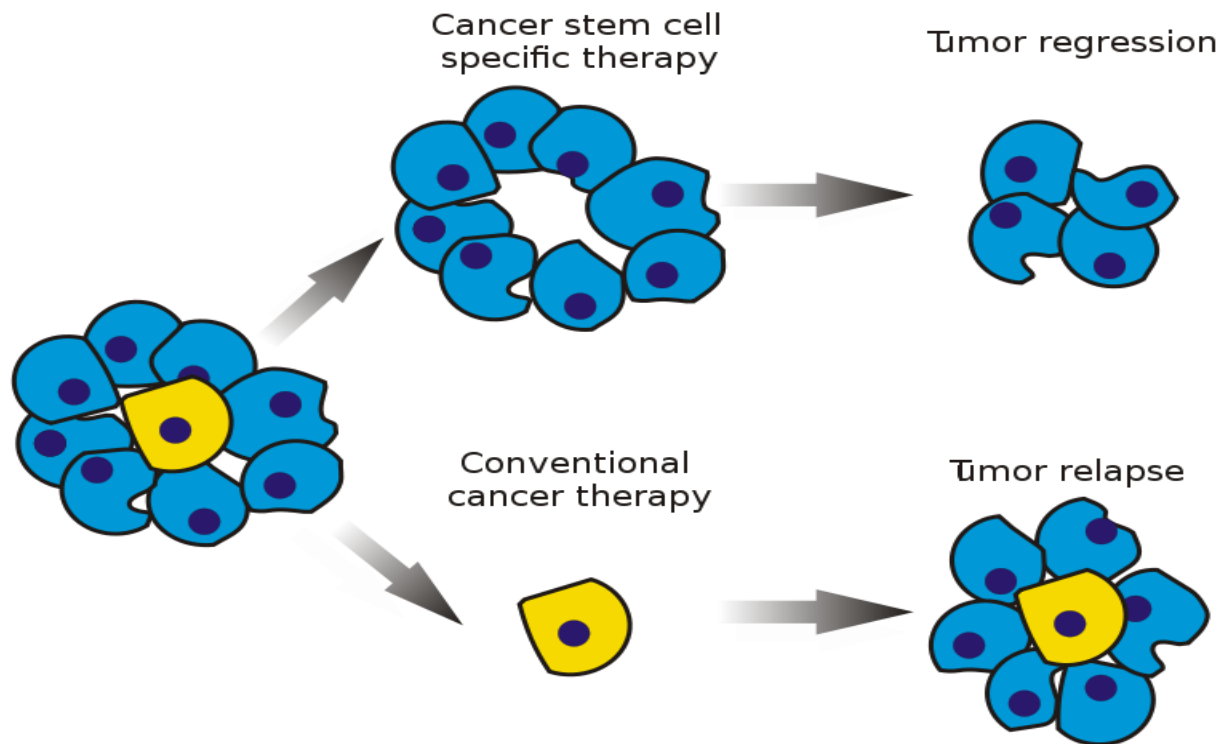
STEM CELLS in relation to the function		STEM CELLS in relation to the source of isolation		
normal	cancer	embryonic	fetal	adult

Cancer stem cells

- *Cancer stem cells* (CSCs) are called tumor cells because they are isolated from tumors, and stem cells because, like normal stem cells, they have the ability to self-renew and differentiate into different types of cells.
- They form a subpopulation of tumor cells that are responsible for tumor recurrence and metastasis.

Cancer stem cells- therapy

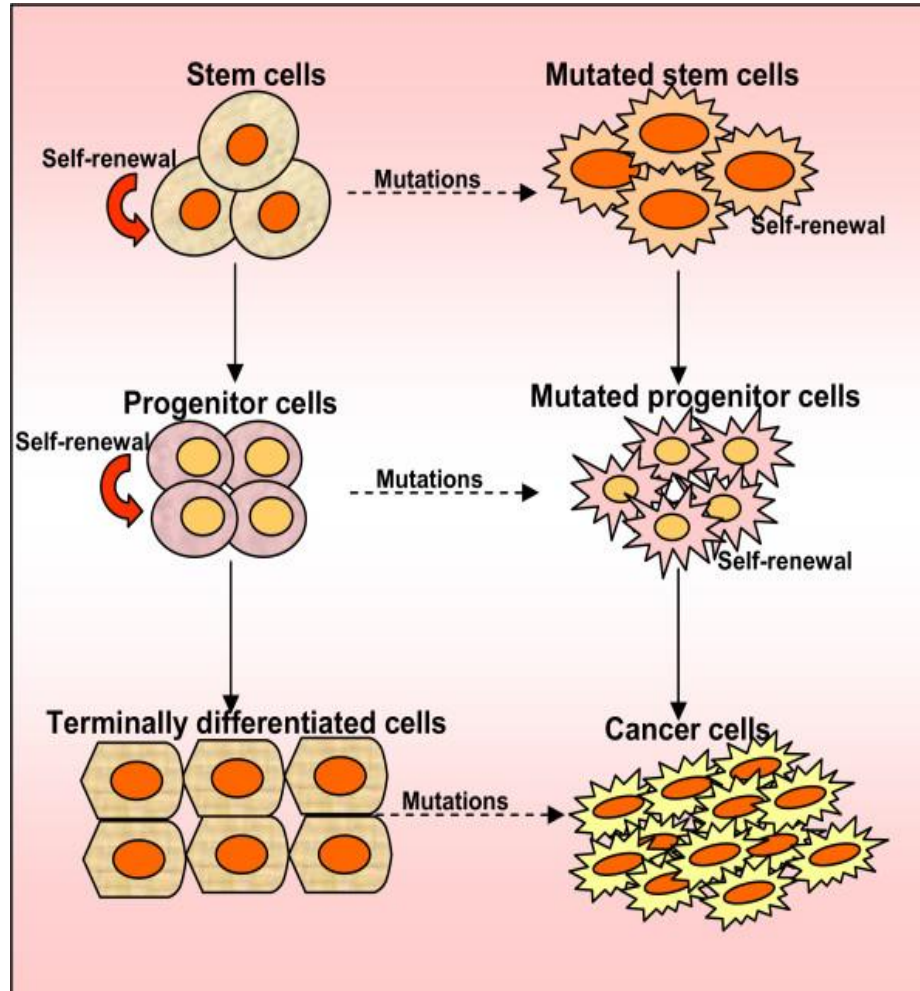
- Conventional chemotherapy is known to act on differentiated cells and cells in the process of differentiation, but not on CSCs, and therefore recurrence occurs



