بسم الله الرحمن الرحيم

Stem Cells & Neurodegenerative Diseases

FINAL

﴿إِنِّي تَوَكَّلْتُ عَلَى ٱللَّهِ رَبِّي وَرَبِّكُمْ ۚ مَّا مِن دَآبَّةٍ إِلَّا هُوَ ءَاخِذٌۢ بِنَاصِيَتِهَآ ۚ إِنَّ رَبِّي عَلَىٰ صِرَٰطٍ مُّسْتَقِيمٍ﴾

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Heba Suliman

Reviewed by: Salwa Alawi

BIOCHEMISTRY

رحلة اليقين مع سورة يس

بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

وَلَوْ نَشَآءُ لَطَمَسْنَا عَلَىٰٓ أَعْيُنِهِمْ فَٱسْتَبَقُوا۟ ٱلصِّرَٰطَ فَأَنَّىٰ يُبْصِرُونَ (٦٦) وَلَوْ نَشَآءُ لَمَسَخْنَٰهُمْ عَلَىٰ مَكَانَتِهِمْ
فَمَا ٱسْتَطَٰعُوا۟ مُضِيًّا وَلَا يَرْجِعُونَ (٦٧) وَمَن نُّعَمِّرْهُ نُنَكِّسْهُ فِى ٱلْخَلْقِ ۖ أَفَلَا يَعْقِلُونَ (٦٨)

{ وَلَوْ نَشَاءُ لَطَمَسْنَا عَلَى أَعْيُنِهِمْ } بأن نُذْهِبَ أبصارهم، كما طمسنا على نطقهم. { فَاسْتَبَقُوا الصِّرَاطَ } أي: فبادروا إليه، لأنه الطريق إلى الوصول إلى الجنة، { فَأَنَّى يُبْصِرُونَ } وقد طمست أبصارهم.

{ وَلَوْ نَشَاءُ لَمَسَخْنَاهُمْ عَلَى مَكَانَتِهِمْ }أي: لأذهبنا حركتهم { فَمَا اسْتَطَاعُوا مُضِيًّا } إلى الأمام { وَلَا يَرْجِعُونَ } إلى ورائهم ليبعدوا عن النار. والمعنى: أن هؤلاء الكفار، حقت عليهم كلمة العذاب، ولم يكن بُدٌّ من عقابهم.

{ وَمَنْ نُعَمِّرْهُ } من بني آدم { نُنَكِّسْهُ فِي الْخَلْقِ } أي: يعود إلى الحالة التي ابتدأ حالة الضعف، ضعف العقل، وضعف القوة. { أَفَلَا يَعْقِلُونَ } أن الآدمي ناقص من كل وجه، فيتداركوا قوتهم وعقولهم، فيستعملونها في طاعة ربهم.

Stem Cells: The New Therapeutics Era

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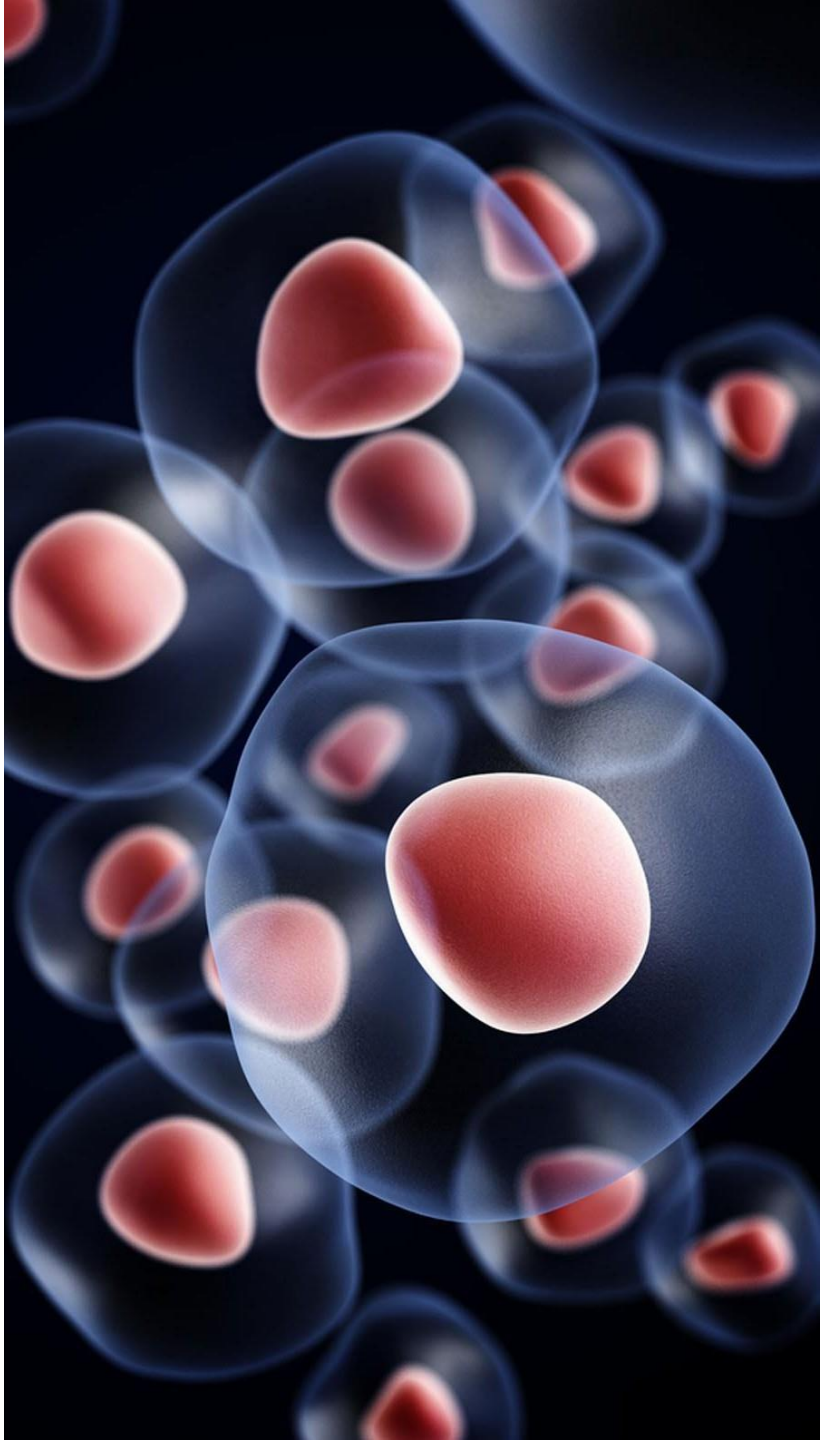
Central Nervous System



