Stem Cells: The New Therapeutics Era

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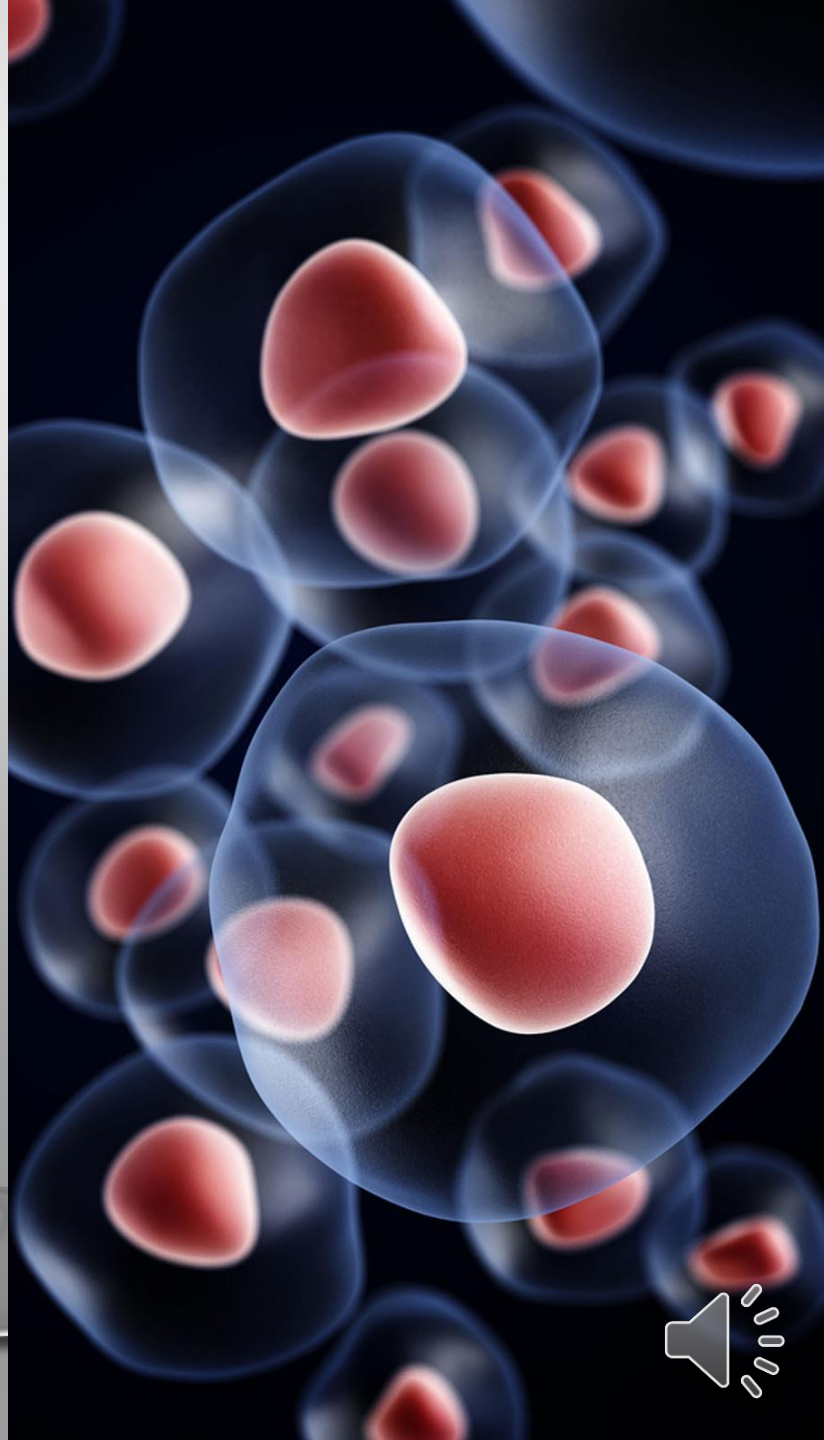
Central Nervous System



What are stem cells?

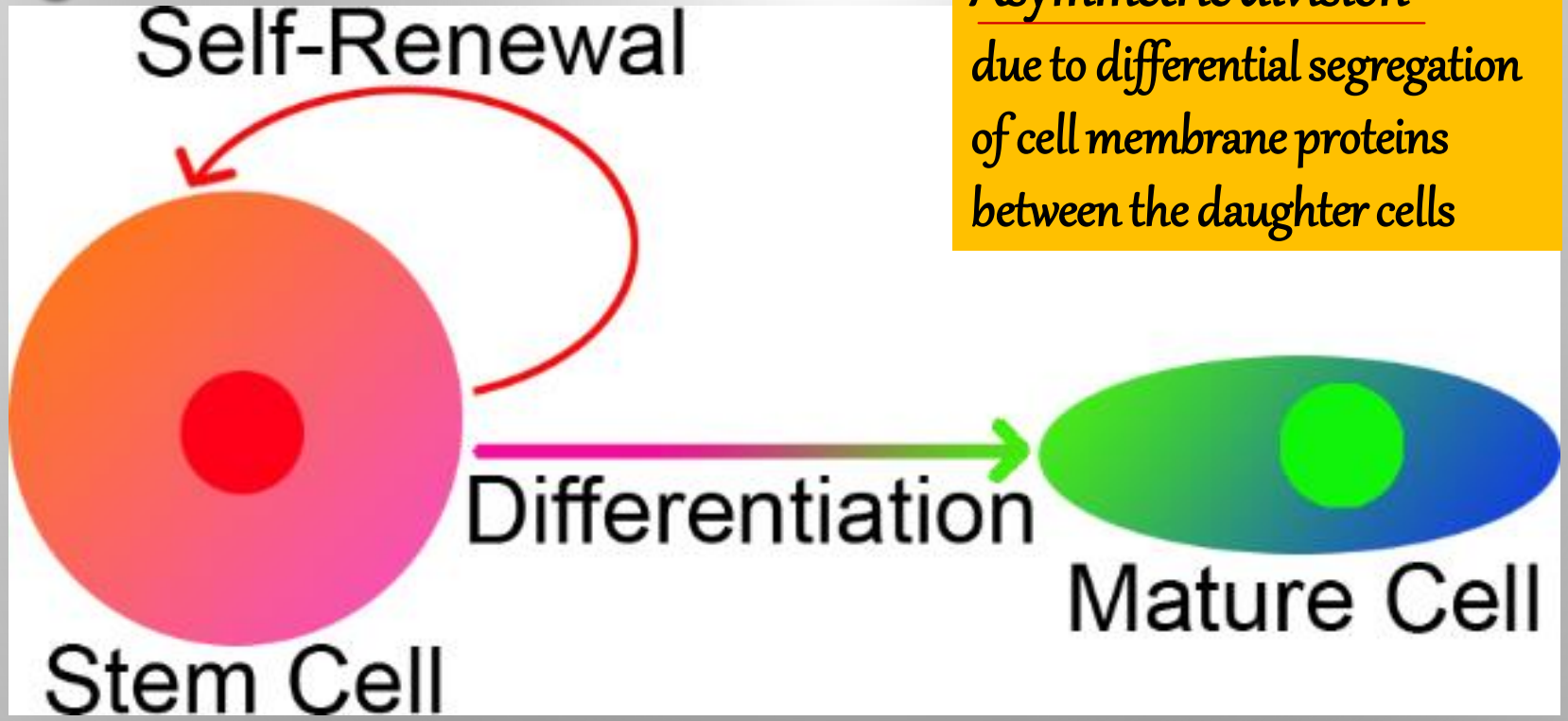
- Are primal cells common to all multicellular organisms that retain the ability to **renew** themselves through cell division and can be **differentiated** into a wide range of specialized cell types.
- All stem cells are unspecialized (**undifferentiated**) cells that are of the same family type (**lineage**).

Differentiation vs self renewal

عشان نخفف الخاصيتين اللي فوق

Asymmetric division

due to differential segregation of cell membrane proteins between the daughter cells



Self-renewal: The ability to go through numerous cycles of cell division while maintaining the undifferentiated state.

How Does Asymmetric Division Occur?