Cancer stem cells

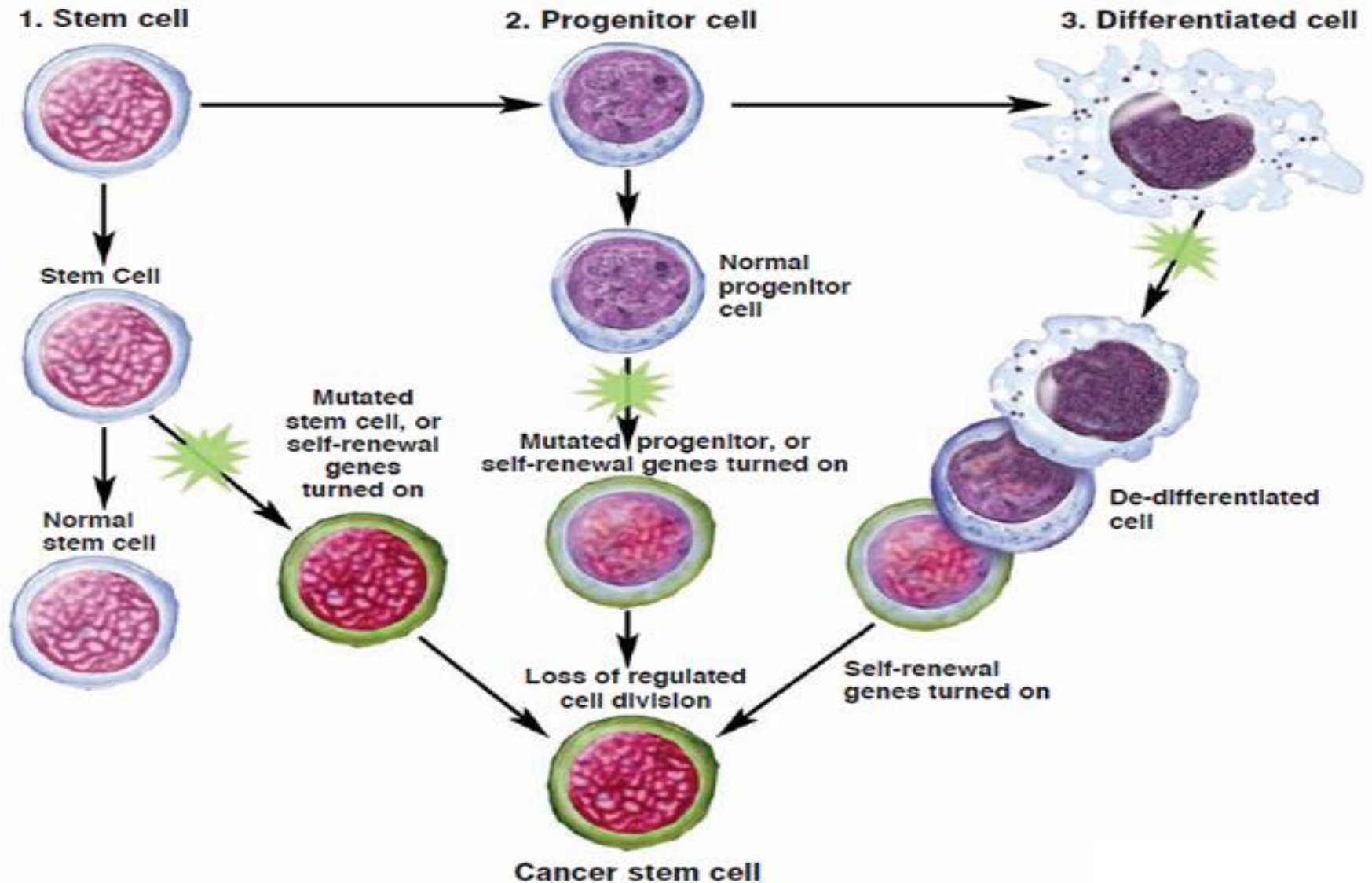
- Bonnet and Dick were the first to publish work on tumor stem cells in Nature Medicine, in 1997.
- They isolated leukemia cells that express the surface marker CD34 and lack CD38.
- The authors confirmed that this subpopulation of CD34+/CD38- cells can initiate tumorigenesis in NOD/SCID mice.