What are stem cells?

- Are primal cells common to all multicellular organisms that are characterized by two main features:

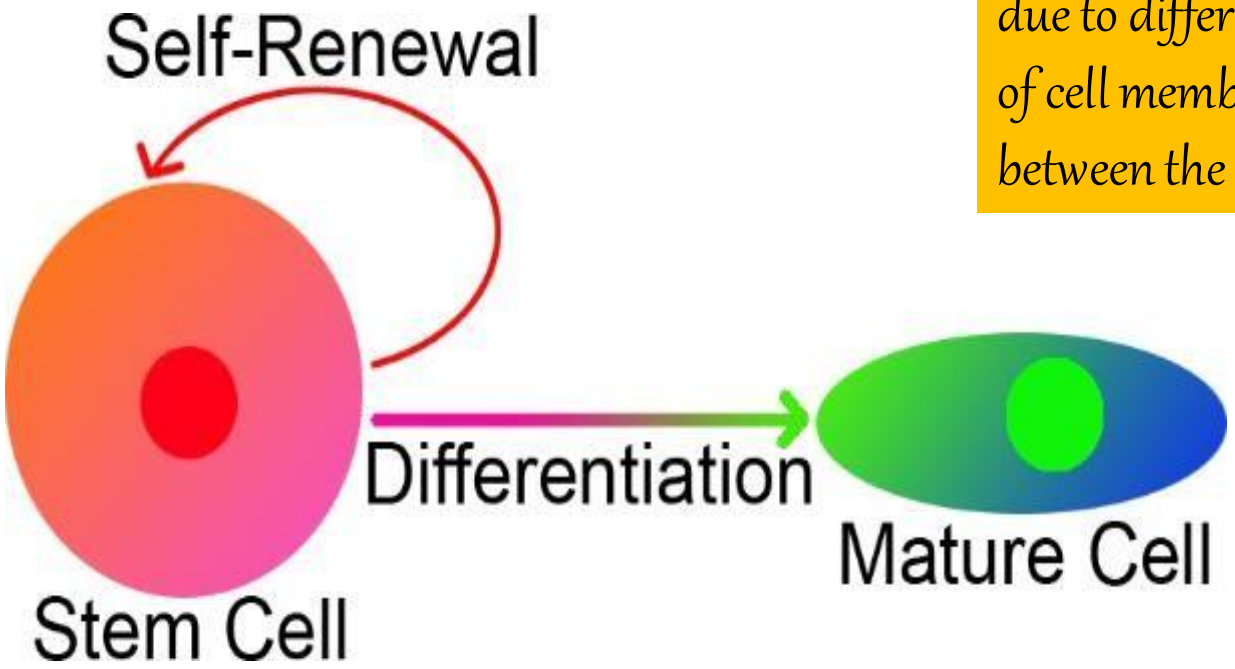
1-retain the ability to **renew** themselves through cell division (keep the population of stem cells).

2-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



Stem cells can divide **asymmetrically** to be able to renew themselves on one side and to differentiate into other cell types on the other side.

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

How Does Asymmetric Division Occur?

