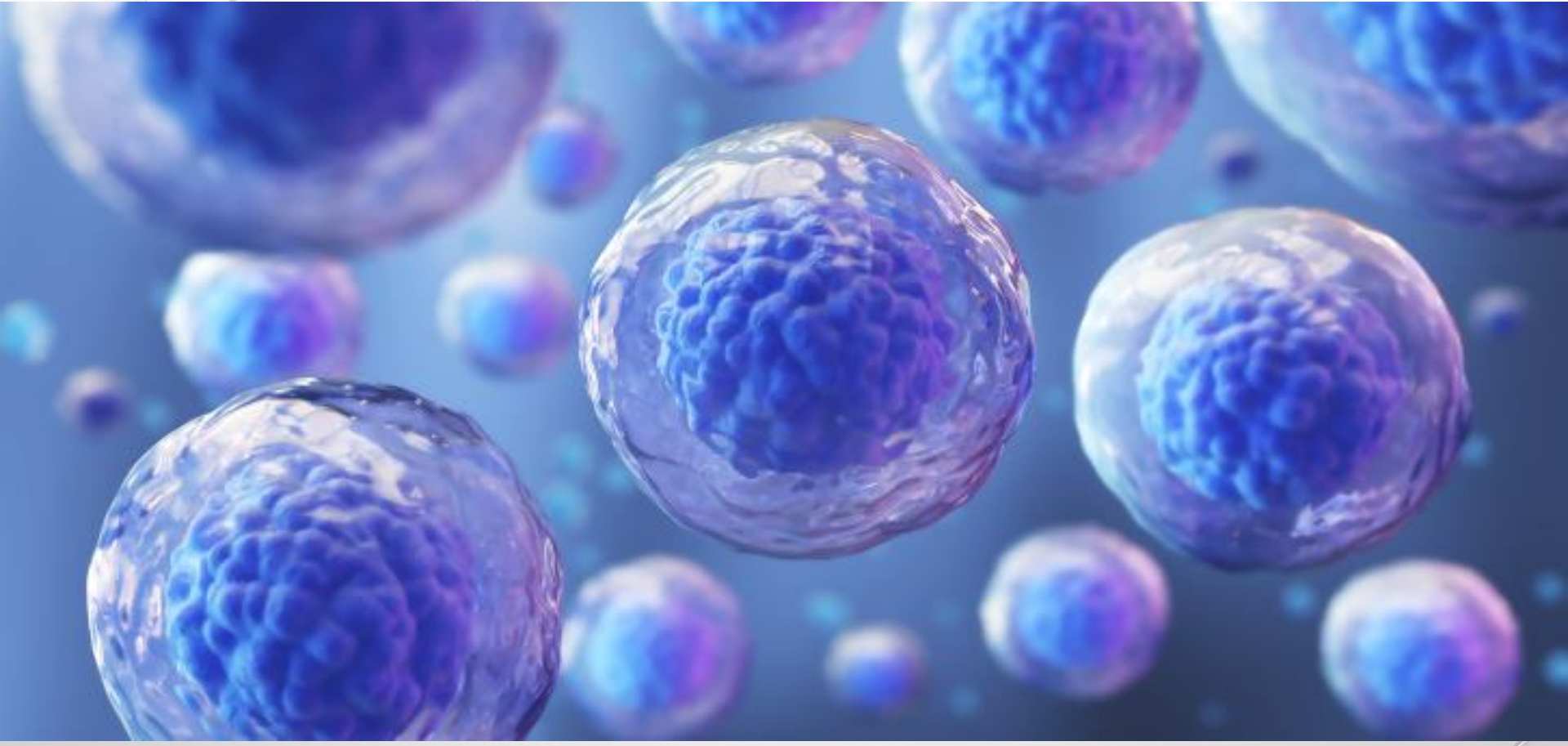


Stem Cells: The New Therapeutics Era

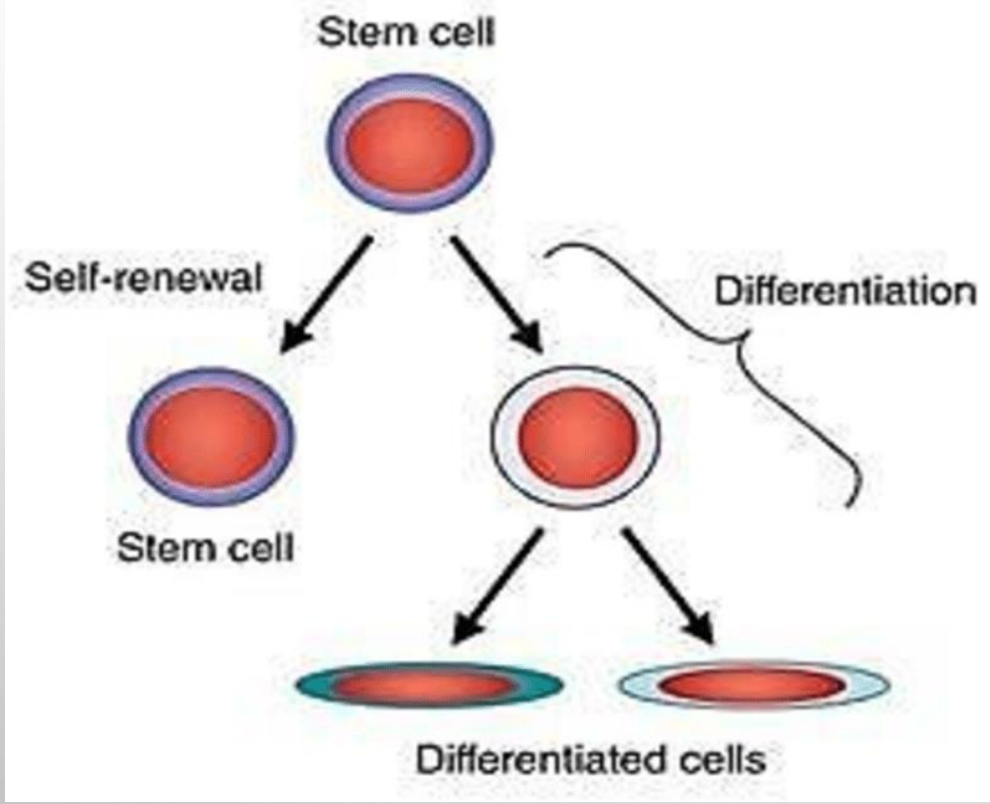
Dr. Diala Abu-Hassan, DDS, PhD

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



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

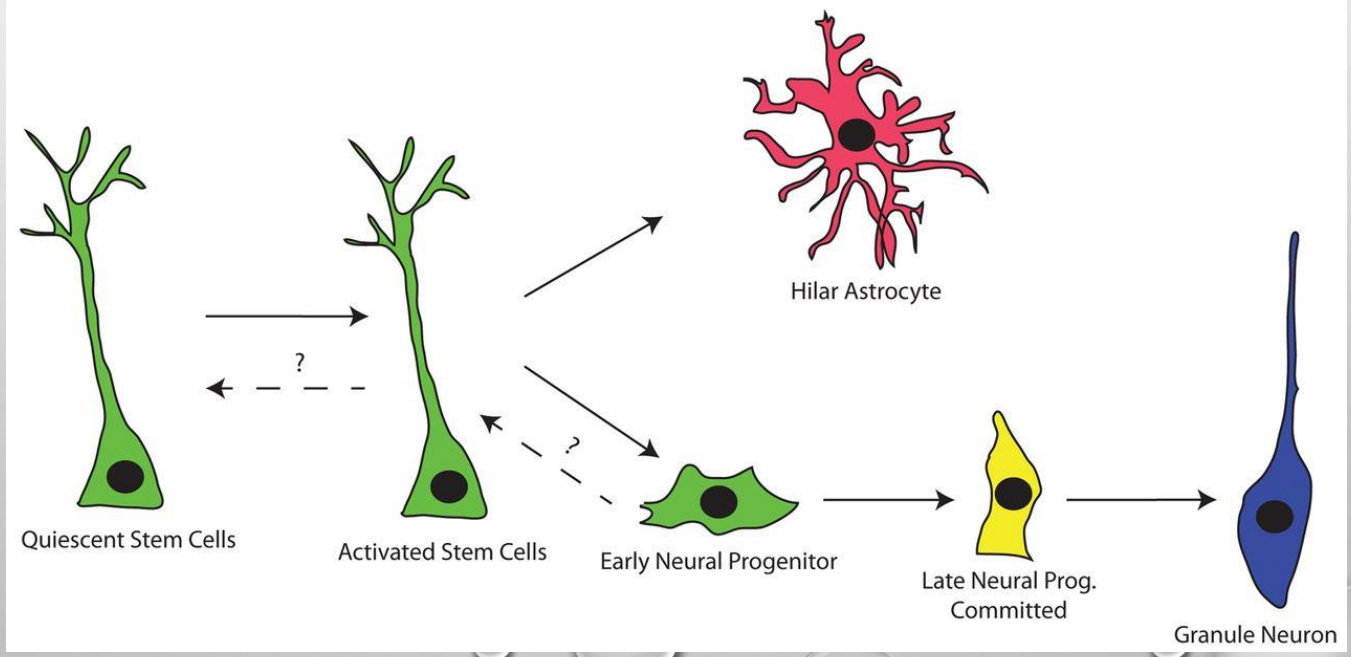
Self-renewal: The ability to go through numerous cycles of cell division while maintaining the undifferentiated state.