The origin of cancer stem cells

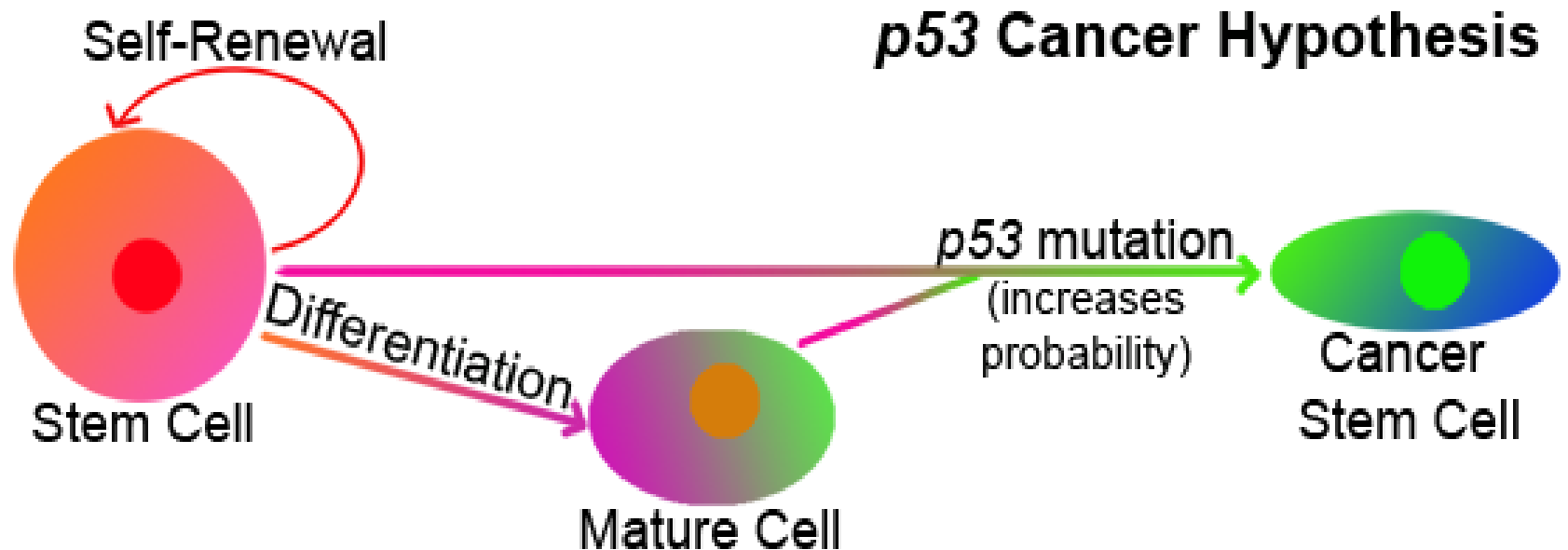
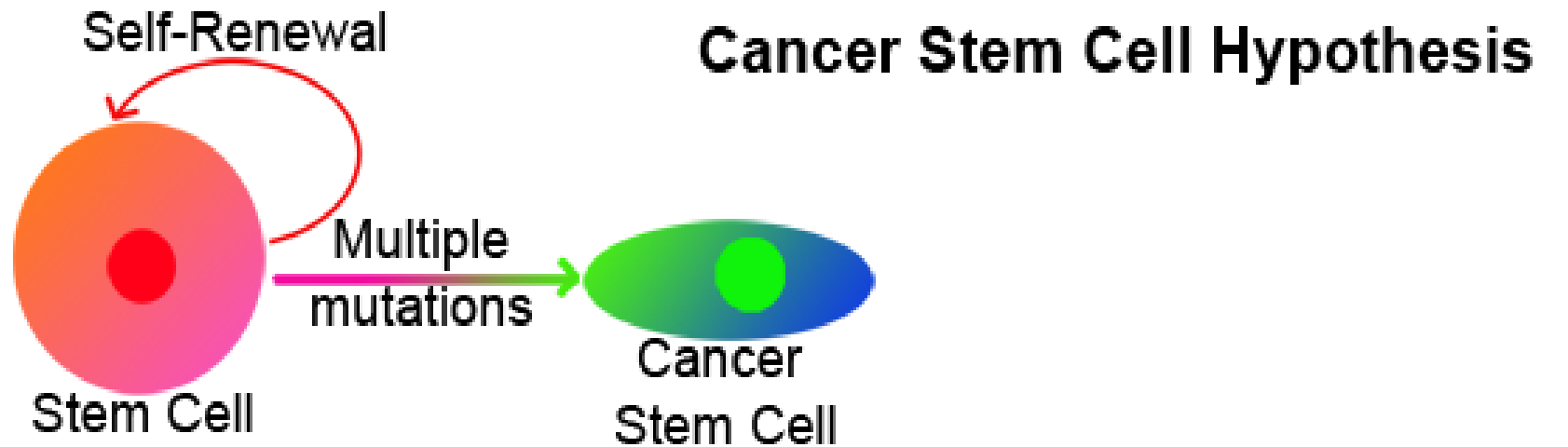


Origin of CSCs from: 1. normal stem cells, 2. progenitor cells, 3. terminally differentiated cells

CSCs arise from the mutation of stem cells, progenitor cells and terminally differentiated cells