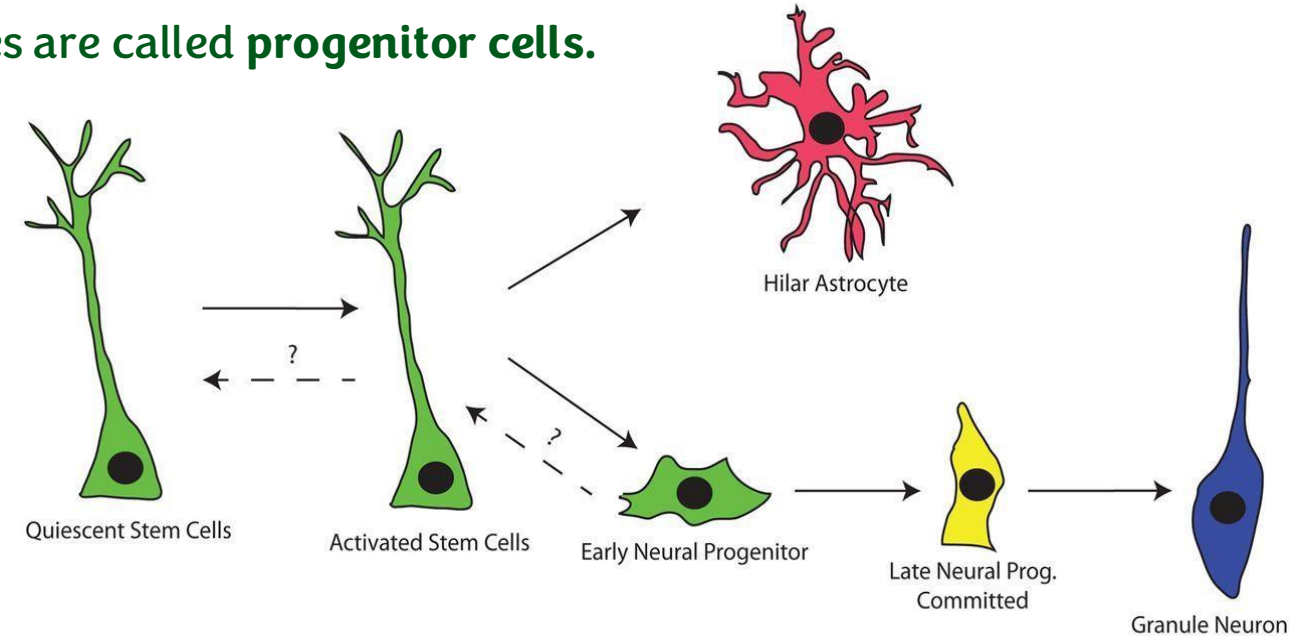
- Differential segregation of cell membrane proteins (such as receptors) between the two daughter cells.

✓ This means that during cell division, the proteins and cell membrane proteins that are important for keeping the stemness of stem cells are going to be located in the cell that renews stem cells population, **whereas** the proteins and the membrane proteins that are important for driving differentiation are going to move to the second cell that goes into differentiation path.

What does stem cell division produce?

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

  - Stem cells do **not** undergo differentiation in a single step. They pass through intermediate cellular steps in which these intermediates are partially differentiated and produce different types of fully differentiated and mature cells.
  - These intermediates are called **progenitor cells.**

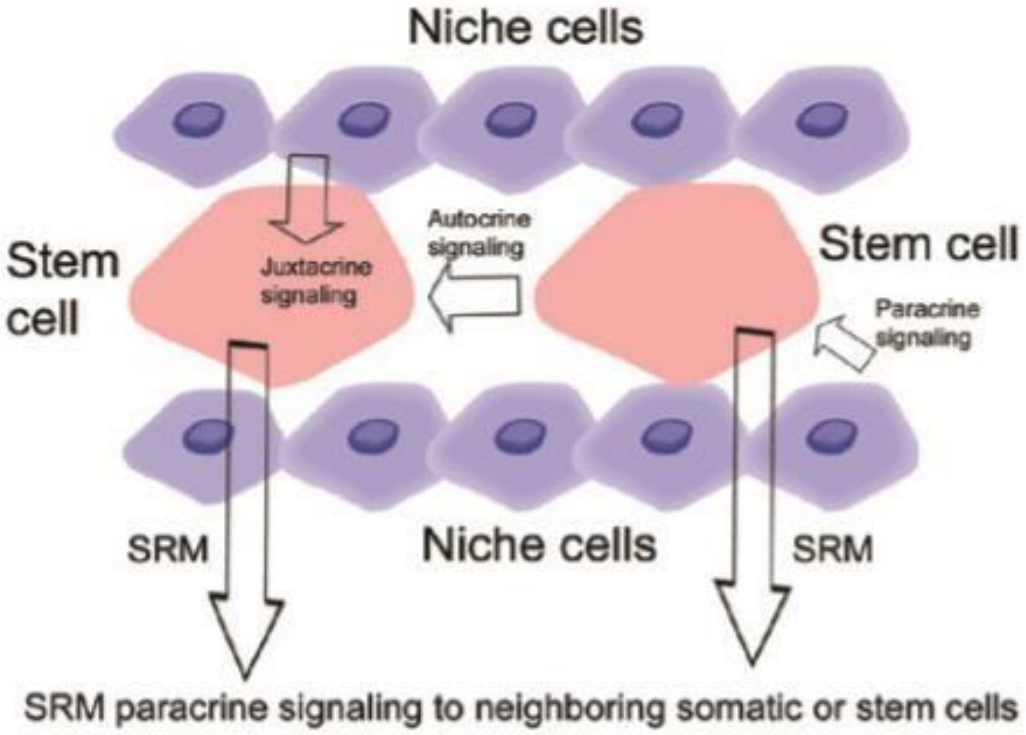


Venere et al 2012

Stem cell niche

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

- To maintain the population of stem cells, they must be surrounded by a **microenvironment (niche)** that supports their self-renewal and provides optimal conditions for their differentiation into fully differentiated and functional cells.