How Does Asymmetric Division Occur?

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

What does stem cell division produce?

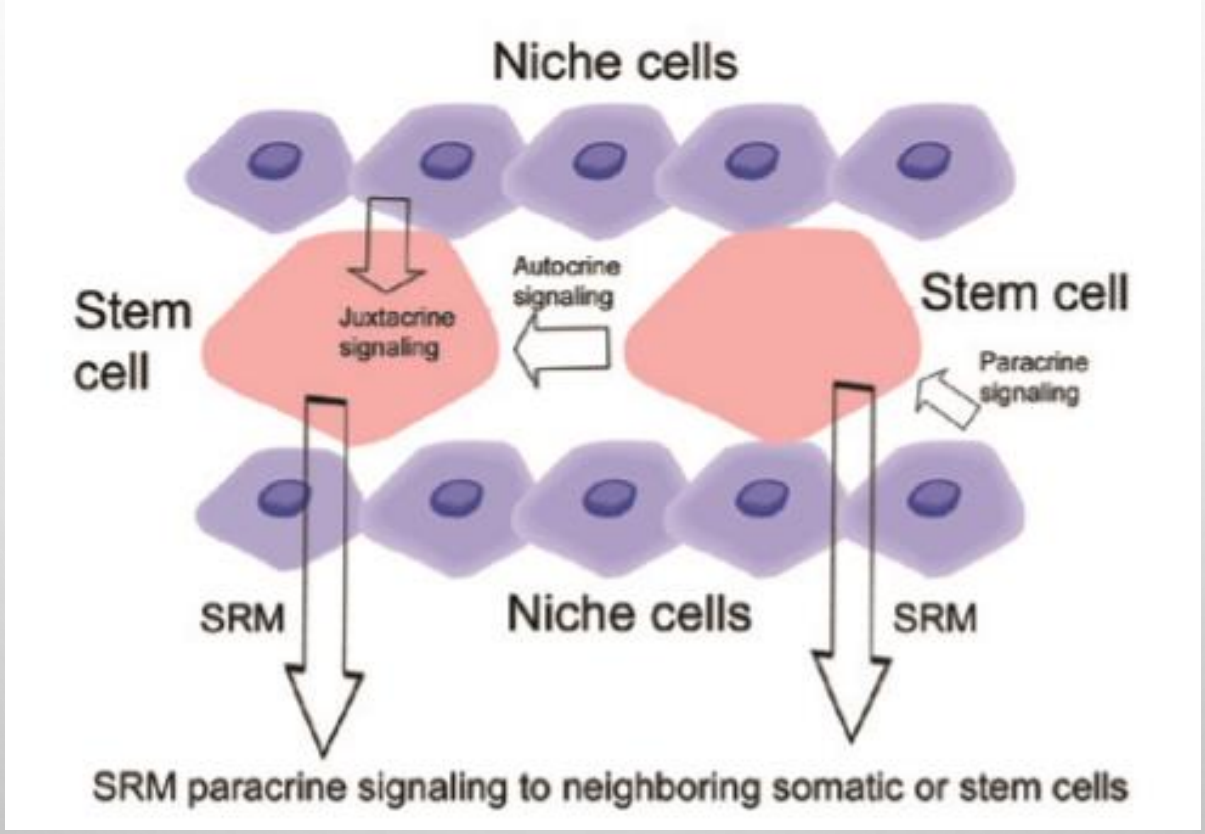
- **Progenitor cell** :Stem cells generate an intermediate cell type or types before they achieve their fully differentiated state.



Venere et al 2012

Stem cell niche

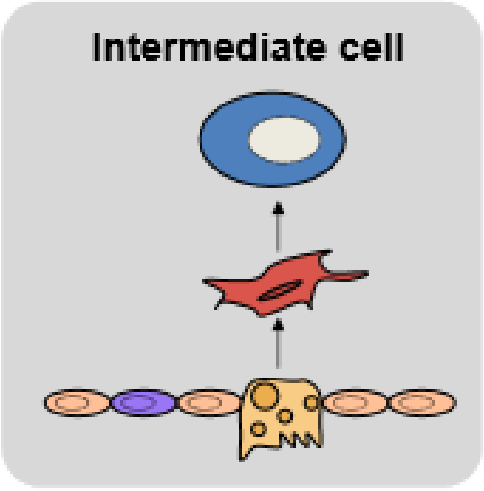
A specialized cellular environment that provides stem cells with the support needed for self-renewal.

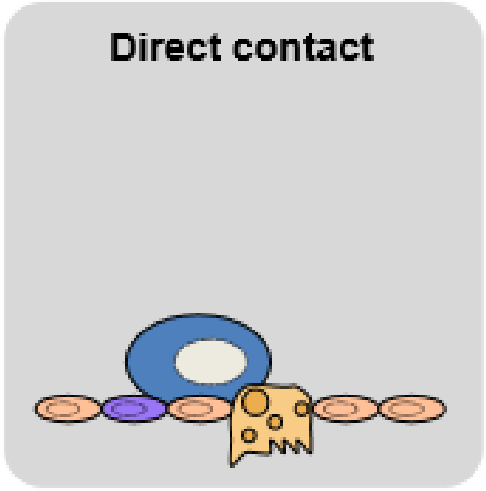


Stem cell niche

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.

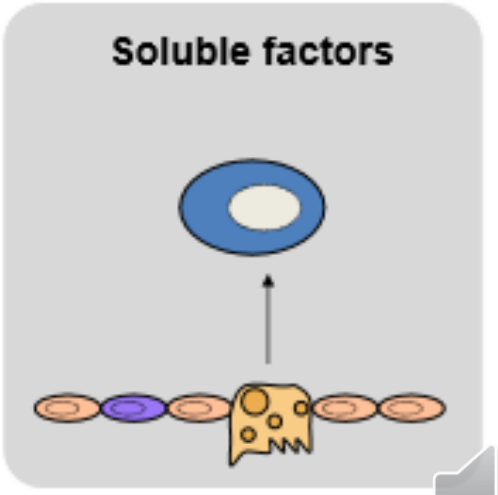




Cells & ECM

Secreted or cell surface factors

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



Why stem cells need a special environment?

- Demands on stem cells necessitate **special support for viability**.
- **Nutritive** function
- Niches might be agents of **feedback control (control of stem cell pool size)**.
- Niches are instruments of **coordination among tissue compartments**.
- Niches are **hubs of inter-lineage coordination**.