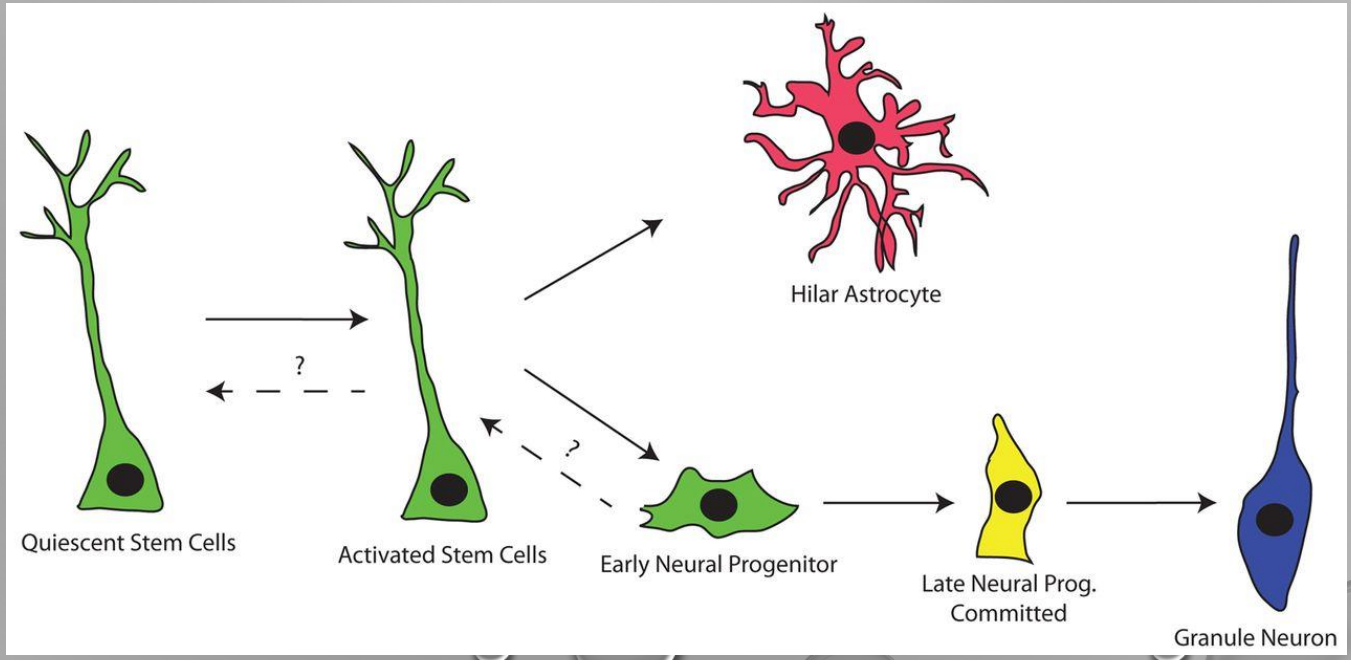
- Differential segregation of cell membrane proteins (such as receptors) between the two daughter cells.

⇒ this means that during cell division, the proteins and cell membrane proteins that imp. for keeping the stemness of stem cells going to be located in the cells that renews the stem cells population, whereas the proteins that imp. for driving differentiation are going to move to the 2nd cells that go into the differentiation path.

What does stem cell division produce?

↳ During differentiation pathways, stem cells don't go differentiation just in single step, they pass through intermediate cellular steps, and these steps (kind of partially differentiated) and they can diverge their paths into several ones, producing different and several types of fully mature cells the intermediate cell.

- **Progenitor cell**:Stem cells generate an intermediate cell type or types before they achieve their fully differentiated state.

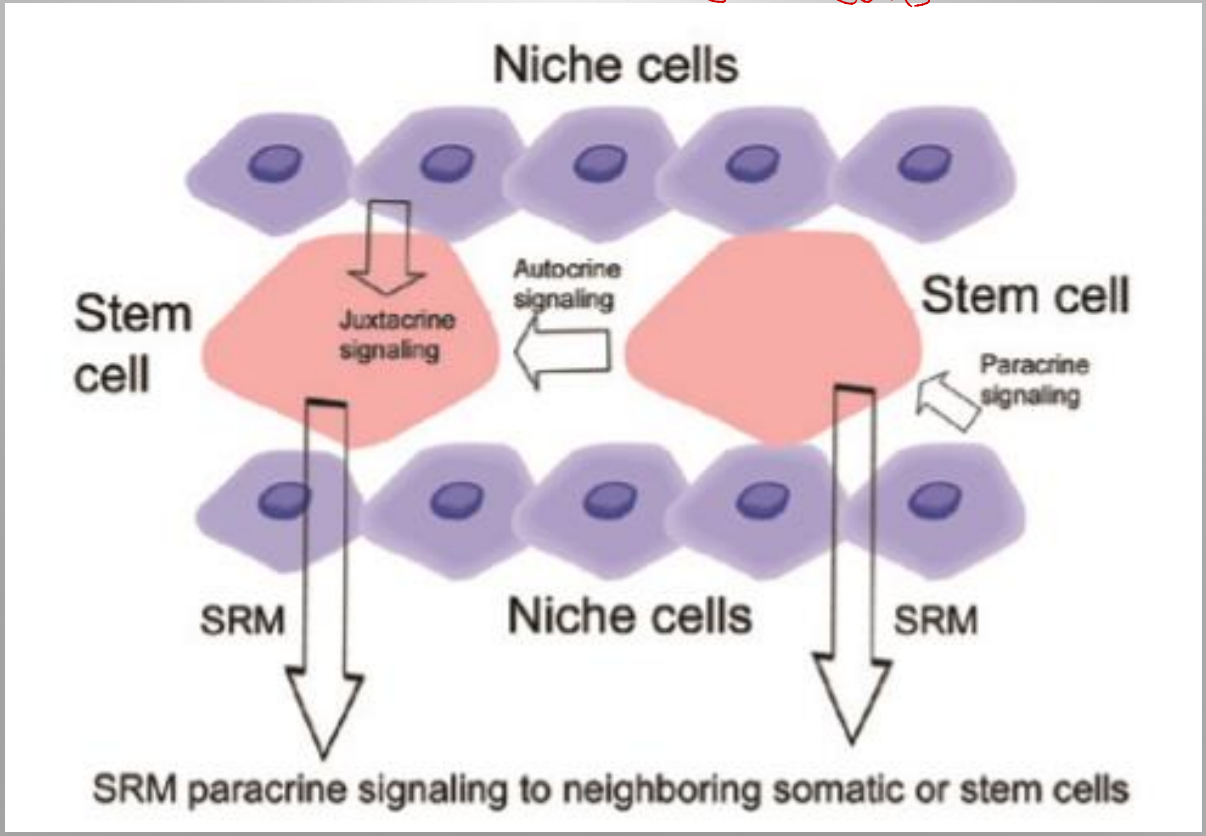


Venere et al 2012

Stem cell niche

A specialized cellular environment that provides stem cells with the support needed for self-renewal.

→ to optimize the conditions for stem cells



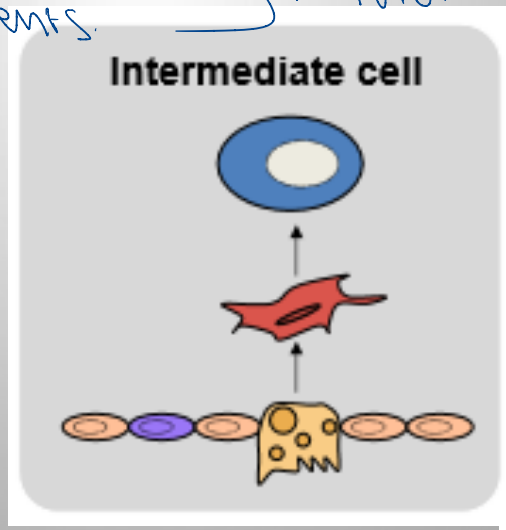
Stem cell niche

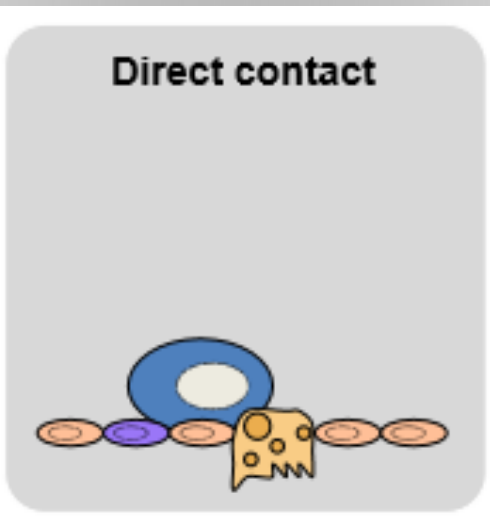
maybe include ∞

* one niche is different from another according to their components.