Stem cell niche

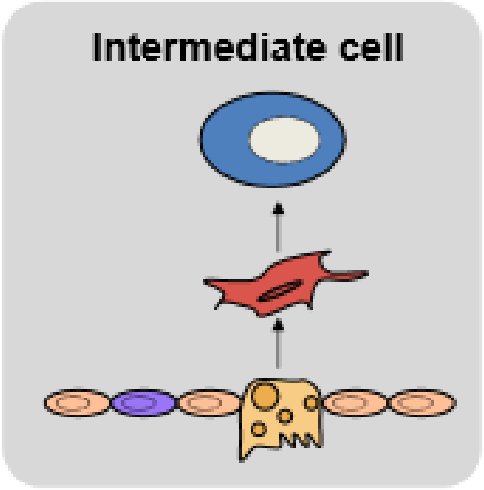
Cells only

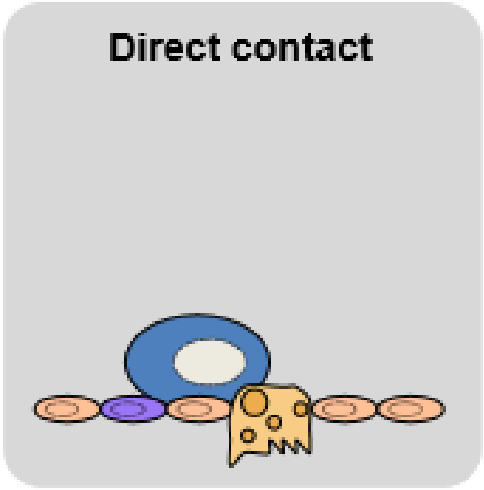
A single cell type, or a whole host of interacting cells. Cells outside the stem cell's lineage, or they may derive primarily from the stem cell's own descendants.

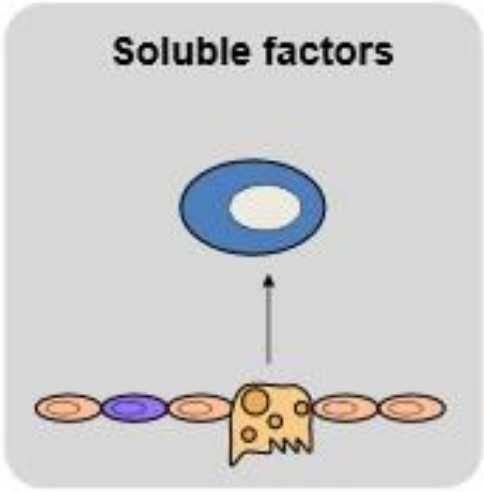
Cells & ECM

Secreted or cell surface factors

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







One niche is different from the other. It may contain just cells or cells and ECM or just soluble factors.

Why stem cells need a special environment?

- Demands on stem cells necessitate **special support for viability and self-renewal.**
- **Nutritive** function
- Niches might be agents of **feedback control (control of stem cell pool size, so it doesn't expand or shrink).**
- Niches are instruments of **coordination** among tissue compartments.
- Niches are **hubs of inter-lineage coordination.**

Niches also act as coordinators between lineages. A stem cell may proceed into several differentiation paths, so there should be some sort of coordination between them to ensure that one does not dominate over the others. The niche acts as a **hub** or center for this coordination.

By interactions or feedback mechanisms, they can **coordinate** size, moving into different differentiation pathways and the production of certain cell types.

POTENCY OF STEM CELLS

- THE DIFFERENTIATION POTENTIAL OF THE STEM CELLS

Potency: the ability to differentiate into several cell types OR how many cell types can be produced from a certain stem cell type.

TYPE OF POTENCY :

1 TOTIPOTENT

These cells are able to differentiate into all cells of the body **and** to extra embryonic tissues including placenta.

2 PLEURIPOTENT

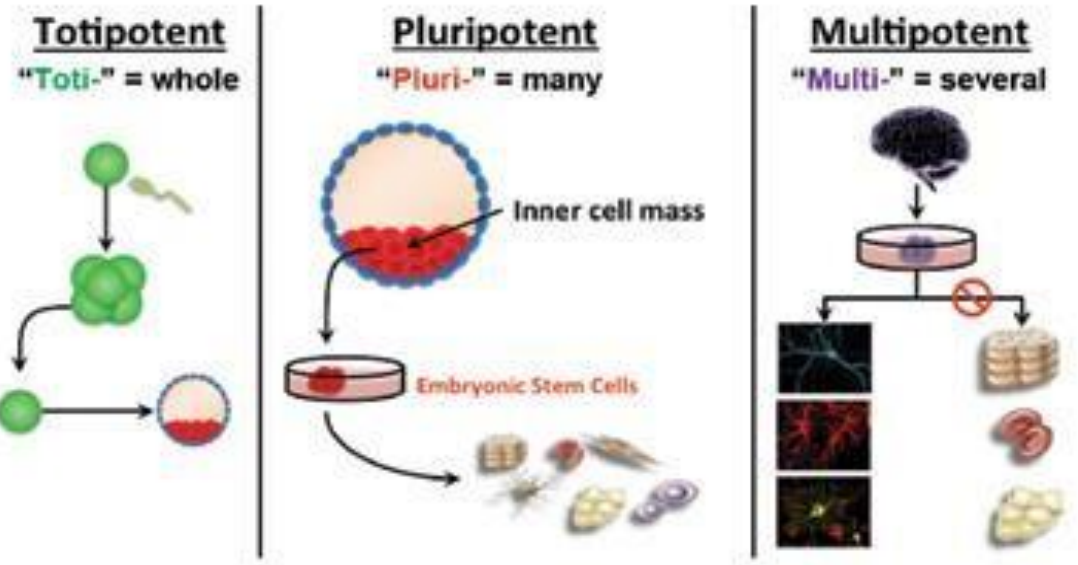
These cells are able to differentiate into all cells of the body **but not** to extra embryonic tissues including placenta.