POTENCY OF STEM CELLS

- The differentiation potential of the stem cells

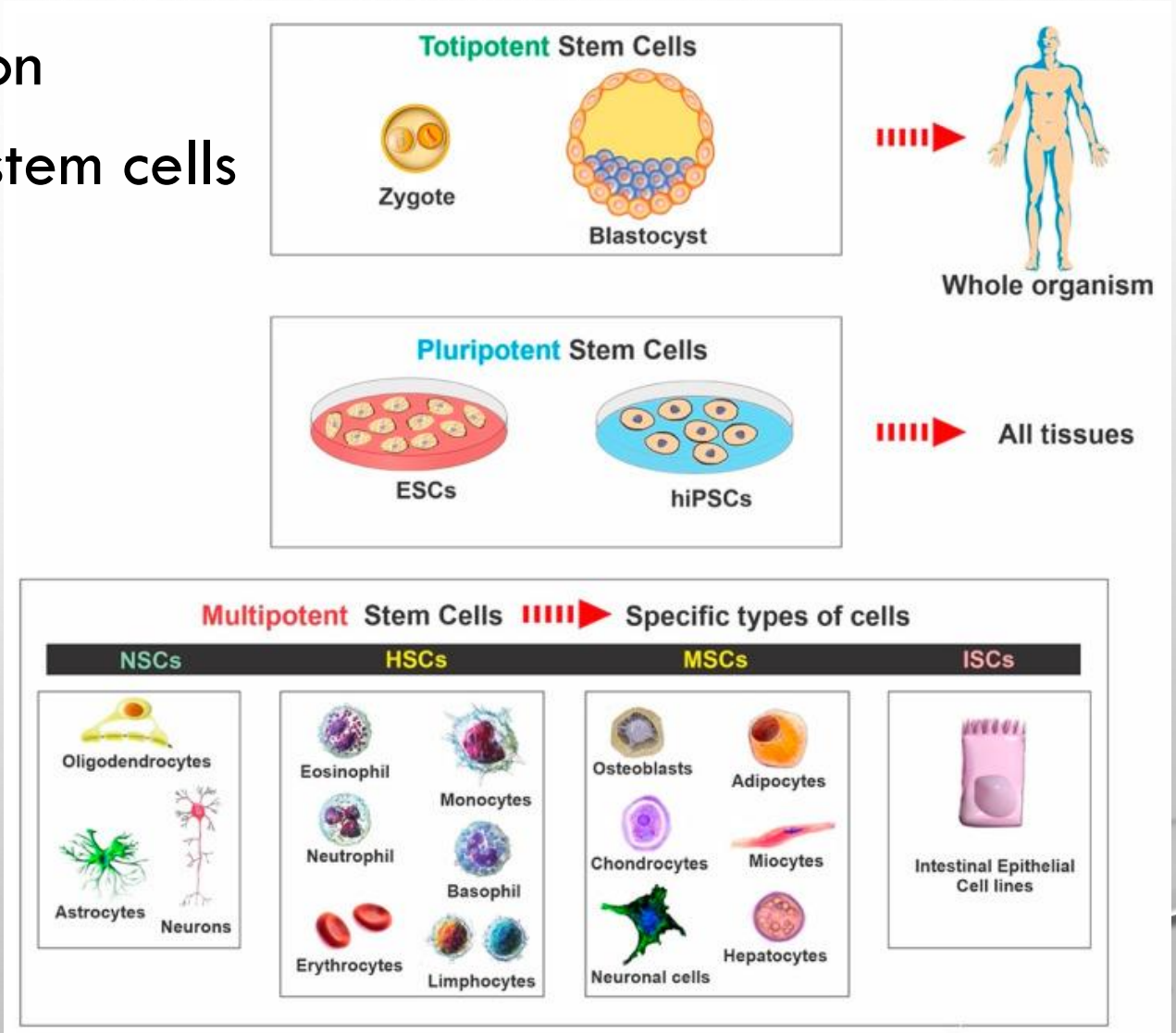
Type of potency :