1. **Cells only**

A single cell type, or a whole host of interacting cells. Cells outside the stem cell's lineage, or they may derive primarily from the stem cell's own descendants.

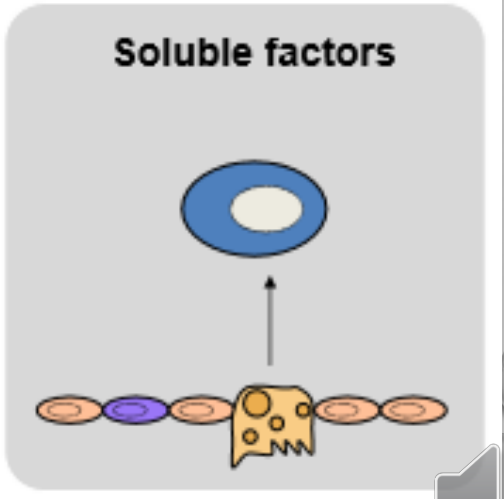




2. **Cells & ECM**

Secreted or cell surface factors

Notch, Wnt, FGF, EGF, TGF-β, SCF, and chemokine families



3. OR / in addition to soluble factors

Why stem cells need a special environment?

it is called niche.

- Demands on stem cells necessitate **special support for viability**.
- **Nutritive** function
- Niches might be agents of **feedback control** (control of stem cell pool **size**).

So it does not expand a lot or shrink.

- Niches are instruments of **coordination among tissue compartments**.

(for size)

- Niches are **hubs of inter-lineage coordination**.

By interactions and feedback mechanisms

As we said the stem cells differentiate into several cell types, so they should have a coordination between them so one does not dominate over the others. and niche act as a hub (center) for this coordination.

POTENCY OF STEM CELLS

classified according to their potency.

- THE DIFFERENTIATION POTENTIAL OF THE STEM CELLS

(How many cell types can produced from certain stem cell).

* ... to produce them ...

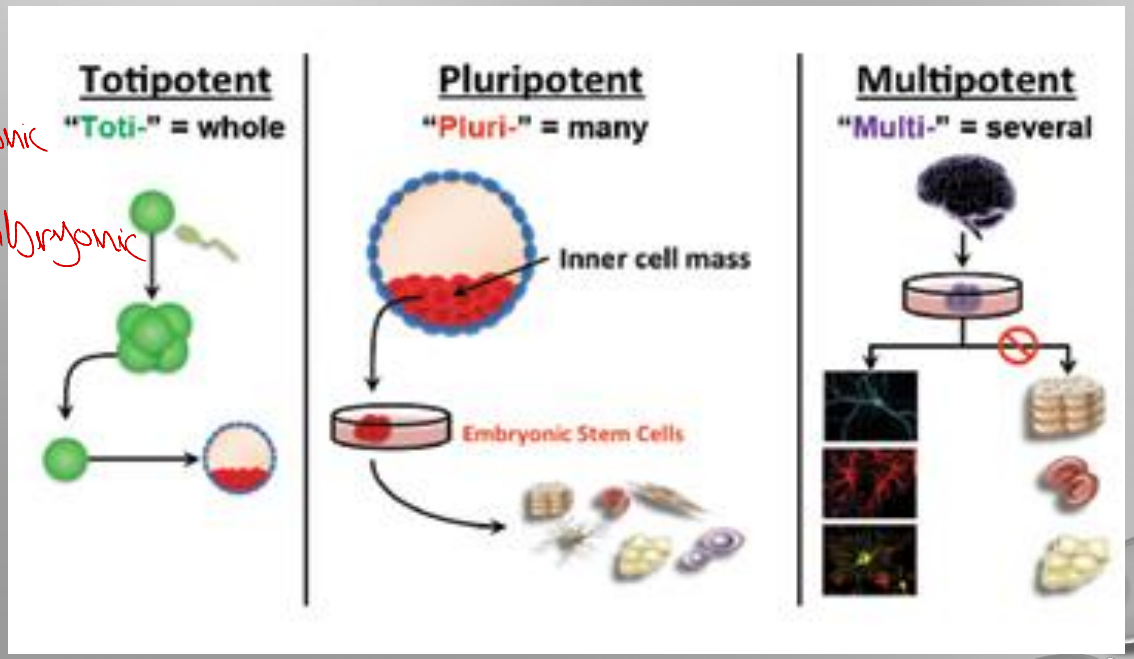
TYPE OF POTENCY :

1-TOTIPOTENT
- into all cells of the body and extraembryonic tissues including placenta.

2-PLEURIPOTENT
- into all cells of the body, but no extraembryonic tissues

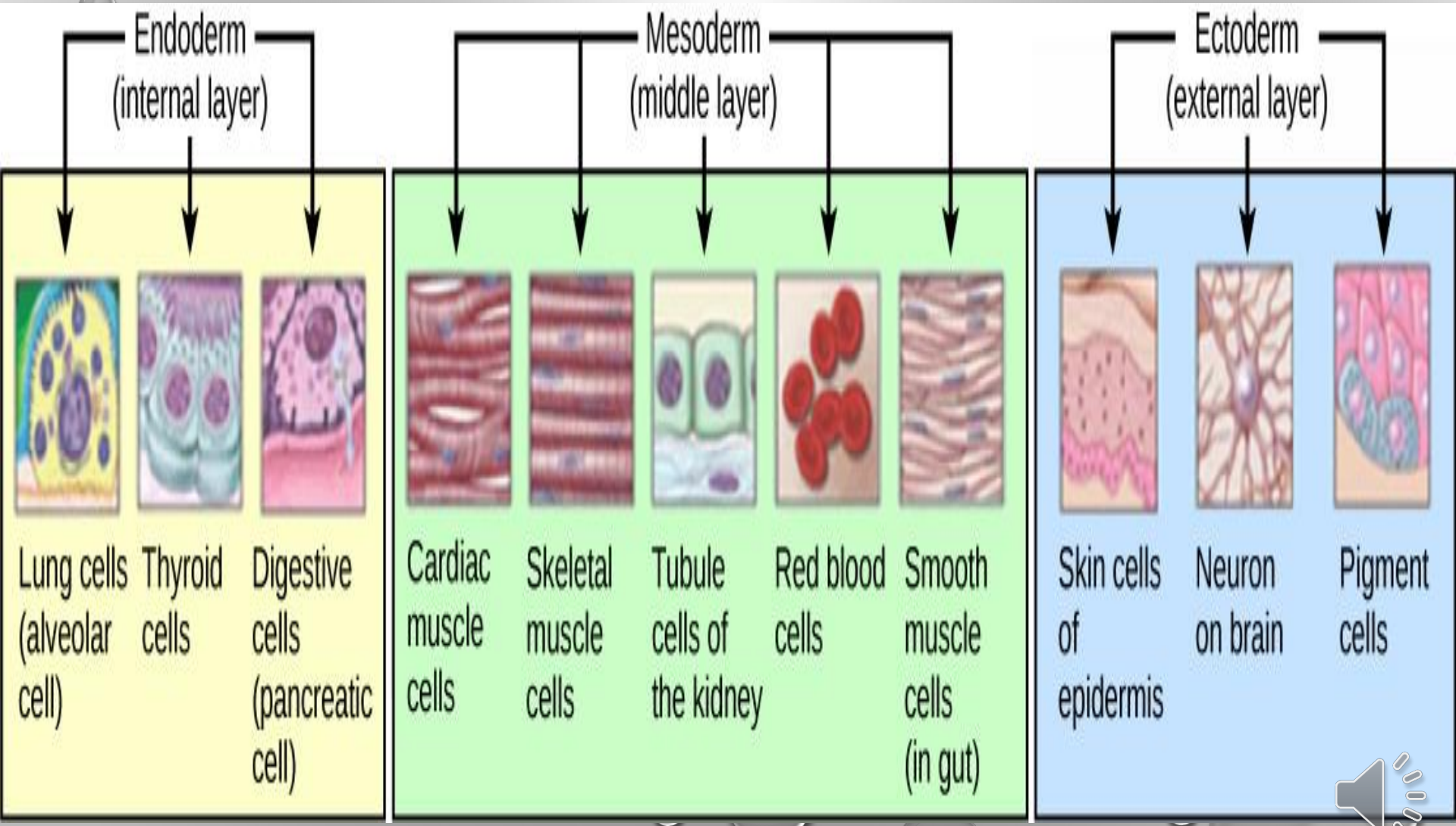
3-MULTIPOTENT
- into several cell types.