Hypotheses about the origin of tumor stem cells



Hypotheses about the origin of tumor stem cells

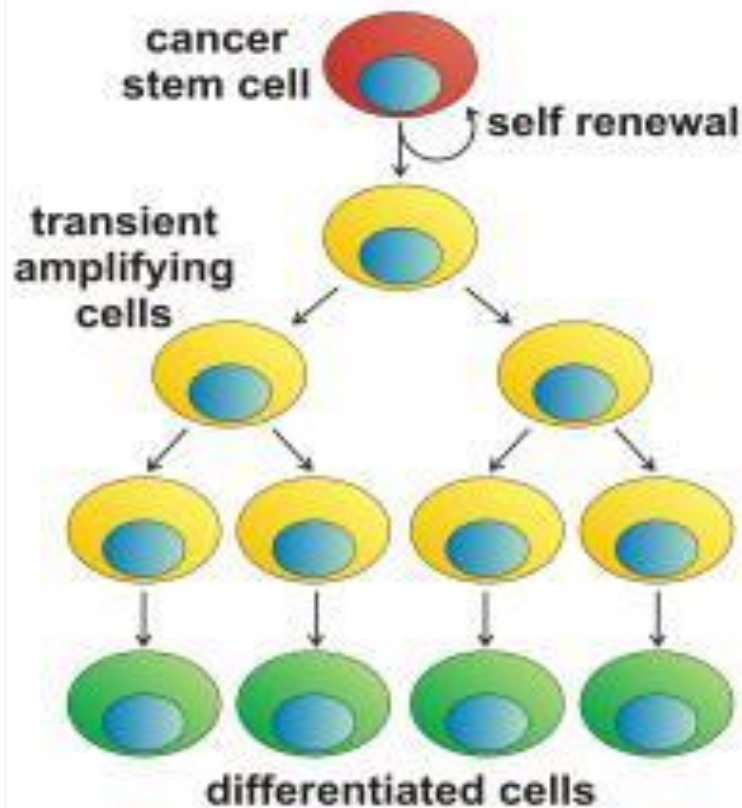
- There are two hypotheses about the origin of tumor stem cells:
- According to the first, "Cancer Stem Cell Hypothesis", cancer stem cells arise only by conversion from stem cells due to multiple mutations. Therefore, according to this theory, tumorigenesis begins with the accumulation of mutations in one type of cell (stem cells from which tumor stem cells, i.e. a tumor) arise.
- According to the second, "p53 Cancer hypothesis", due to mutation and impaired function of p53, tumor stem cells, i.e. a tumor, can arise from any body cell (and not only stem cells).
- So, in summary, according to the first theory, tumor stem cells and tumors can only arise from mutations in stem cells, and according to the second - all cells of the body have the potential for carcinogenesis.

Two models of tumor growth

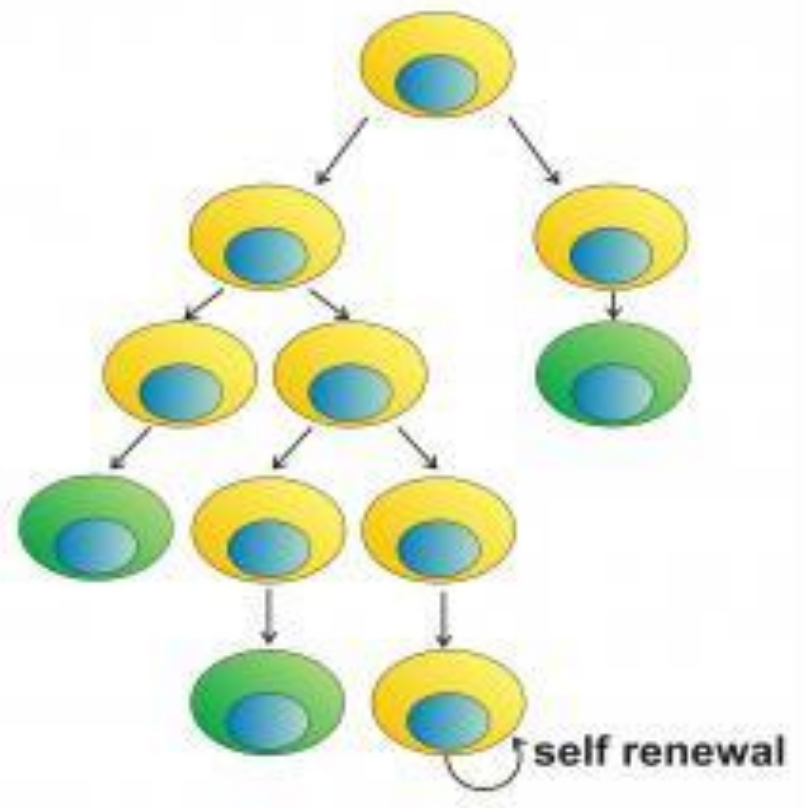
- According to the first theory, tumor tissue grows like other normal tissues of the body. That is, from the stem cell (which is the highest in the hierarchy) progenitor cells arise, and from them differentiated or specialized cells. At the same time, stem cells have the ability to self-renew. That is, the number of both stem cells and TA (transit amplifying cells) increases with division. TAs divide several times and then give rise to a differentiated cell that no longer has the ability to divide. So, according to this theory, tumor formation is an organized process where all tumor cells arise from the tumor stem cell.
- Unlike the previous theory, according to the stochastic theory, each tumor cell has the possibility of division and self-renewal. Thus, tumor formation is not an organized and orderly process and according to the principle of randomness (stochastically) either differentiation or self-renewal of tumor cells occurs.
- It is likely that both theories are correct, depending on the type of tumor. That is, the first theory probably corresponds to the formation of some tumors, and the second stochastic theory to some.