1-Totipotent

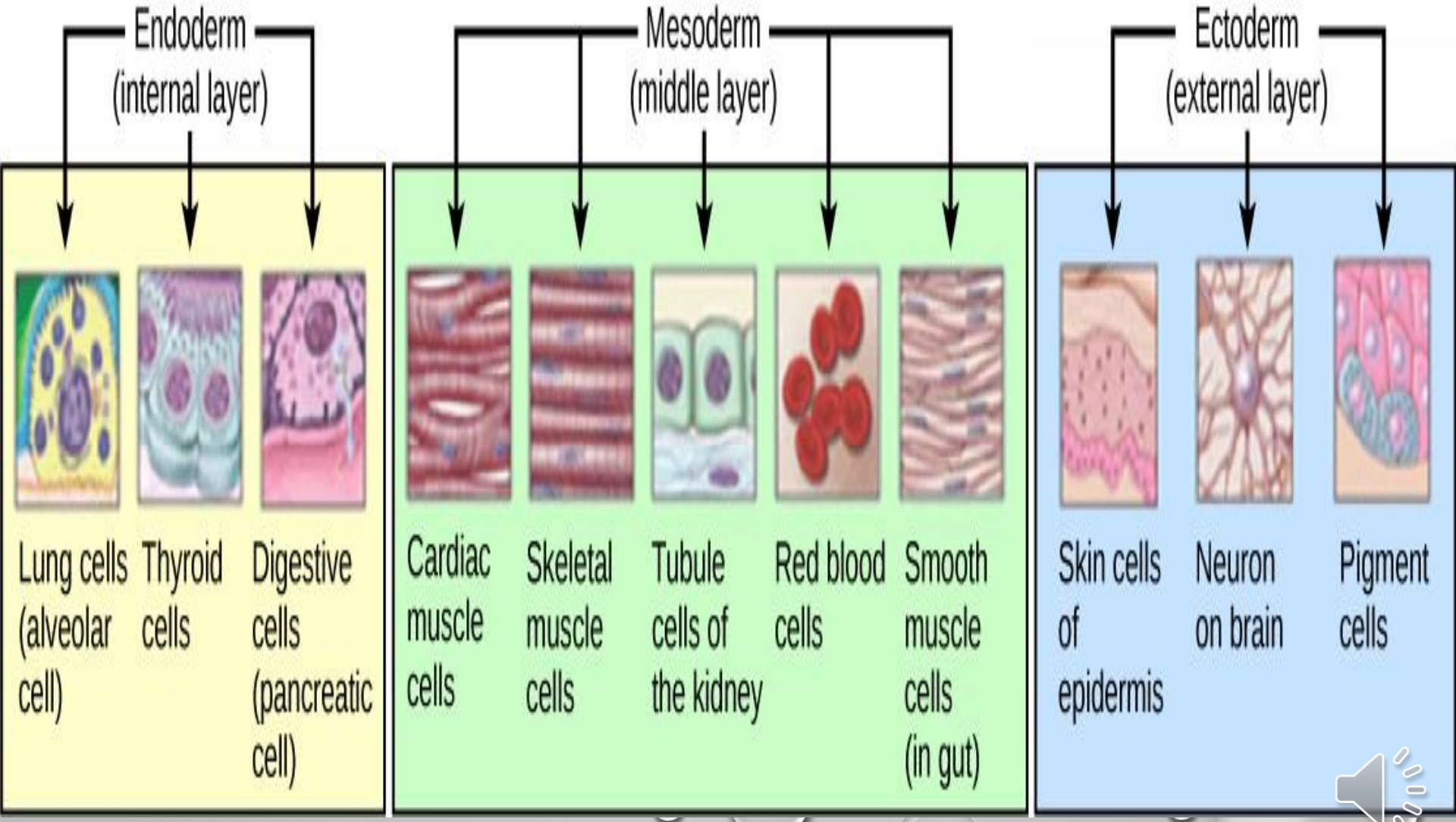
2-Pleuripotent

3-Multipotent

4-Unipotent



THREE GERM LAYERS



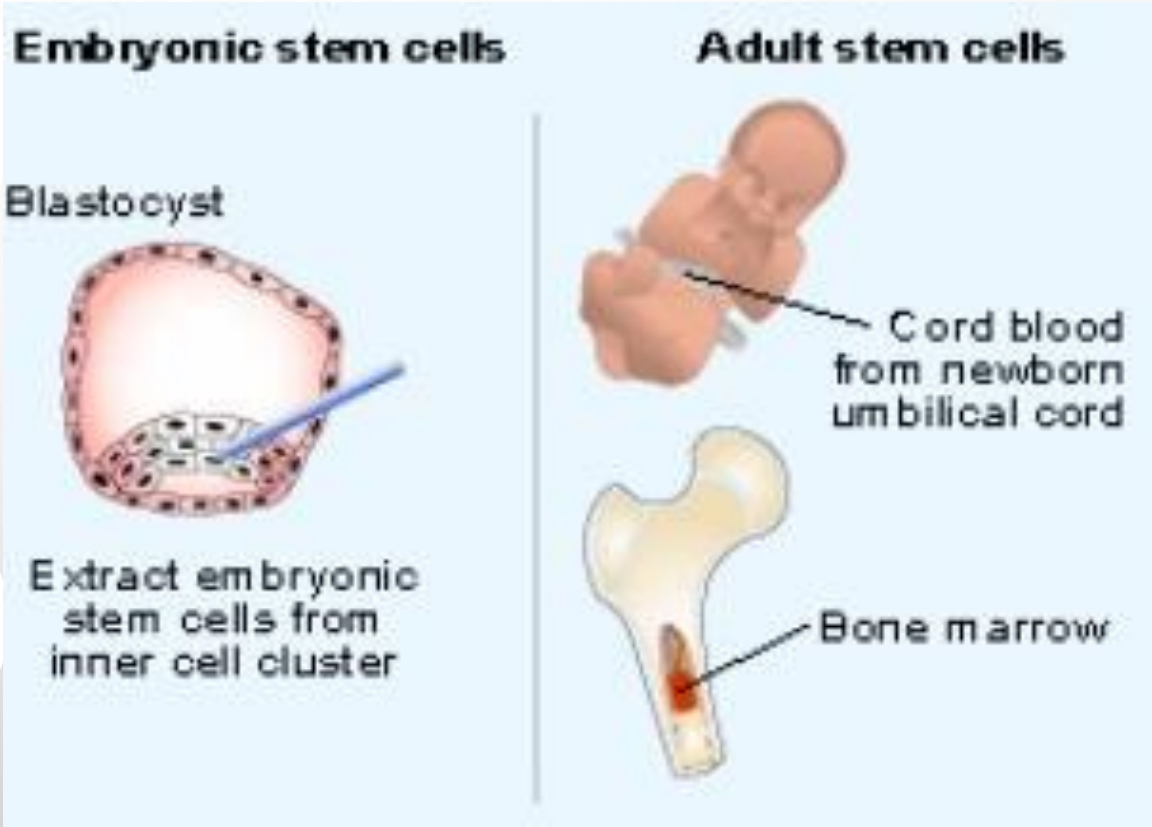
Types of stem cells

Embryonic stem cells and Induced Pluripotent stem cells

- Are able to differentiate into all the specialized
- embryonic tissue

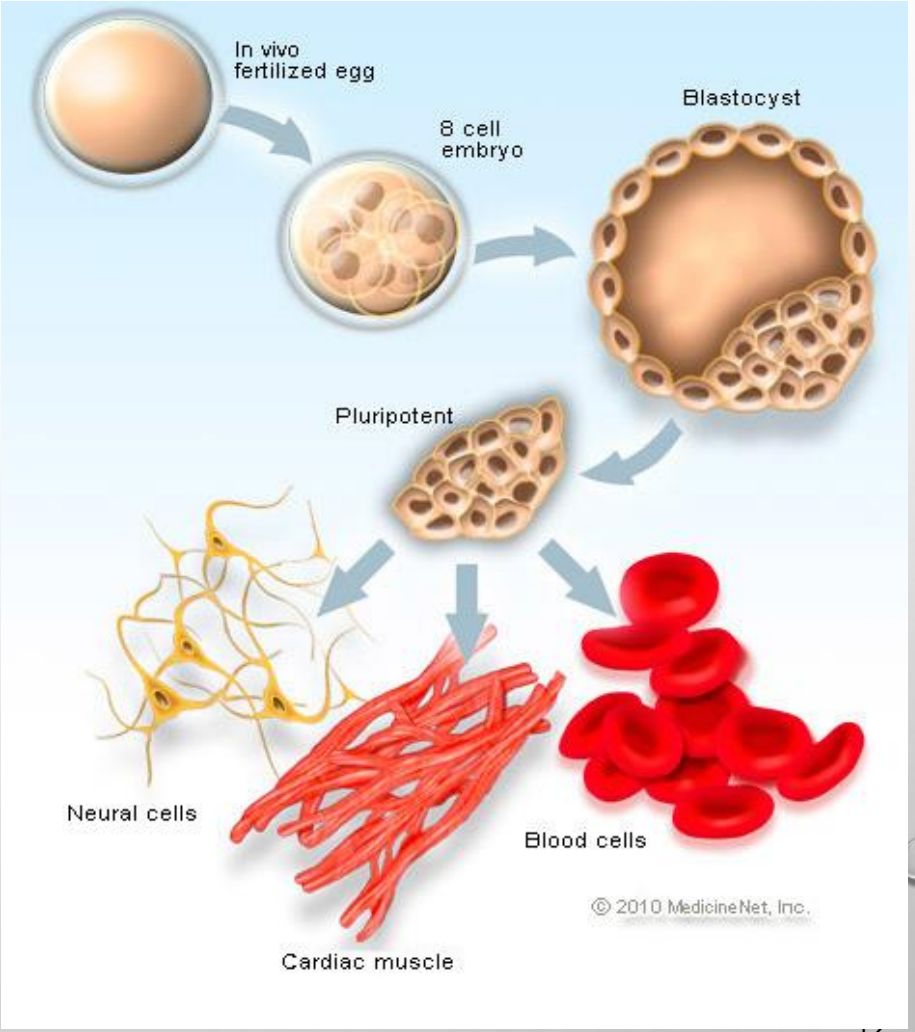
Adult stem cells

- 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
- ✓Develop before implantation in the uterus