3 MULTIPOTENT

Able to differentiate into **several** cell types.

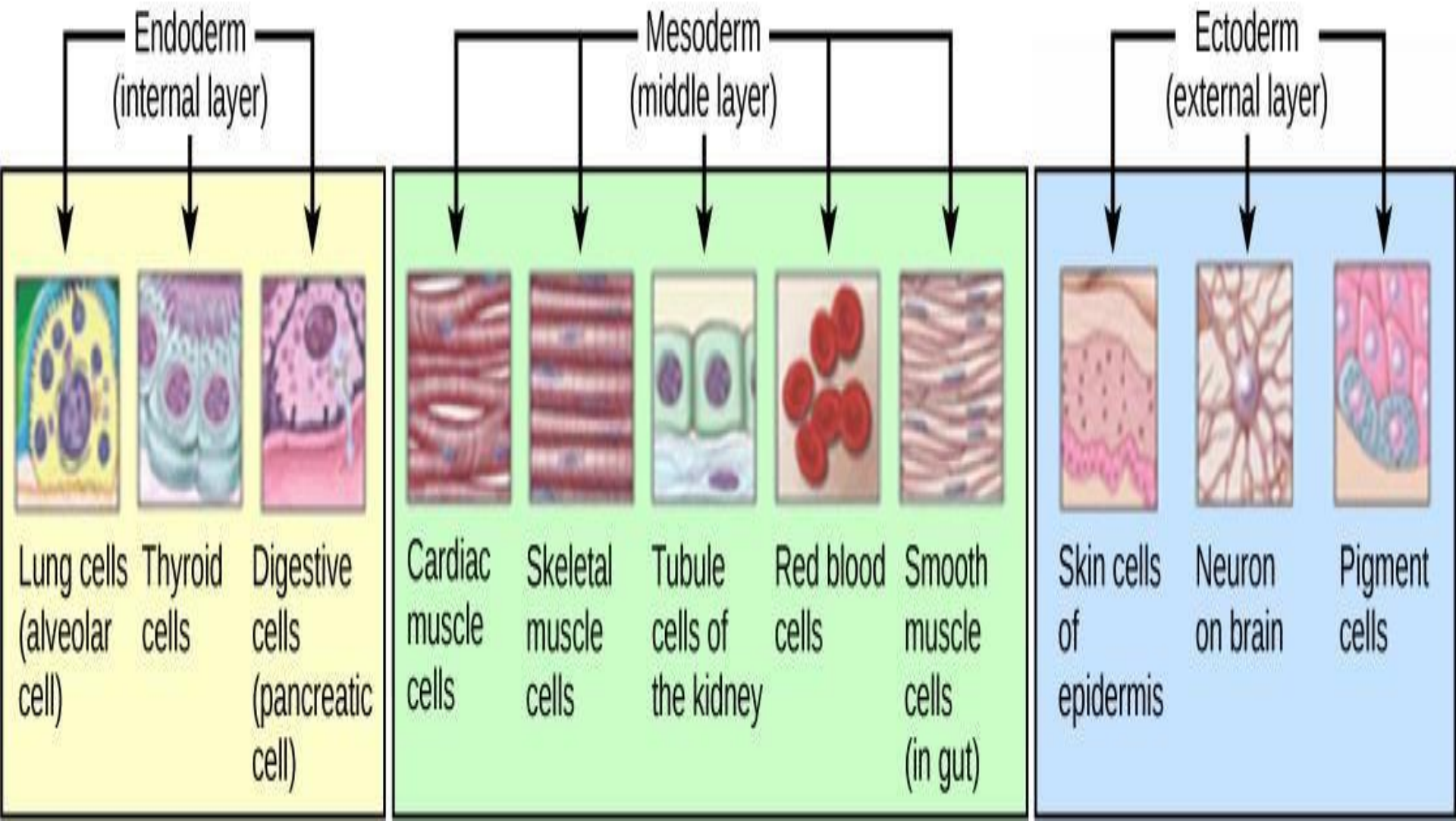
4 UNIPOTENT

Differentiate into a **single** cell type.



THREE GERM LAYERS

If we take a pluripotent stem cell population and expose it to differentiation conditions, they should be able to give rise to cells from **all three germ layers**, as seen in the figure, and give arise to a wide variety of cells from these layers (if they are pluripotent).