Cancer stem cell model and stochastic model

The cancer stem cell model

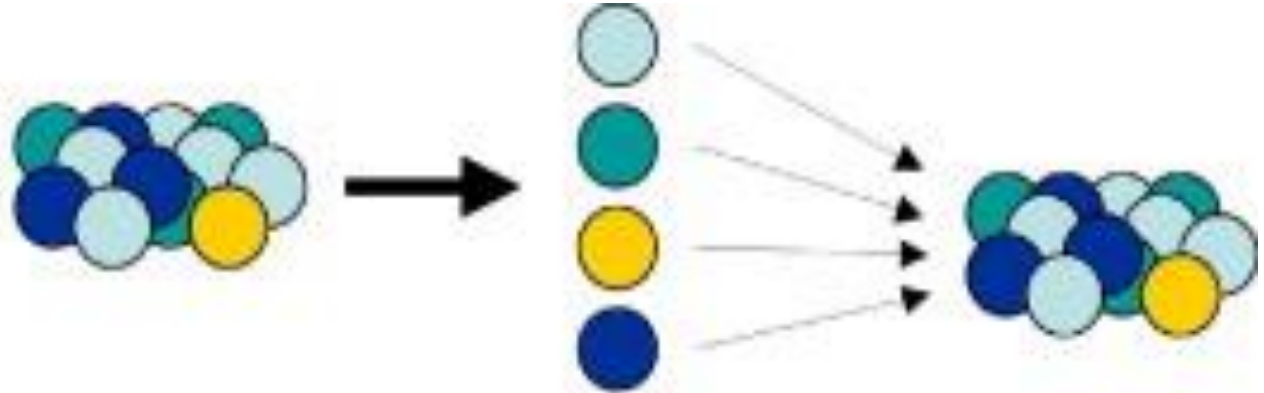


The stochastic model

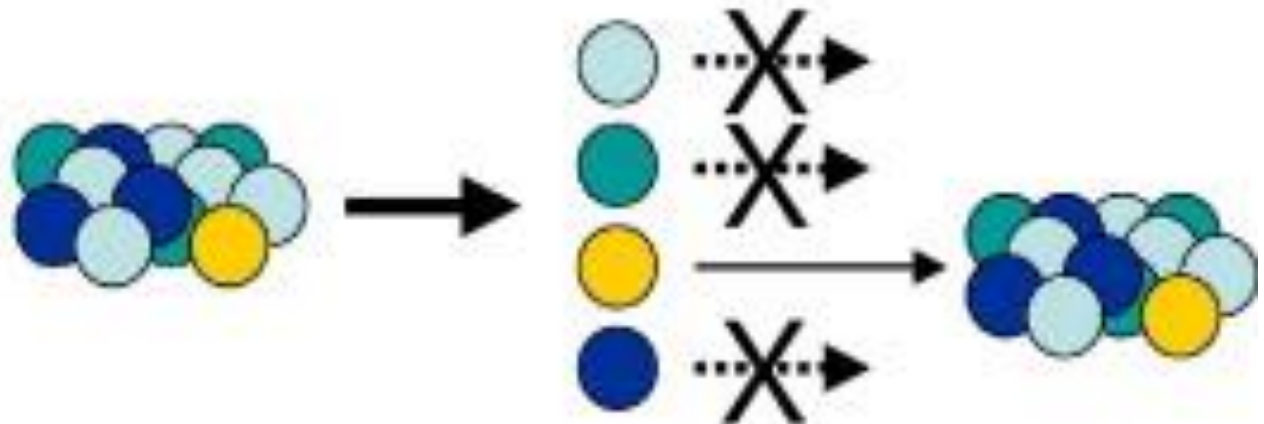


Cancer stem cell model and stochastic model

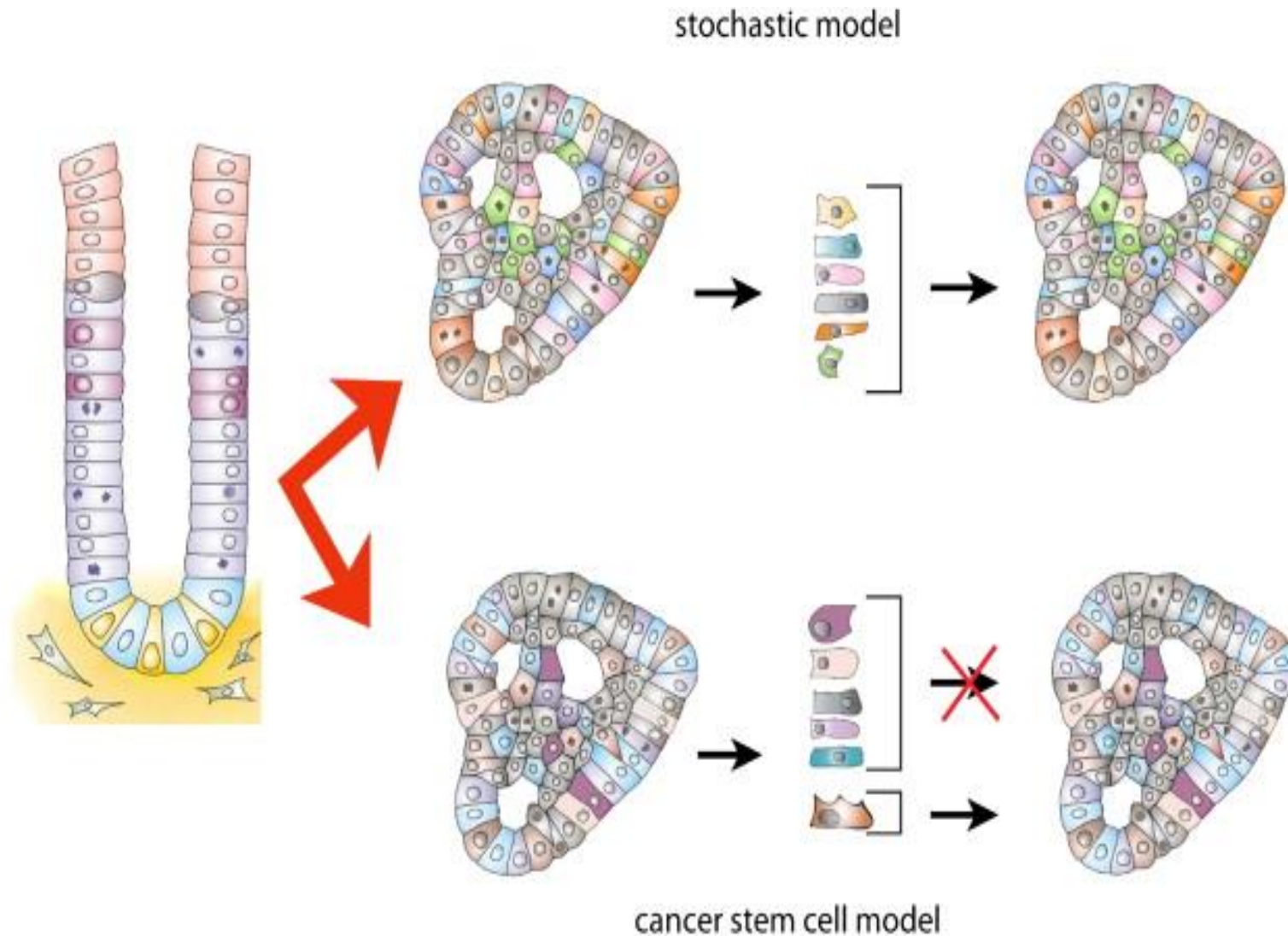
Random
Stochastic



Hierarchical
Cancer stem cell

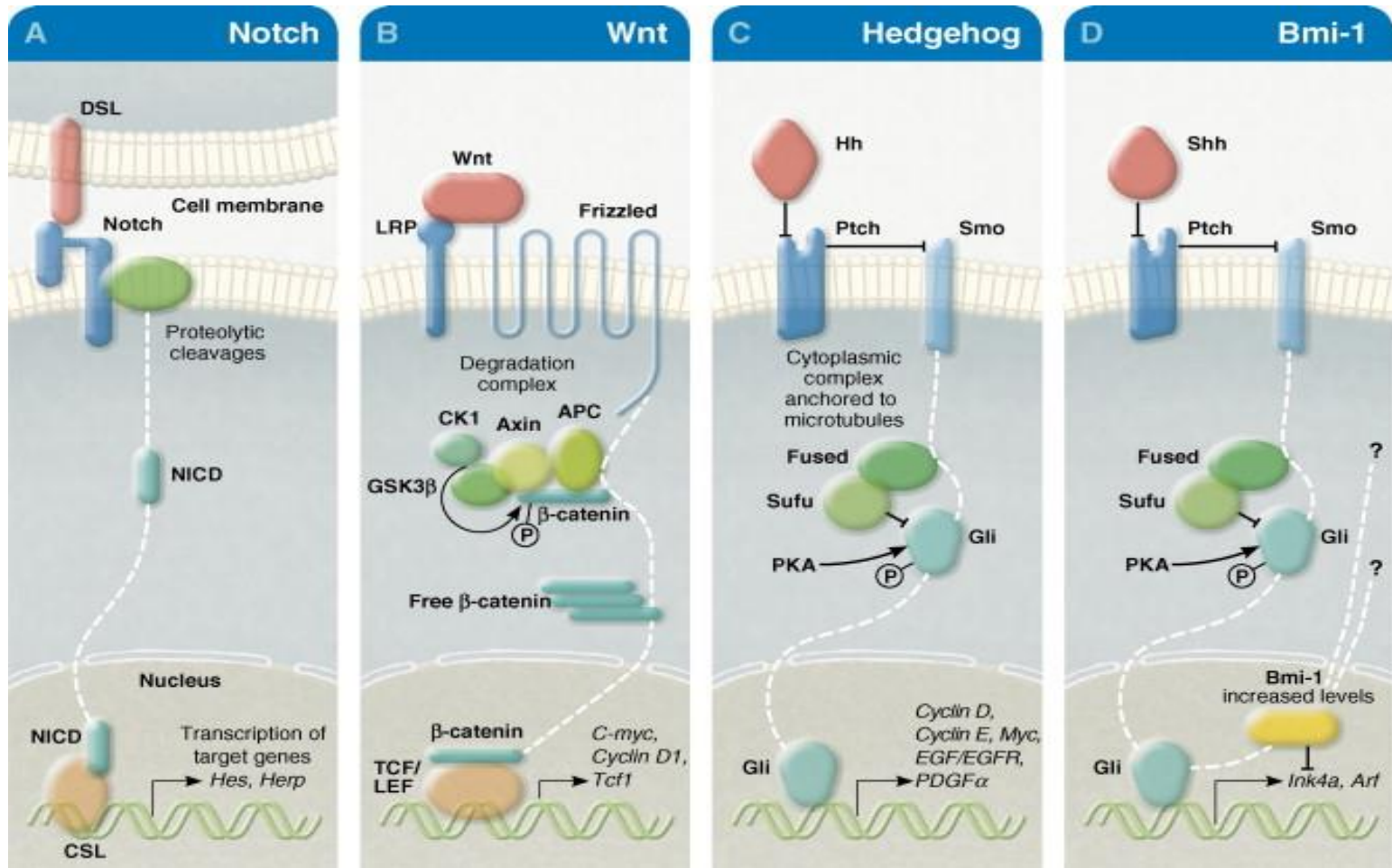