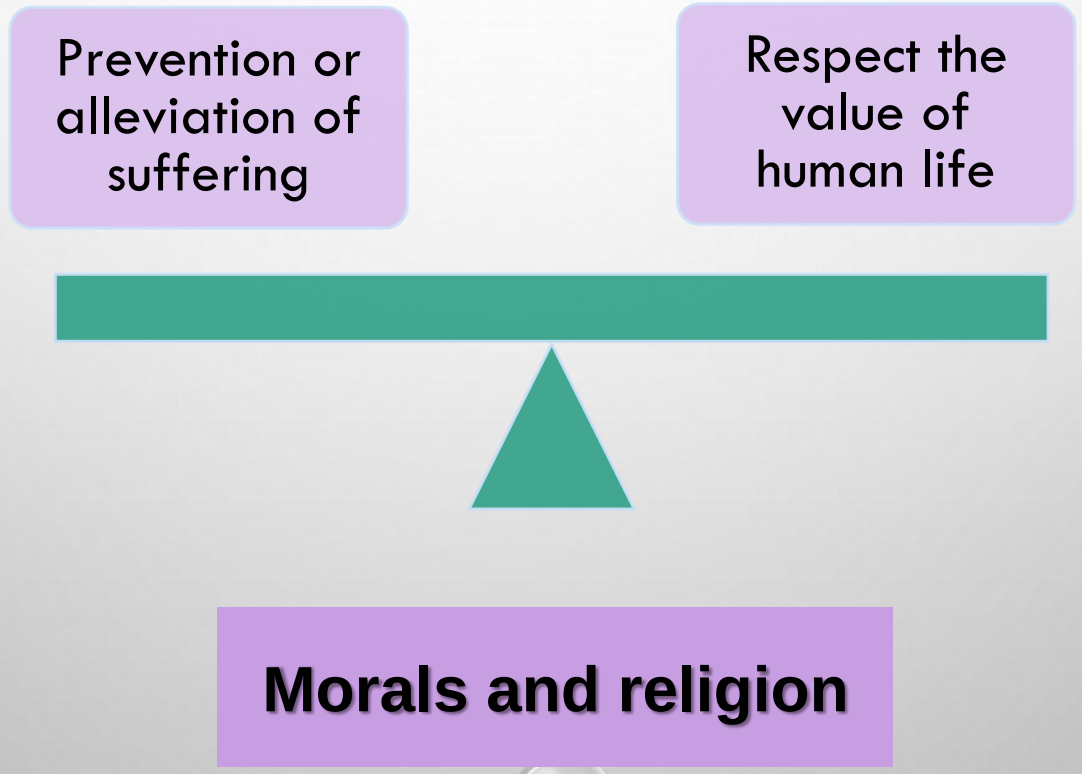


Pluripotency of ESCs

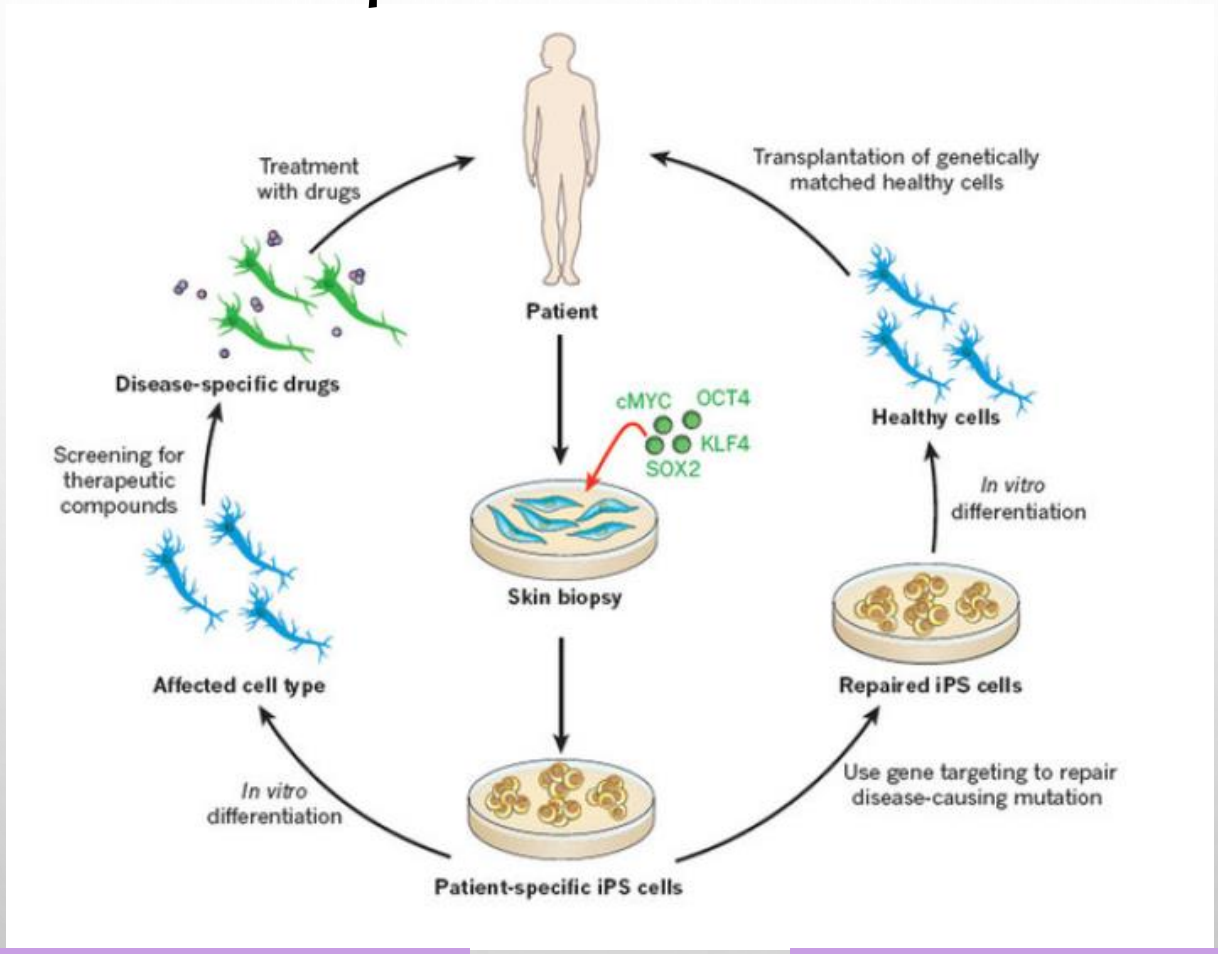
Pluripotency transcription factors:

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

The Ethical Dilemma of ESCs



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.**

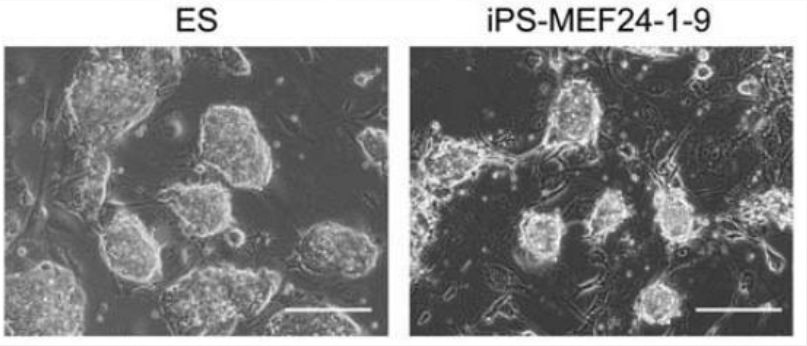
Yamanaka's comparison of iPS and ES cells

Surface antigens

Morphology

Gene expression

Telomerase activities



iPS cells are indistinguishable from ES cells in:

Epigenetic status of pluripotent cell-specific genes

In vitro differentiation

Proliferation

Teratoma formation

Promoter activities

Adult stem cells

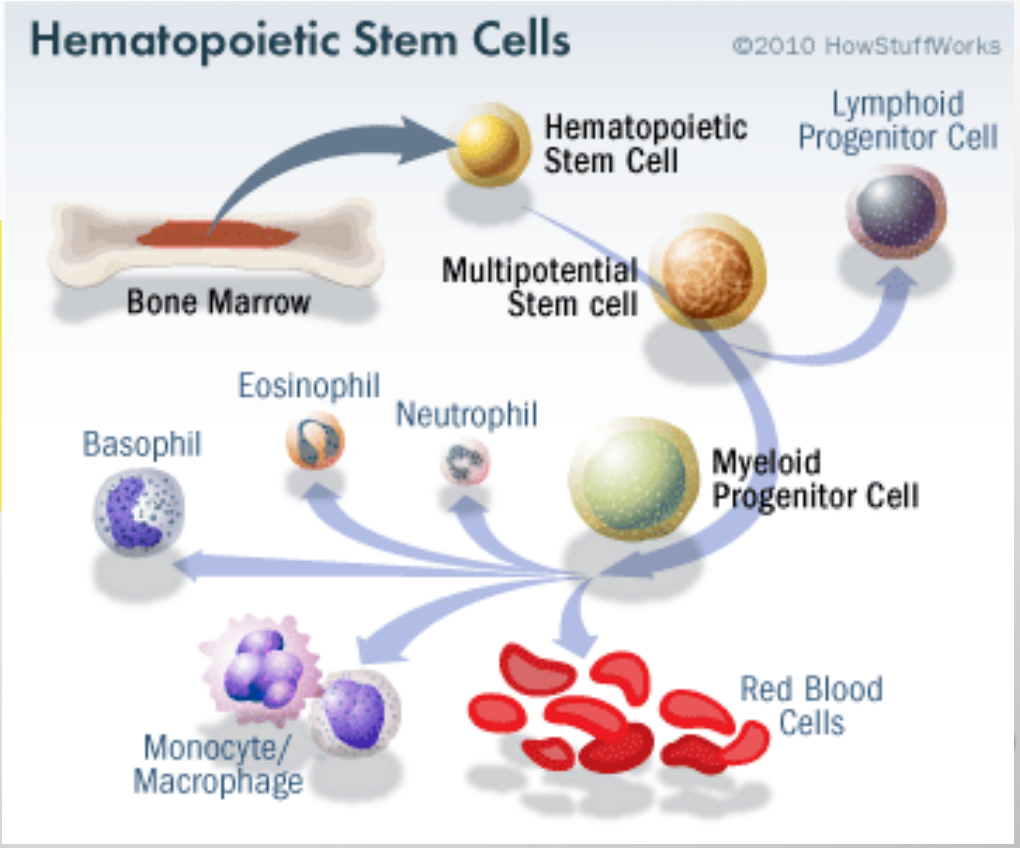
Undifferentiated cells found through out the body.