4-UNIPOTENT
- into single cell type.



*If we take pleuripotent stem cell population, and expose it to differentiation conditions or drive their differentiation, they should be able to give rise to cells from all 3 germ layers (ectoderm, endoderm and mesoderm) and give a rise to a wide variety from these 3 layers

THREE GERM LAYERS



*Another classification of stem cells depends on their time of presence

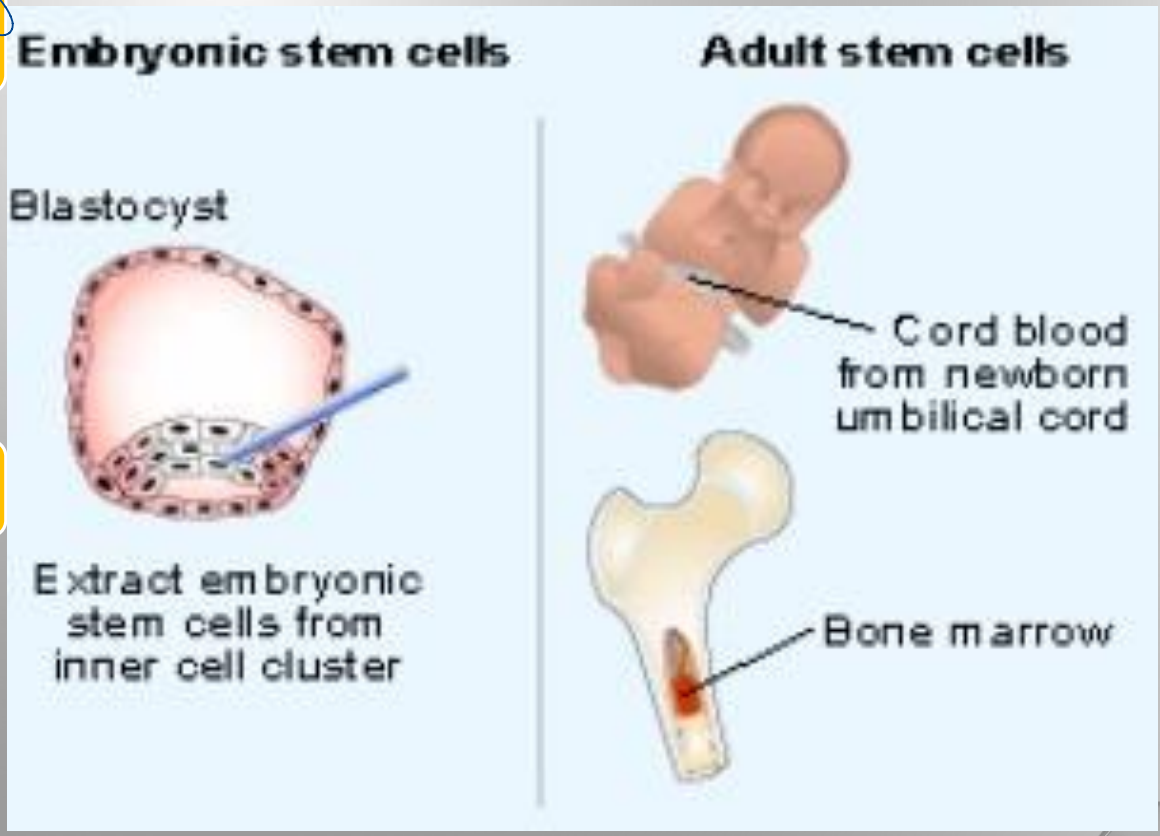
Types of stem cells

Embryonic stem cells *Appears during embryonic development

- Are able to differentiate into all the specialized embryonic tissue

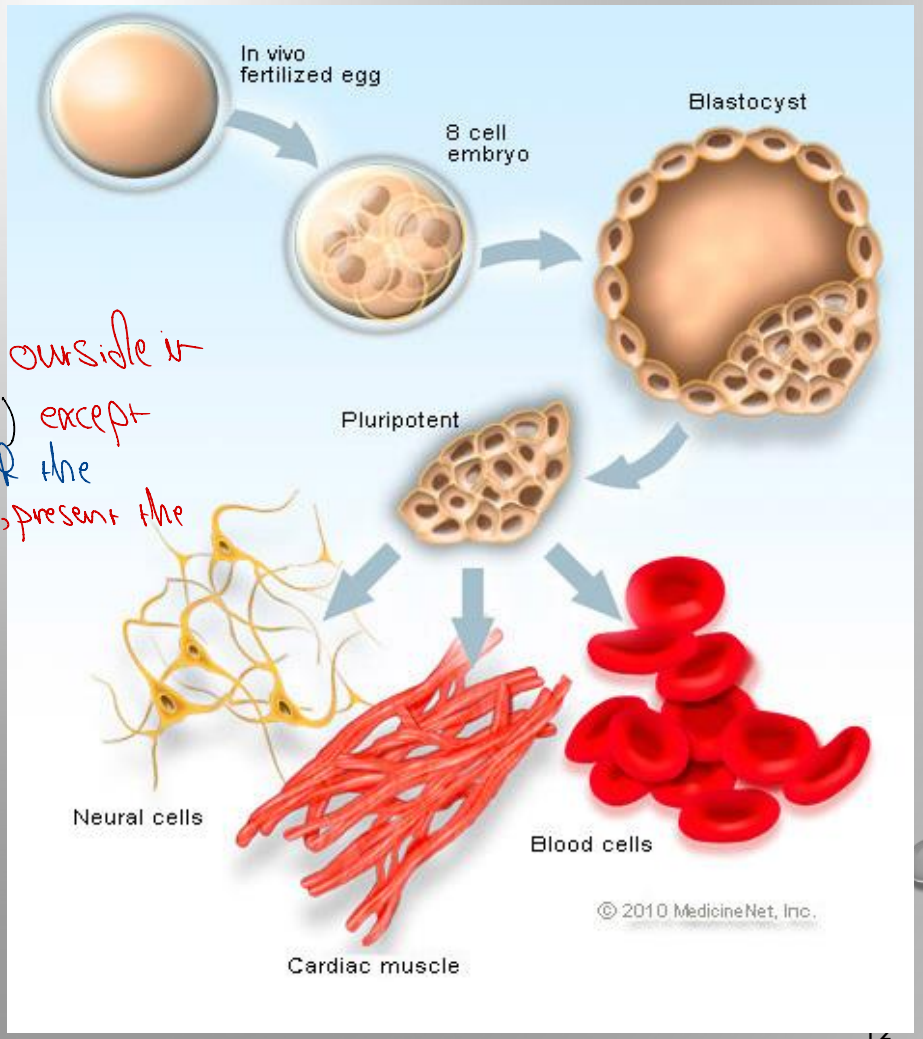
Adult stem cells *Appears later

- Act as a repair system for the body replacing specialized damaged cells



Embryonic Stem Cells (ESCs)

- ✓ ES cells are derived from inner cell mass of mammalian blastocysts => have a layer of cells outside it and the inside is just hollow (there is no cells) except in one side of it (where there is an accumulation of the cells called inner cell mass) inside the inner cell mass, present the pleuripotent stem cell.
- ✓ Develop before implantation in the uterus