Cancer stem cell model and stochastic model in the small intestine



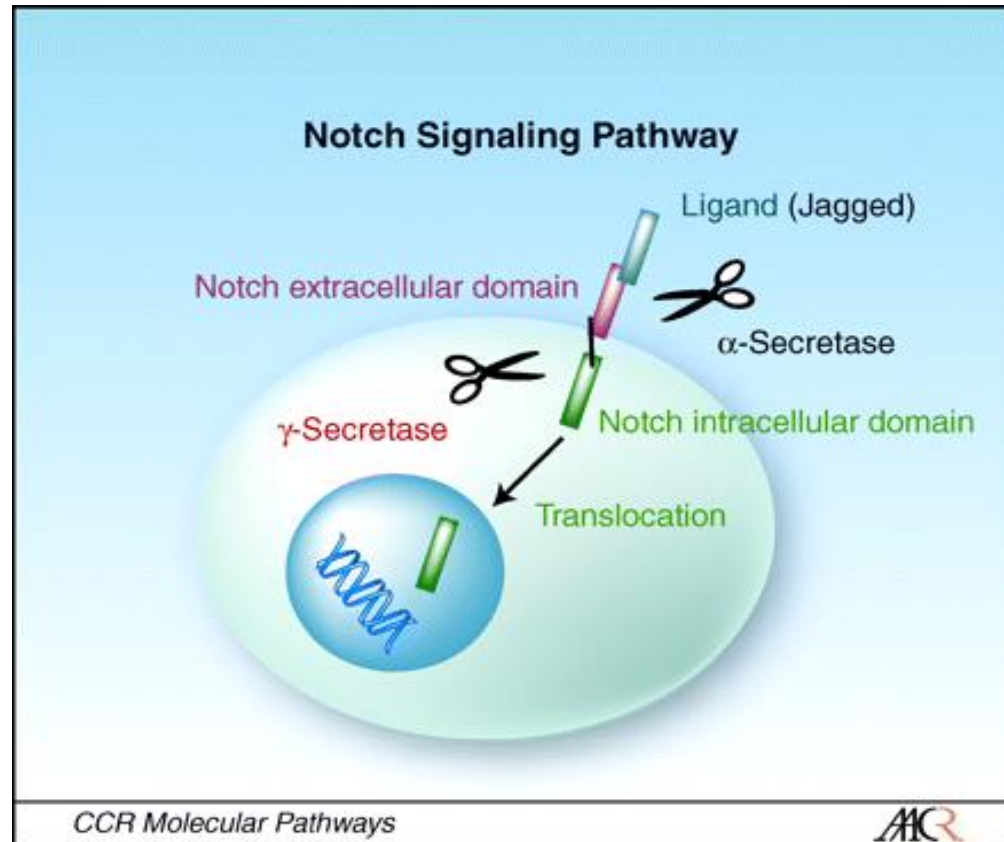
Signaling pathways of cancer stem cells

- The most important signaling pathways for cancer stem cells are the Notch and Wnt signaling pathways, but recent research also indicates the importance of the Hedgehog and Bmi-1 signaling pathways.