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

Types of adult stem cells

1. Bone marrow stem cells

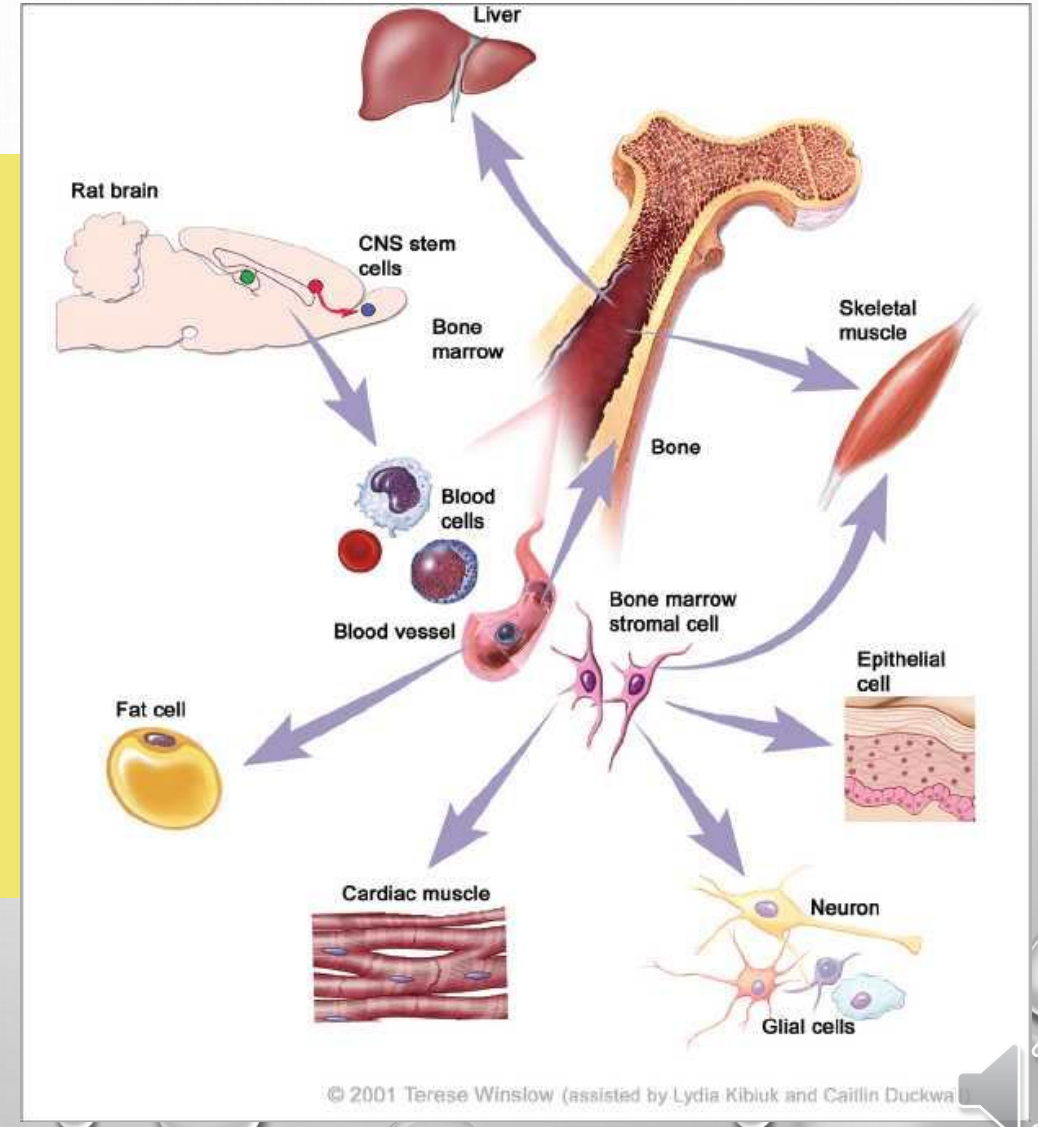
A. Hematopoietic stem cells



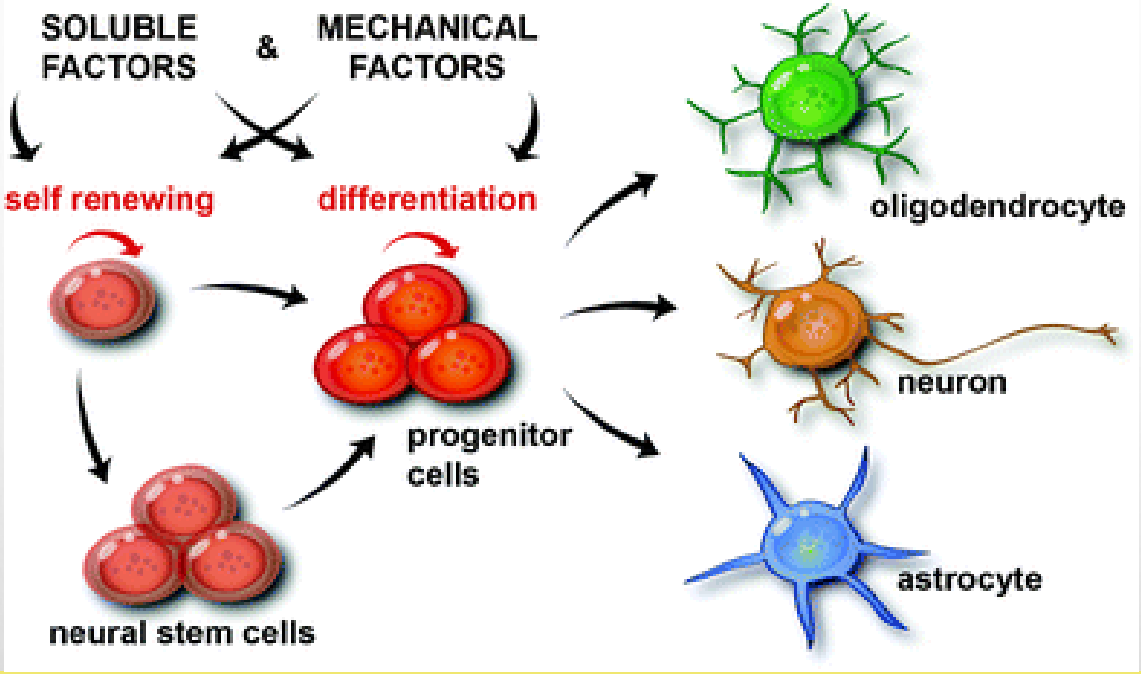
Types of adult stem cells

1. **Bone marrow stem cells**

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

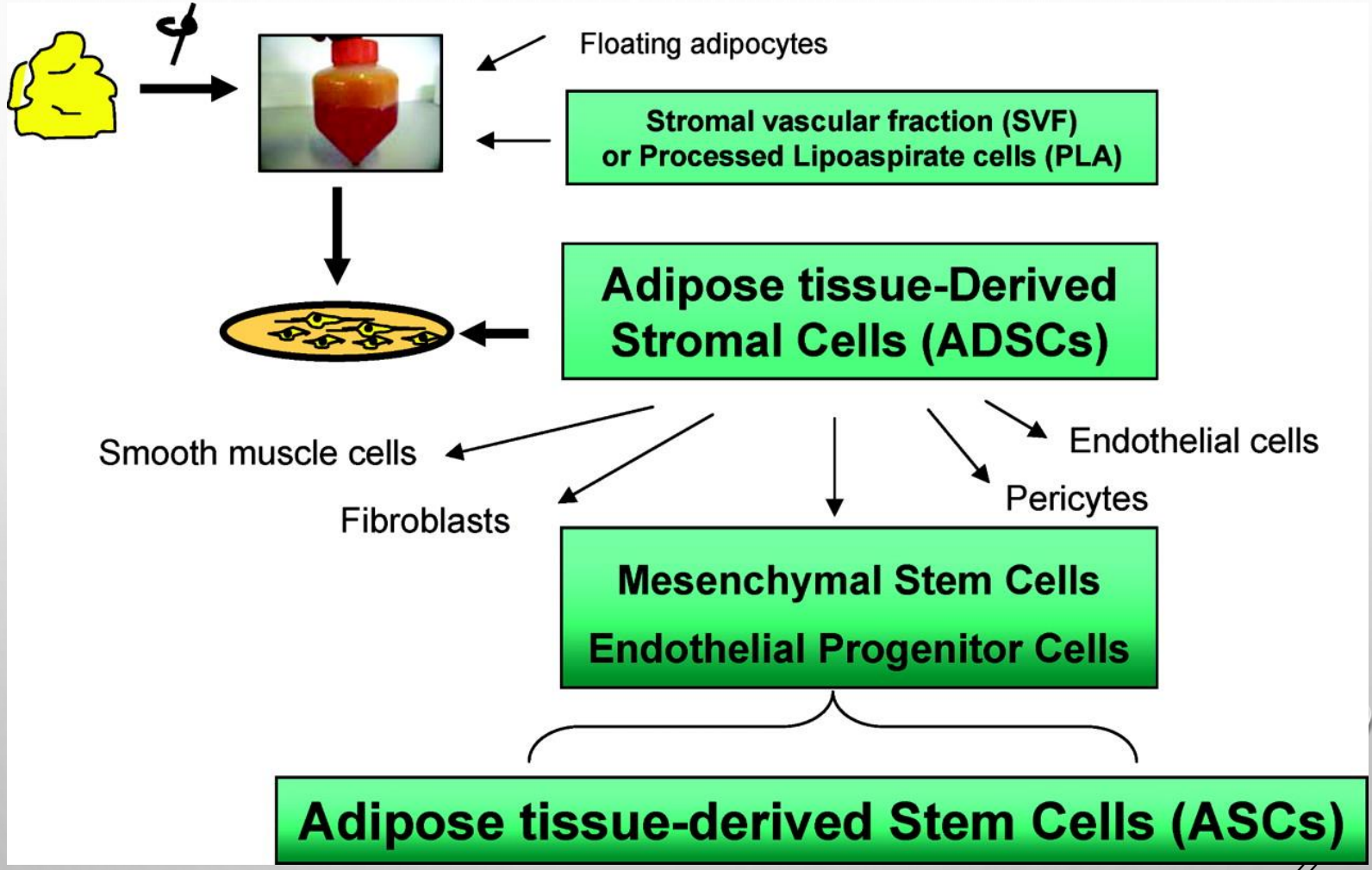