Types of stem cells

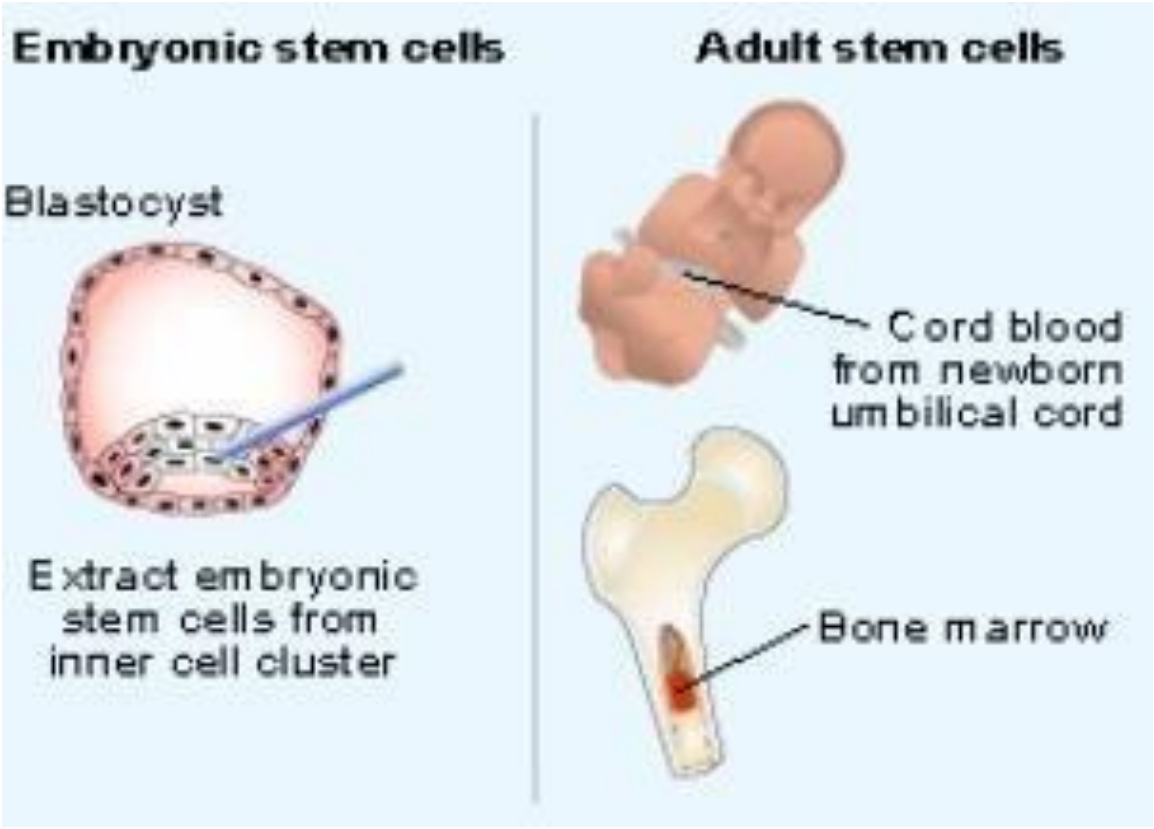
Another classification of stem cells depending on the time of presence during development.

Embryonic stem cells

- Are able to differentiate into all the specialized embryonic tissue
- Appear during embryonic development and are important for fetus development

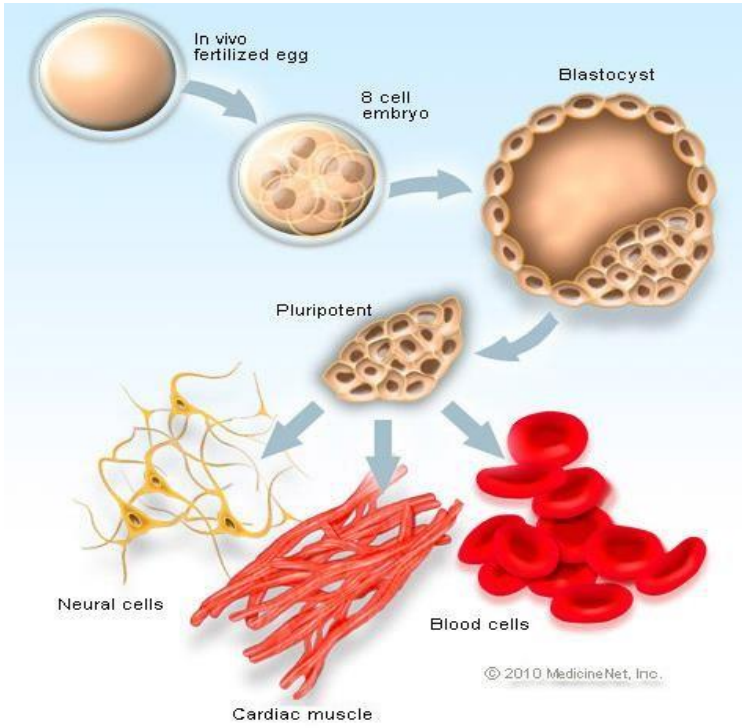
Adult stem cells

- Act as a repair system (regeneration) for the body **replacing** specialized damaged cells
- Appear after birth or later in adult life.



Embryonic Stem Cells (ESCs)

- ✓ ES cells are derived from inner cell mass of mammalian blastocysts
- ✓ Develop before implantation in the uterus



- Quick review of fetal development up to the inner cell mass:

- It starts with fertilization of an egg to form a zygote. The zygote then divides until it reaches the 8-cell stage (we still have a ball that is full of cells from the inside and outside). After that, a blastocyst forms. Its structure consists of an outer layer of cells, while the inside is mostly hollow, except for one side where there is an accumulation of cells called **the inner cell mass.**