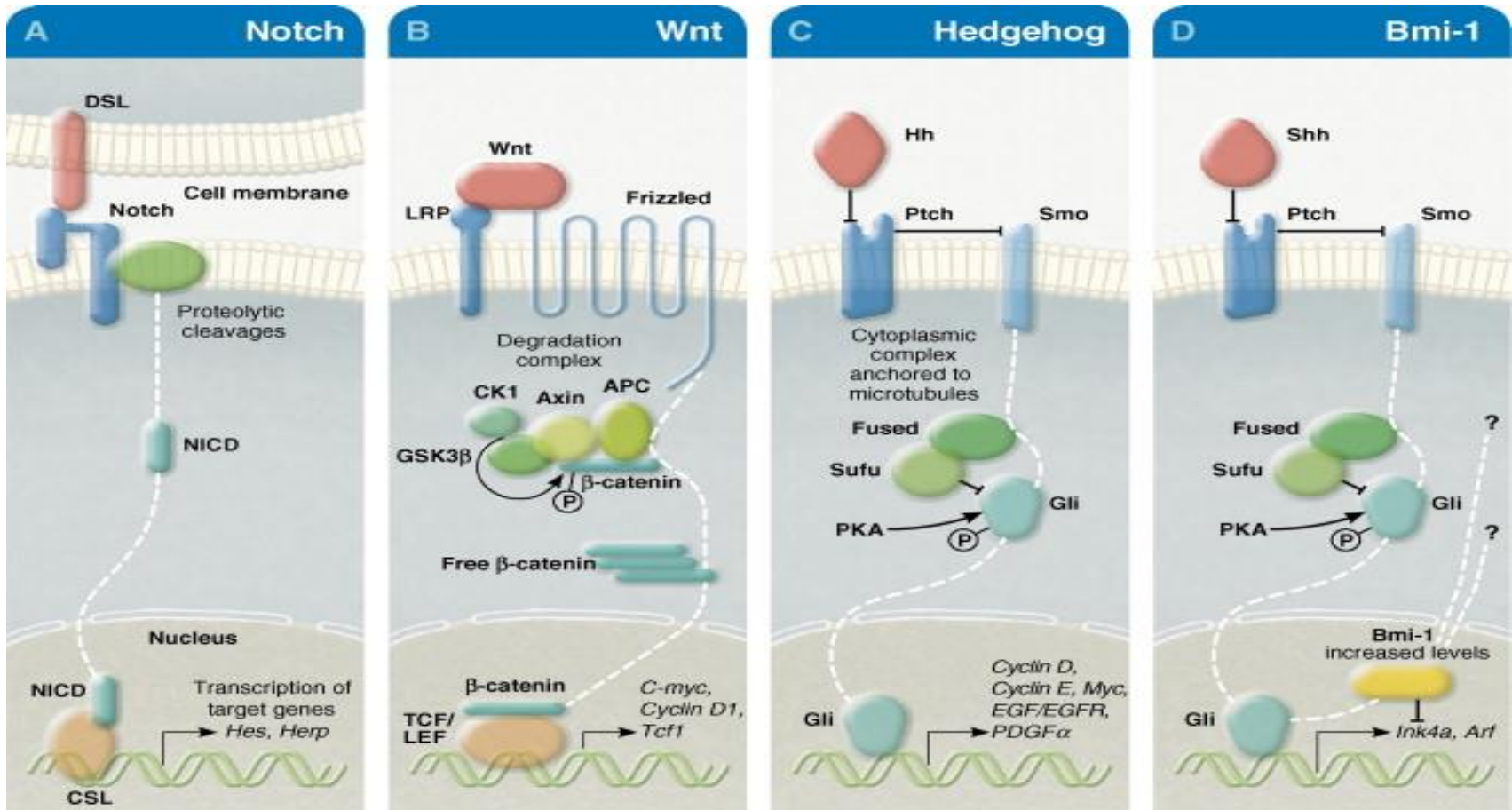
Notch signaling pathway

- Upon binding of DSL ligands (Delta, Serrate, Lag-2) to the Notch transmembrane receptor of a neighboring cell, the receptor is proteolytically degraded and the Notch Intra-Cellular Domain (NICD) is released, and moved to the nucleus.