Types of adult stem cells



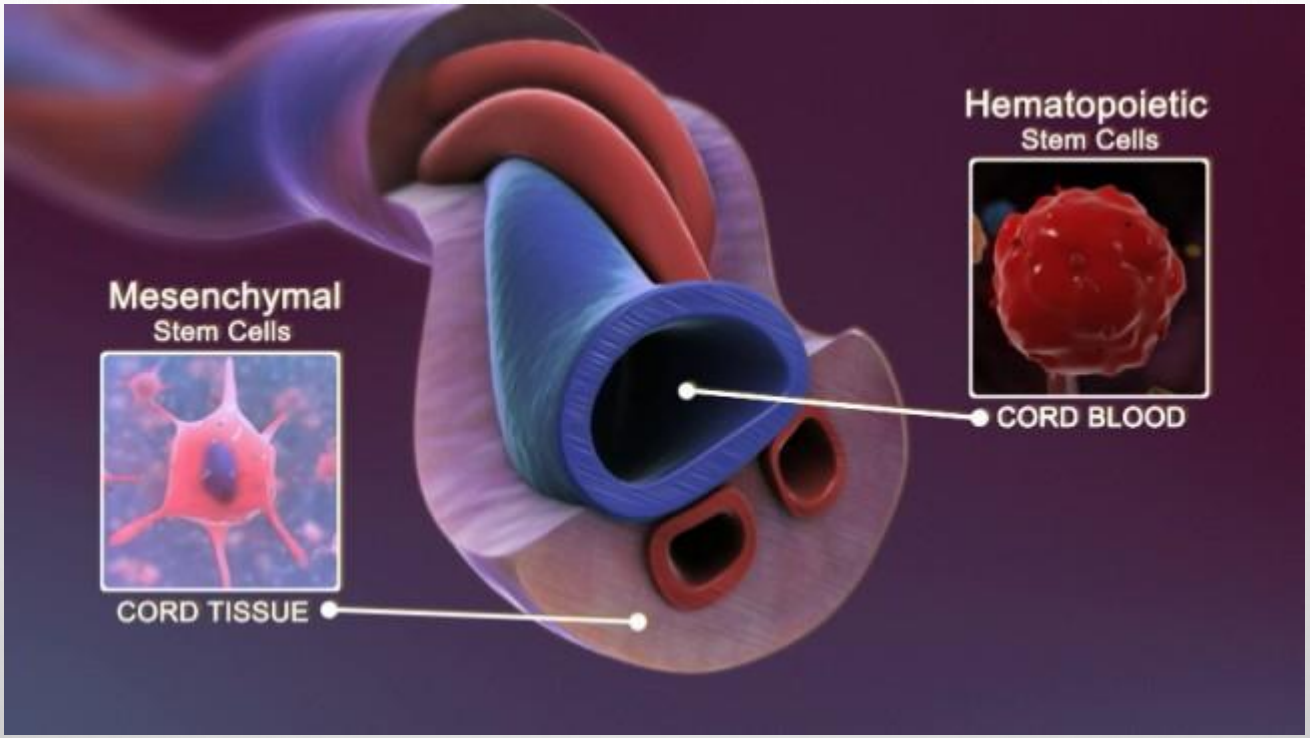
2. Neural stem cells : *neurospheres* – *floating heterogenous aggregates of cells, containing a large proportion of stem cells responsible for adult neurogenesis in* **subventriculare zone**, *which lines the* **lateral ventricles of the brain, and the dentate gyrus of the hippocampal formations**.