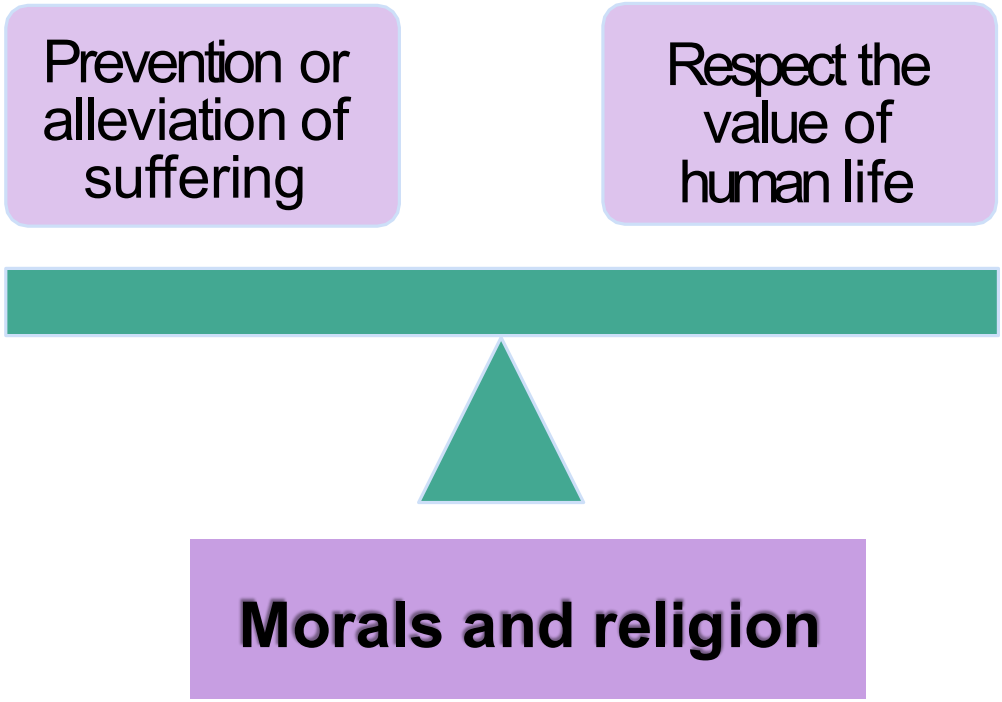
- The pluripotent or embryonic stem cells that are necessary for fetal development are located within the inner cell mass.

Pluripotency of ESCs

Pluripotency transcription factors:

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

The Ethical Dilemma of ESCs



The Ethical Dilemma of ESCs

- What is the problem in using ESCs from embryos?

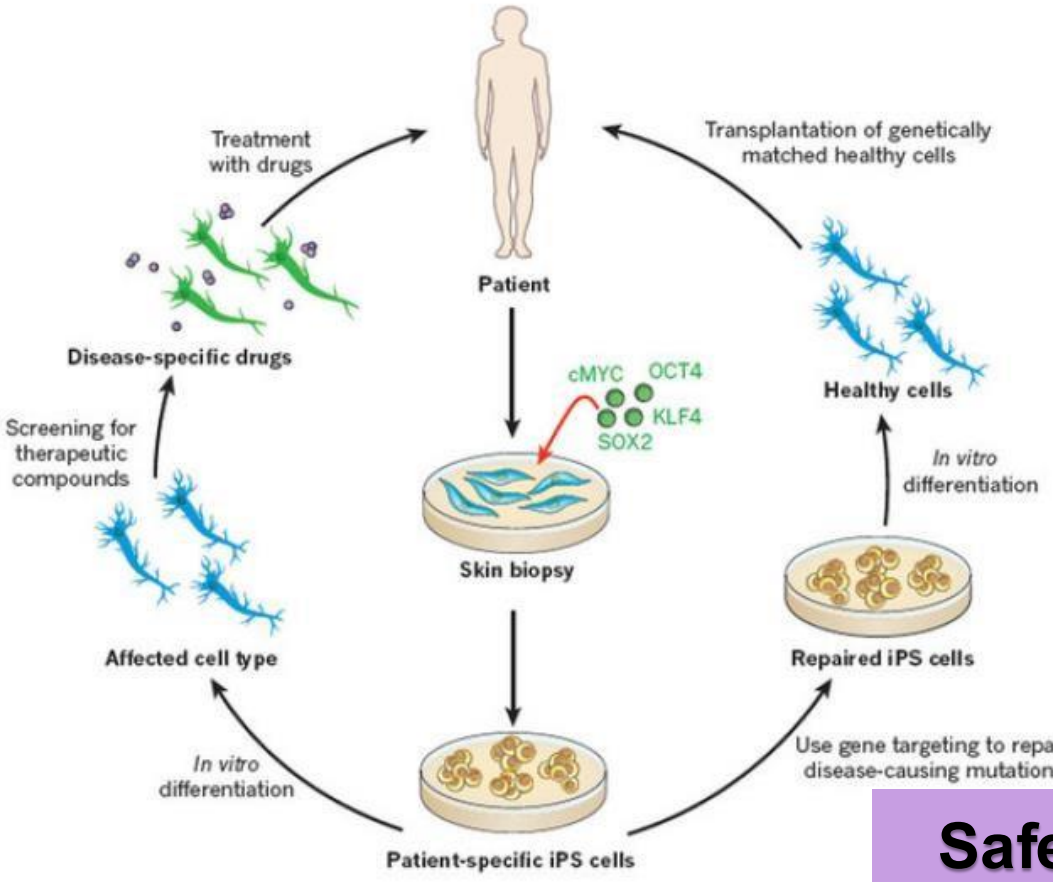
- One of the problems presented with ESCs and their usage in the treatment of diseases is that we need to isolate them from embryos, which means we are basically going to kill the embryo after it started to develop. So there is an **ethical dilemma**, However, they will be used to alleviate the suffering of patients.
- ✓ This raises the need to find a balance between morals and religion.