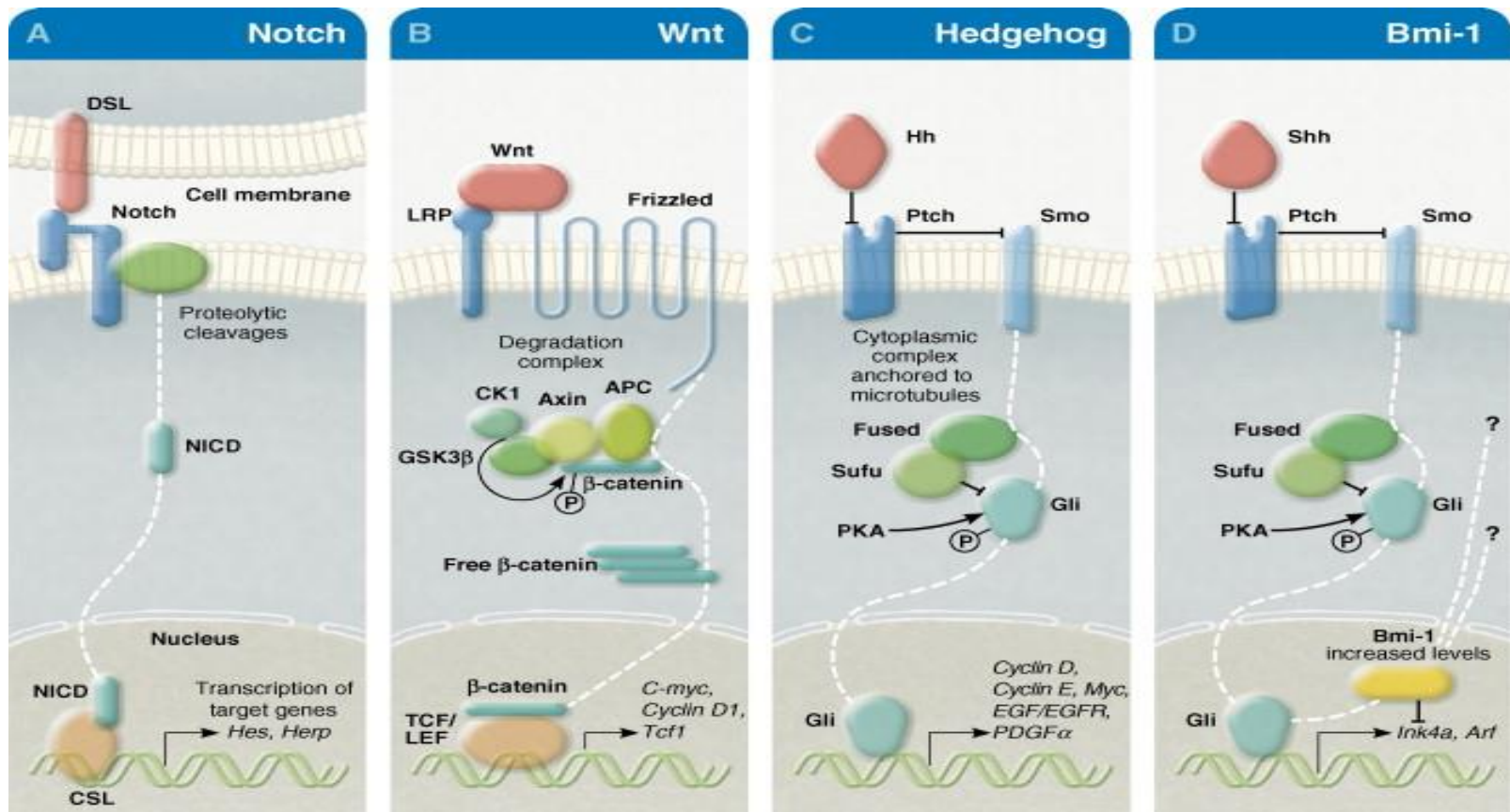
Notch signaling pathway

- Upon translocation to the nucleus, NICD interacts with the DNA binding protein CSL. After that, CSL "turns" into a transcriptional activator of Notch target genes (Hes and Herp), which activates the cell to remain in an undifferentiated form.



Wnt signaling pathway

• By binding the Wnt protein to the surface Frizzled receptor, it leads to the activation of the DSH protein (Dishevelled family proteins), which has the role of inhibiting the axin/GSK-3/APC complex. β -catenin enters the nucleus and interacts with transcription factors from the TCF/LEF family and affects the expression of certain genes



Hedgehog signaling pathway

It starts with the binding of Hedgehog proteins (Sonic Hedgehog (Shh), Indian Hedgehog (Ihh), Desert Hedgehog (Dhh)) to the transmembrane Patched receptor, which inhibits its activity, resulting in phosphorylation and translocation of the Smoothened protein to the cell surface.

Gli proteins are involved in the intracellular transmission of signals from the Smoothed protein, whose degradation is prevented in the presence of the Hedgehog protein.

Gli proteins that are further transported to the nucleus where they activate gene transcription.