Pluripotency of ESCs

Pluripotency transcription factors:

1. Oct 4
2. Nanog
3. Wnt-β-catenin signaling
4. Other TFs

*problems with embryonic stem cells and their use for treatment of diseases and transplantation for the treatment purposes => is that we need to isolate them from embryos and this means that we are going to kill the embryo after it started to develop

The Ethical Dilemma of ESCs

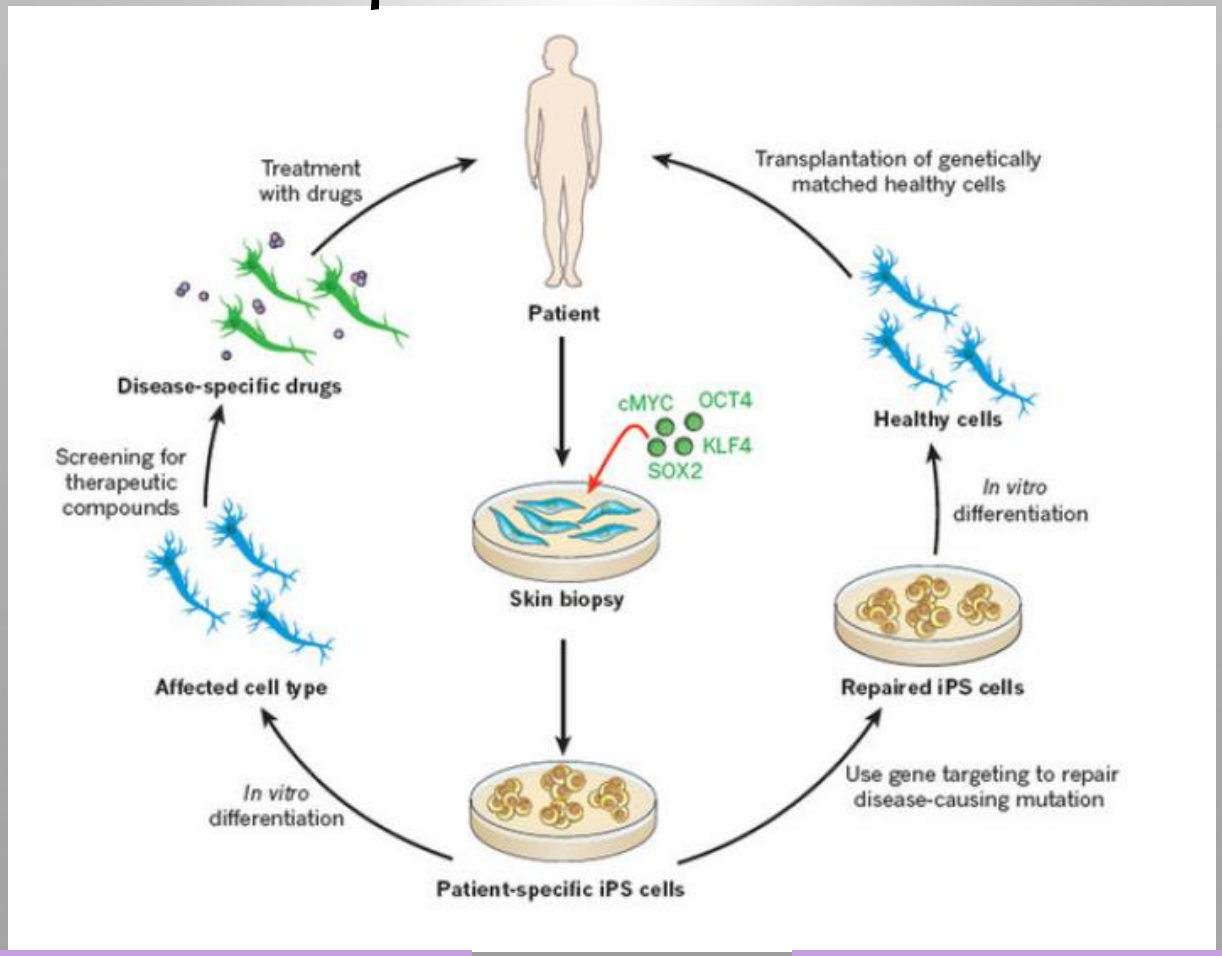
*Another problem to put it in consideration is the immune rejection (when we put foreign body from the embryo to the patient even if they are siblings)

*Prevention or alleviation of suffering

Respect the value of human life

Morals and religion

Induced Pluripotent Stem Cells (iPSCs)



Ethical

Autologous

Patient-specific

Safer

Generation of iPSCs

- **iPS cells were obtained by transducing embryonic and adult fibroblasts with defined transcription factors.**
  - **OCT3/4, SOX2, c-Myc, KLF4**

Takahashi K, Yamanaka S. 2006. *Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors.* **Cell 126:663–676.**

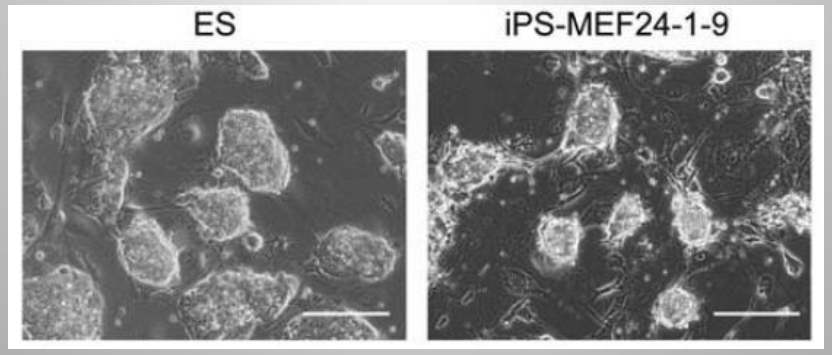
Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. 2007. *Induction of pluripotent stem cells from adult human fibroblasts by defined factors.* **Cell 131:861–872.**

*After they collected the cells that were programmed, they tested them and check whether they are really active like embryonic stem cells because under the microscope they look morphologically the same.

Yamanaka's comparison of iPS and ES cells

⇒ They compare the following between them as

1. Surface antigens
2. Morphology
3. Gene expression
4. Telomerase activities
5. Epigenetic status of pluripotent cell-specific genes
6. Promoter activities
7. Teratoma formation
8. Proliferation



iPS cells are indistinguishable from ES cells in:

→ when you inject them in mice, they exhibit to form this tumor which is 3 germ layers

Adult stem cells

- They might be just multipotent or unipotent → they can't be pluripotent

Undifferentiated cells found through out the body.