Types of adult stem cells



3. Adipose stem cells (ASCs).

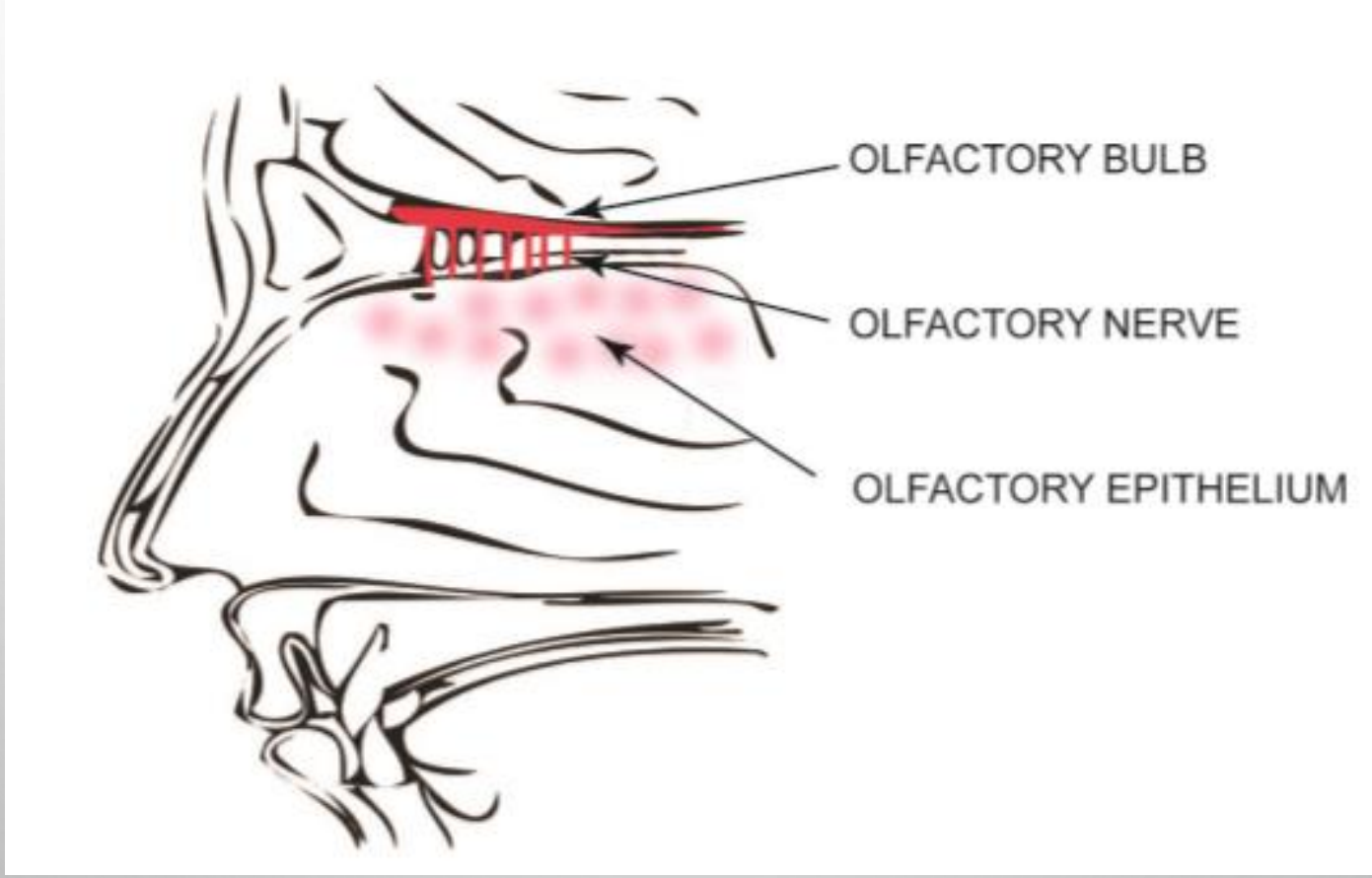
Types of adult stem cells



4. Umbilical cord stem cells

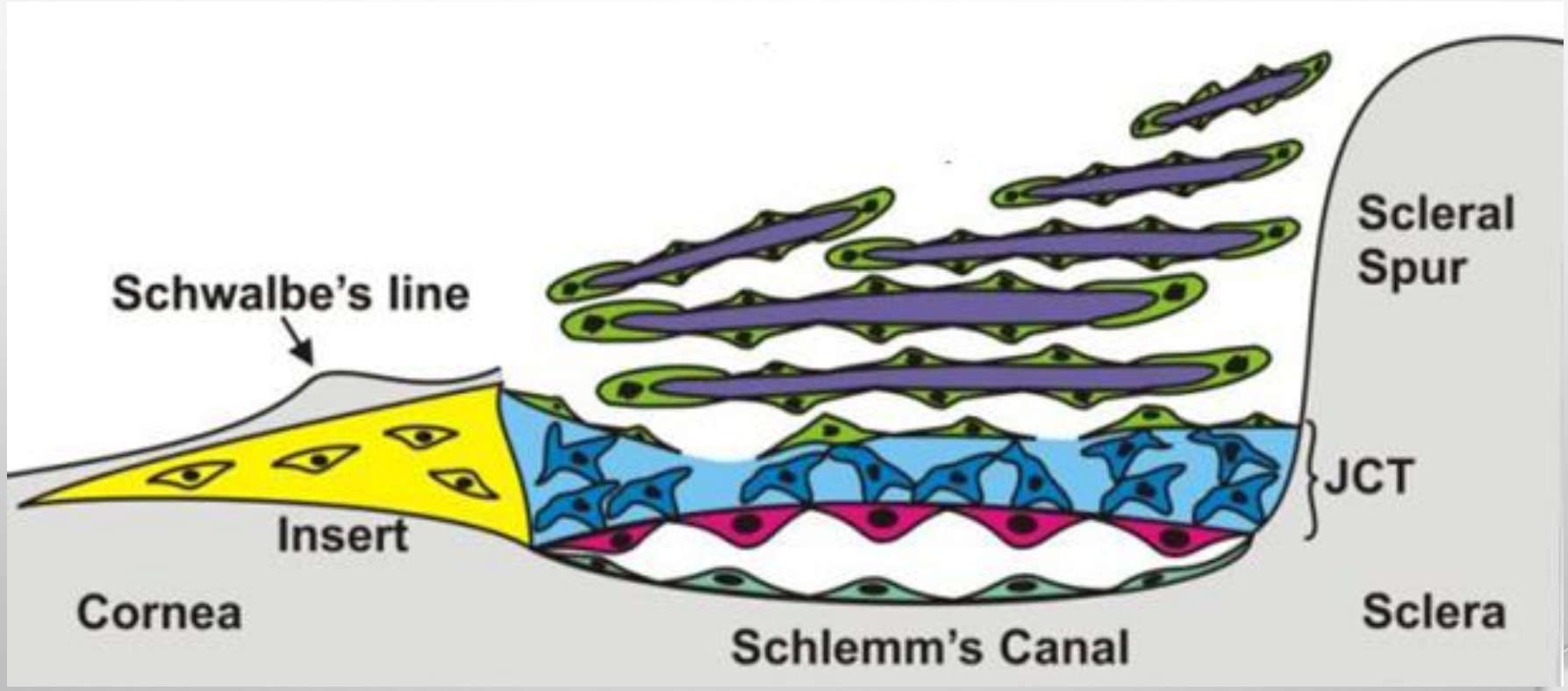
Types of adult stem cells

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



Types of adult stem cells

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



A comparison between different stem cell types

Comparison between the various types of stem cells. This side-by-side comparison includes their origin and the inherent clinical advantages and disadvantages of using these cells.

Stem Cell Type	Origin	Advantages	Disadvantages
ESCs (pluripotent)	Embryo (blastocyst)	✓ Unlimited proliferation	✓ Ethical problems ✓ Risk of immune rejection ✓ Unpredictable differentiation ✓ High risk of tumor formation
IPSCs (pluripotent)	Reprogrammed adult cells: fibroblasts, hepatocytes, circulating T cells, and keratinocytes	✓ No ethical problems ✓ Low risk of immune rejection ✓ High accessibility	✓ High risk of tumor formation ✓ Risk of susceptibility to the original pathology of the patient ✓ Genetic and epigenetic abnormalities
MSCs (multipotent)	Adult tissues (bone marrow, skin, blood, umbilical cord, etc.)	✓ No ethical problems ✓ High accessibility ✓ Easy isolation methods ✓ Autologous cells generation ✓ Self-renewal capacity ✓ Low risk of immune rejection	✓ Risk of tumor formation
NSCs (Multipotent)	Embryo, human fetal brain and brain tissue of adults (SVZ and SGZ of hippocampus)	✓ Low risk of tumor formation	✓ Risk of immune rejection ✓ Limited differentiation ✓ Low self-renewal capacity ✓ Limited proliferation and expansion ✓ Limited availability ✓ Difficult isolating methods

USES OF STEM CELLS

- 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
- Immune rejection
- Infection
- Genetic instability following a prolonged time in culture

✓ 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.

2-In vitro systems for manipulating adult stem cell populations are often not well defined

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

4-Multipotency of ASCs