Function: they divide to replenish dying cells and regenerate damaged tissue

Types of adult stem cells

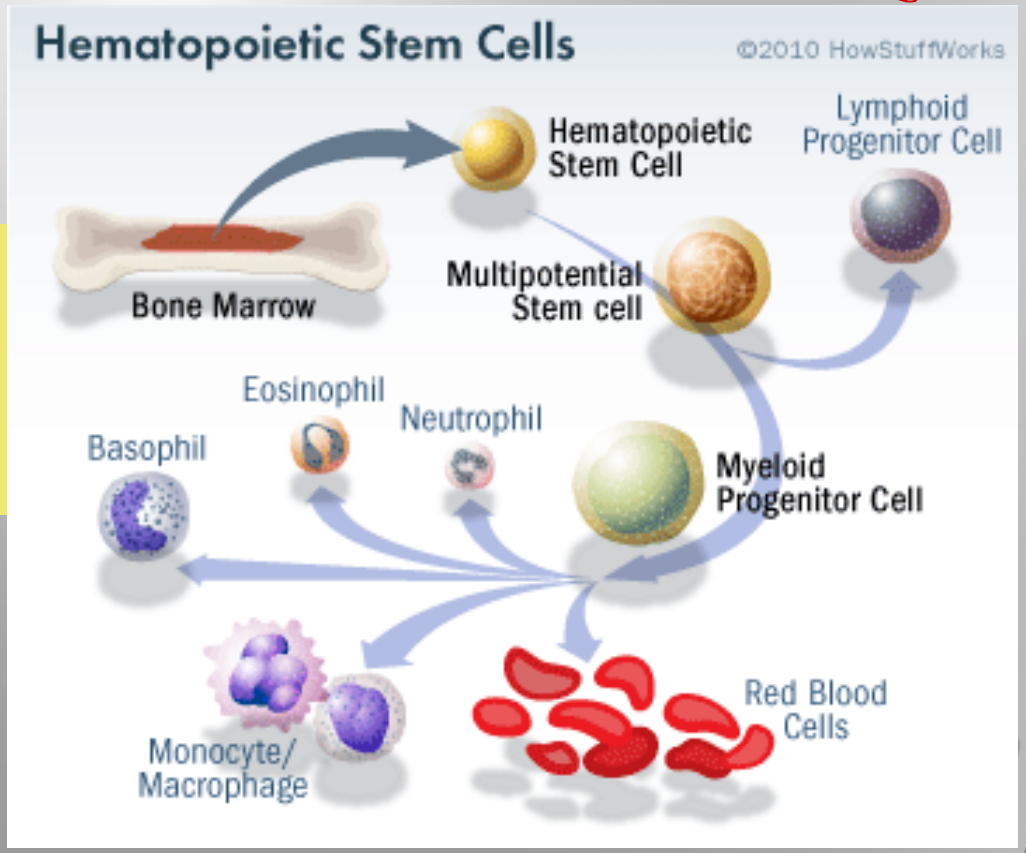
* To regenerate the tissues and damages occur through life.

→ Divided into 2 types A + B

1. **Bone marrow stem cells**

A. **Hematopoietic stem cells**

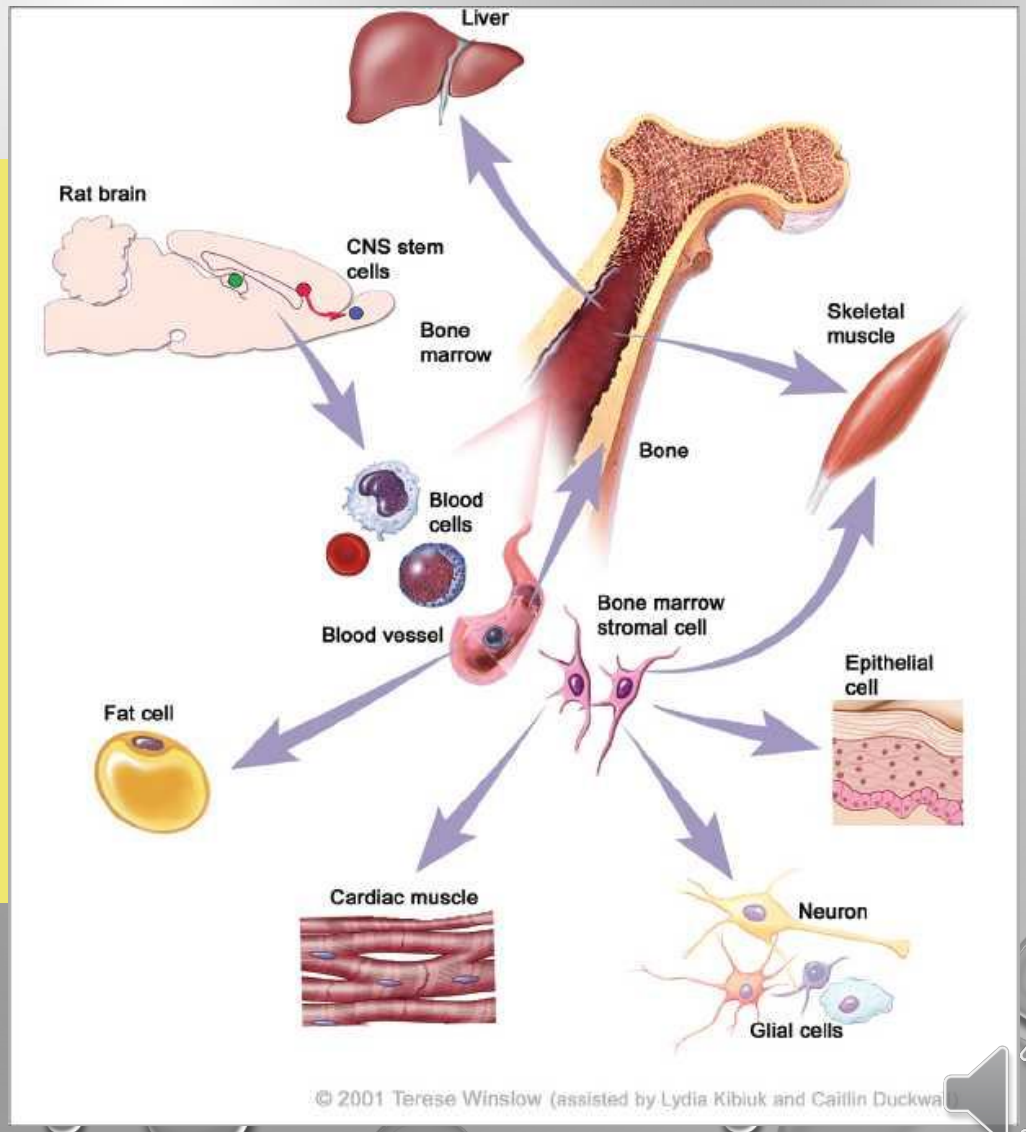
give rise to all cells of Blood.



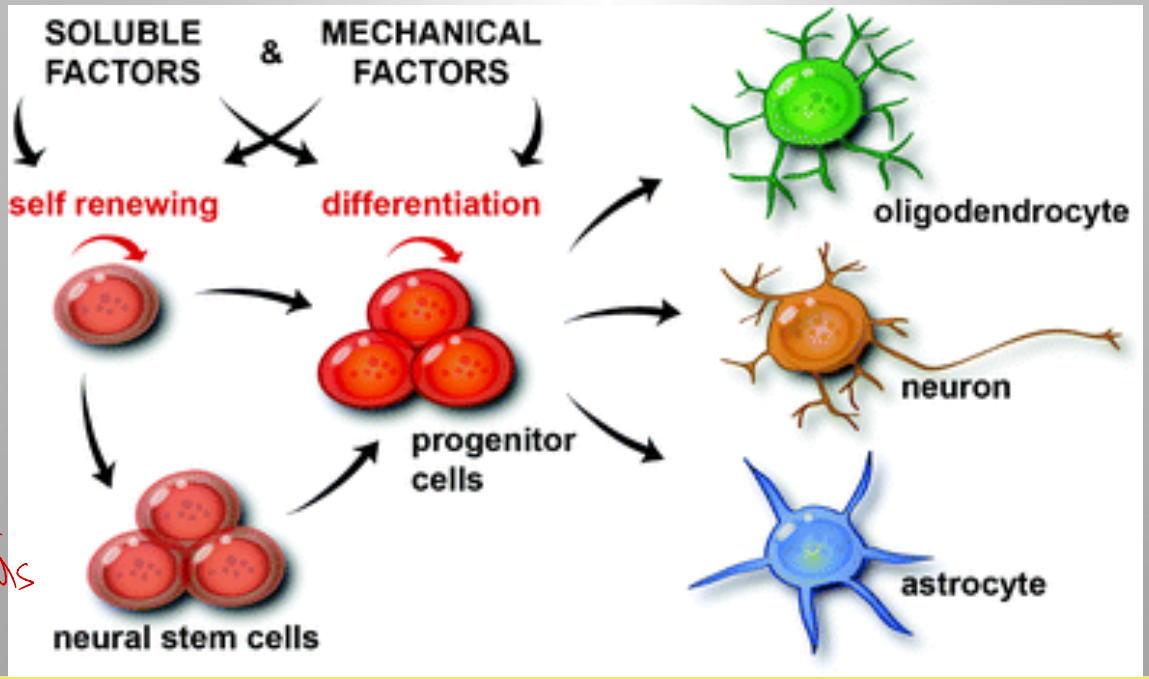
Types of adult stem cells

1. **Bone marrow stem cells**

B. **Somatic stem cells** such as mammary stem cells and mesenchymal stem cells (osteoblasts, chondrocytes, myocytes, adipocytes, neuronal cells). and the memory stem cells.



Types of adult stem cells



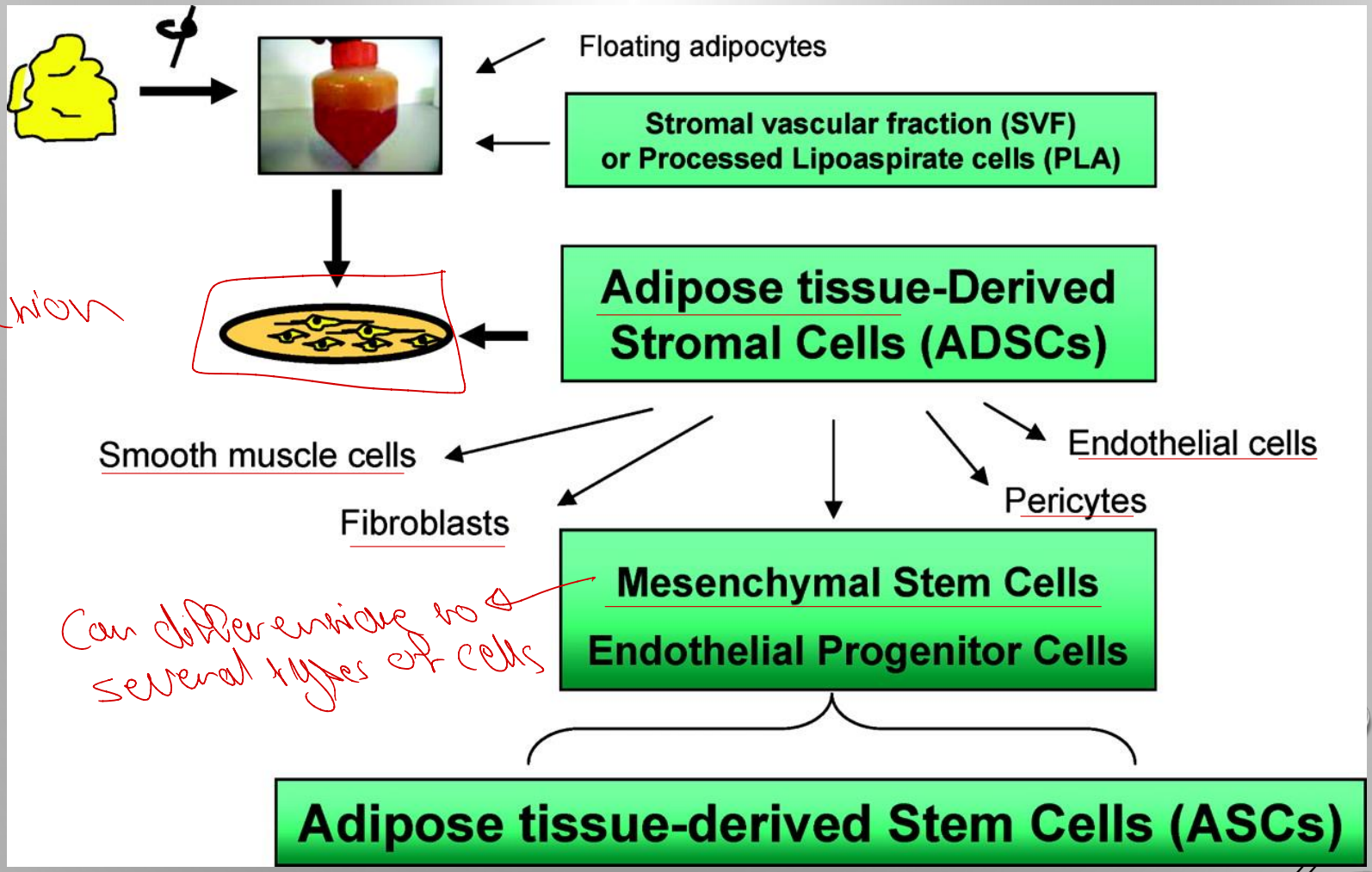
*another ex of adult stem cells

2. Neural stem cells : neurospheres – floating heterogenous aggregates of cells, containing a large proportion of stem cells responsible for adult neurogenesis in **subventriculare zone**, which lines the **lateral ventricles of the brain, and the dentate gyrus of the hippocampal formations**.

*limited ability to regenerate neurons

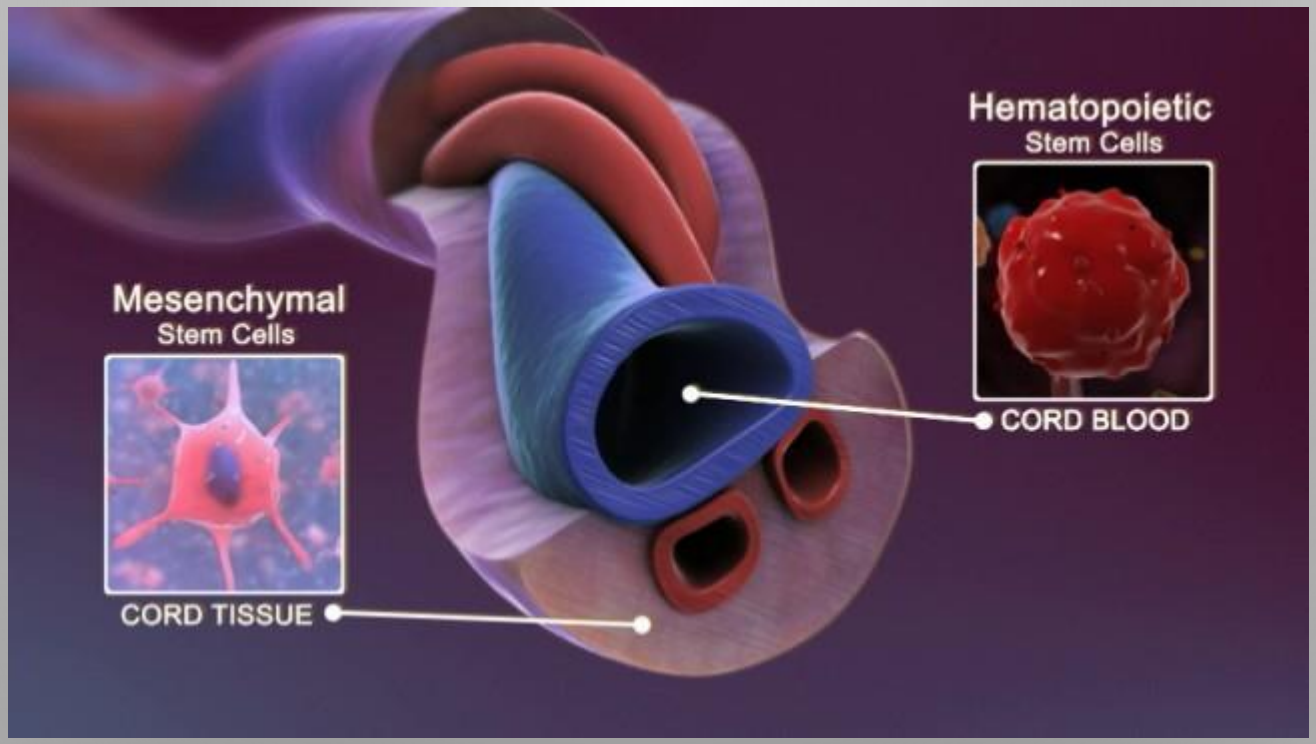
Types of adult stem cells

*Another type is adipose stem cells.



3. Adipose stem cells (ASCs).

Types of adult stem cells



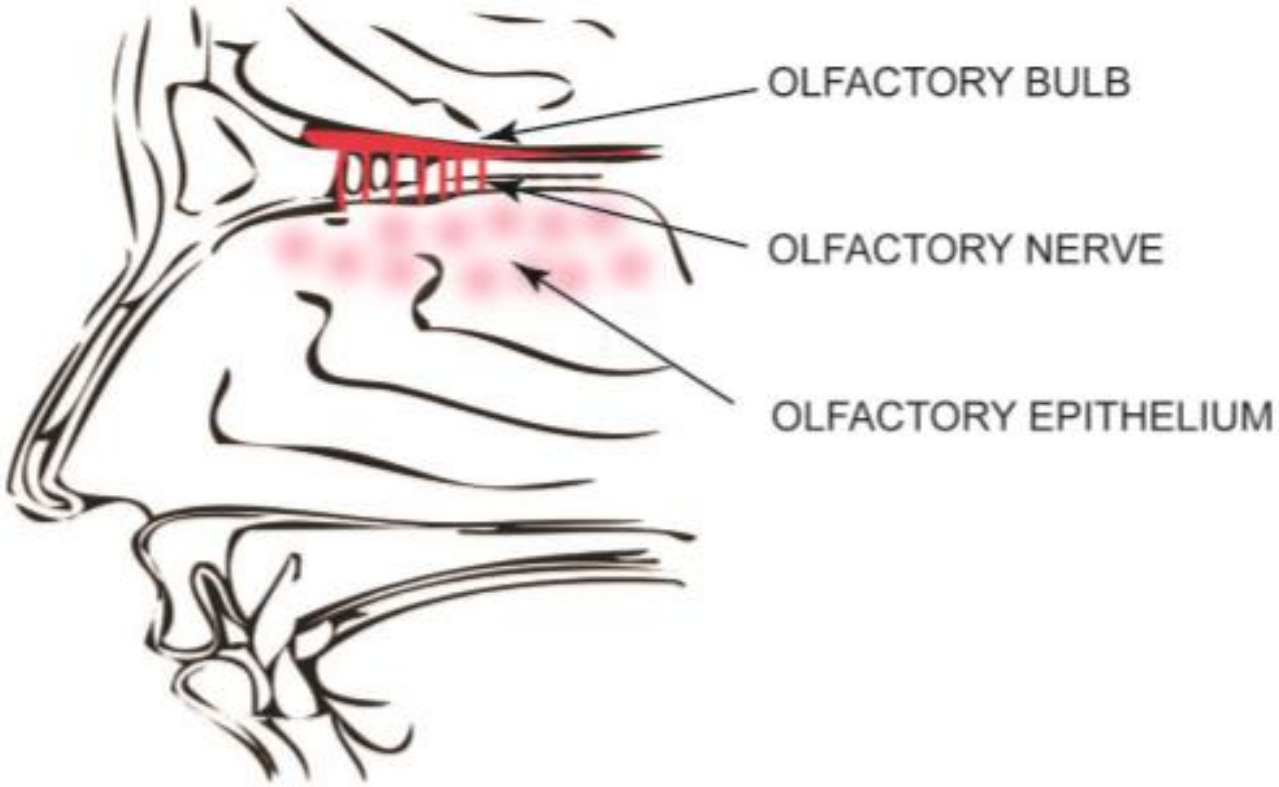
4. Umbilical cord stem cells

- Contains 2 types of stem cells => 1) the blood of umbilical cord contains hematopoietic stem cells
2) the cord tissue itself contains mesenchymal stem cells

Types of adult stem cells

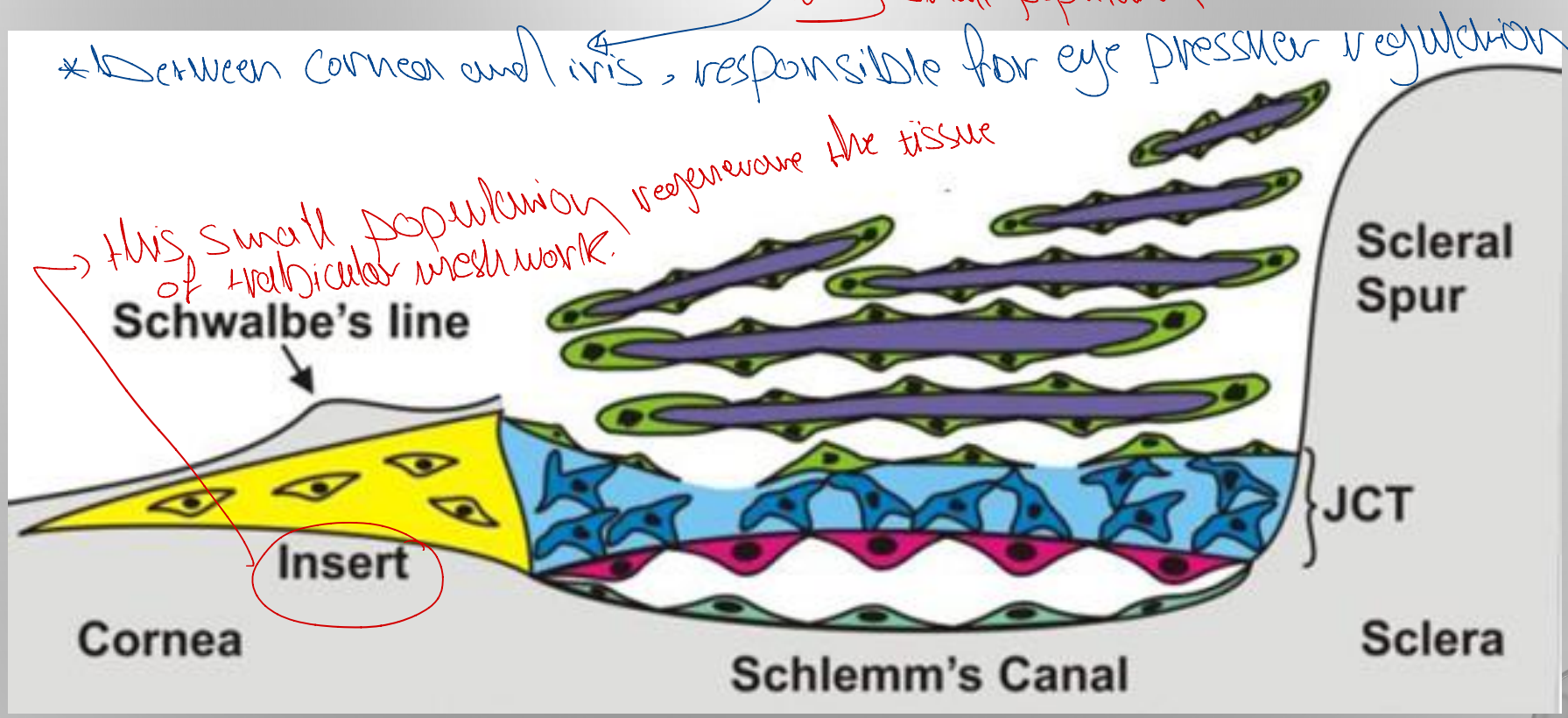
5. Olfactory adult stem cells: *found in olfactory mucosal cells*

to regenerate these sensory receptors



Types of adult stem cells

6. **Tissue stem cells** in cornea, trabecular meshwork, etc.



USES OF STEM CELLS

(not for treatment only)

- TO STUDY THE SPECIFIC SIGNALS AND DIFFERENTIATION
- GENETIC THERAPY
- DRUG TESTING
- CELL BASED THERAPIES
- STEM CELLS FOR CANCER TREATMENT BY ACTIVATION OF CHEMOTHERAPEUTIC AGENTS

STEM CELL THERAPY LIMITATIONS

✓ Stem cell therapy has disadvantages such as

- Carcinogenicity If it transplanted as stem cells.
- Immune rejection
- Infection (control is when you transplant stem cells from one individual to others).

✓ These factors make the usage of stem cell limited.

LIMITATIONS OF USING ADULT STEM CELLS

1-Lack of stem cell markers resulting in difficulties to separate and identify cells. (If we don't have specific markers we can't isolate them efficiently).

2-In vitro systems for manipulating adult stem cell populations are often not well defined (If I don't know how to manipulate the stem cells in order to be correctly differentiated then can be a problem).

3-In vivo :our understanding of how adult stem cells are regulated within their niche is in its infancy.

4-Multipotency of ASCs

↳ limited ability to differentiate compared to embryo.

According to Dr's video => 23:36.