- Another problem to consider is that transplanting cells from one embryo into another patient (even if they are siblings) is introducing foreign cells into the patient's body which may cause **immunological problems and immune rejection**. So it is not just an ethical problem, there are other problems.

- ✓ That's why scientists started to think about another source of pluripotent stem cells but this time from the patients themselves (endogenous source), so it is not foreign. And on the other hand to avoid ethical dilemma and problems related to embryonic stem cells.

Induced Pluripotent Stem Cells (iPSCs)

- In labs, scientists reprogram and **reverse the differentiation** of fully differentiated cells from the patient by expressing the transcription factors necessary to maintain stemness of cells under certain conditions, so they are reversed to stem cells.
- Only some of the reprogrammed cells can be very potent again, these cells are called **iPSCs**.



Ethical

Autologous

Patient-specific

There should be no immunological problems related to them.

Safer

As they are from the same patient.

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.

The first scientist who was able to do this was (Yamanaka) back in 2006. He was able to reverse differentiation or reprogramme a fibroblast into **iPSC** by a set of **4 transcription factors**: OCT3/4, SOX2, c-Myc, KLF4.

Another group at the same time was able to do it using another set of transcription factors, but both groups were able to do it by **4 transcription factors.**

Yamanaka's comparison of iPS and ES cells

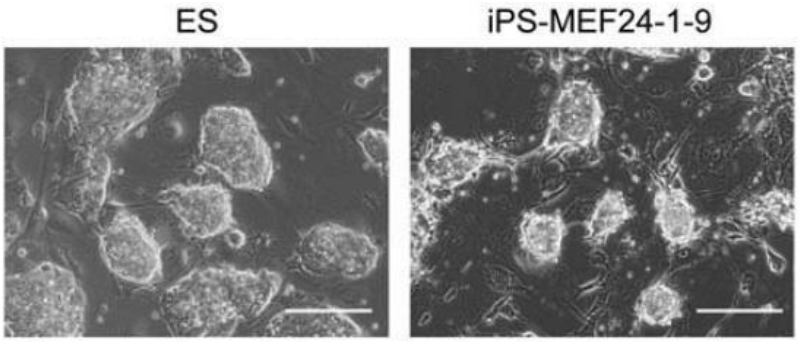
- After isolating the reprogrammed cells, they conducted tests to verify whether these cells really acting like embryonic stem cells, which cannot be distinguished by microscopy alone.
- So they compared the following features:

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 And active genes

A **teratoma** is a tumor that contains cells derived from all three germ layers.

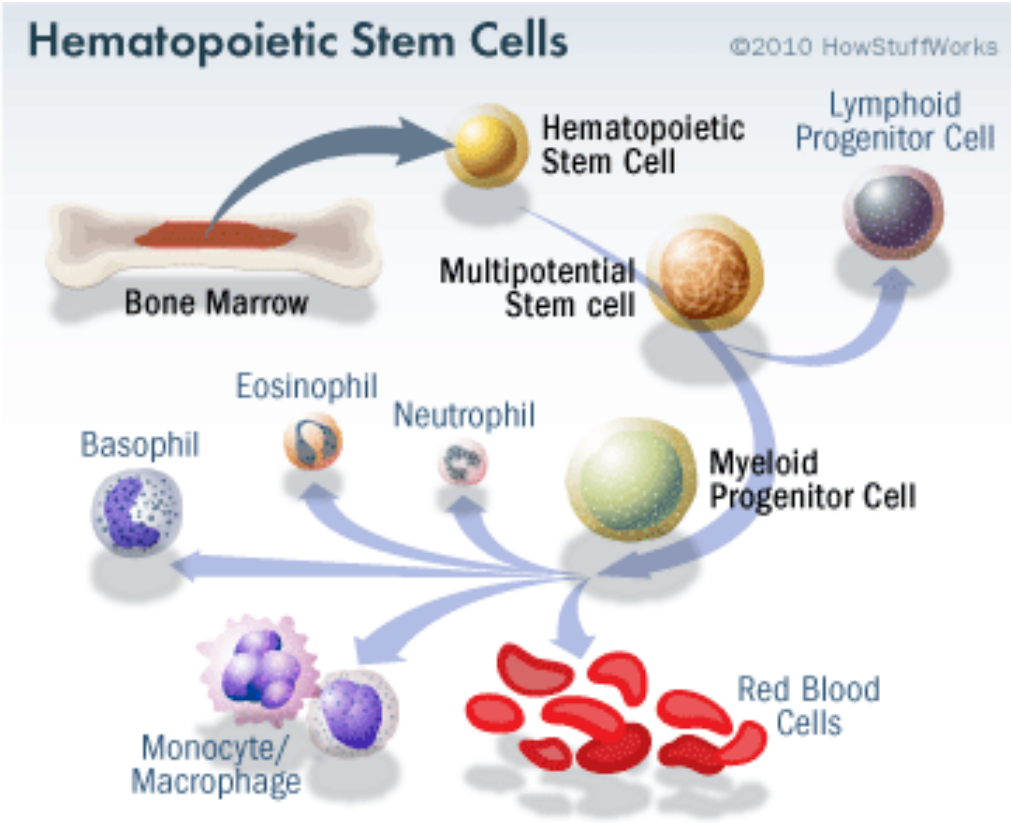
Adult stem cells

- They have **less differentiation ability** than a pluripotent stem cells.
- They might be just either **multipotent or unipotent**.
- 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.
Can be divided into:

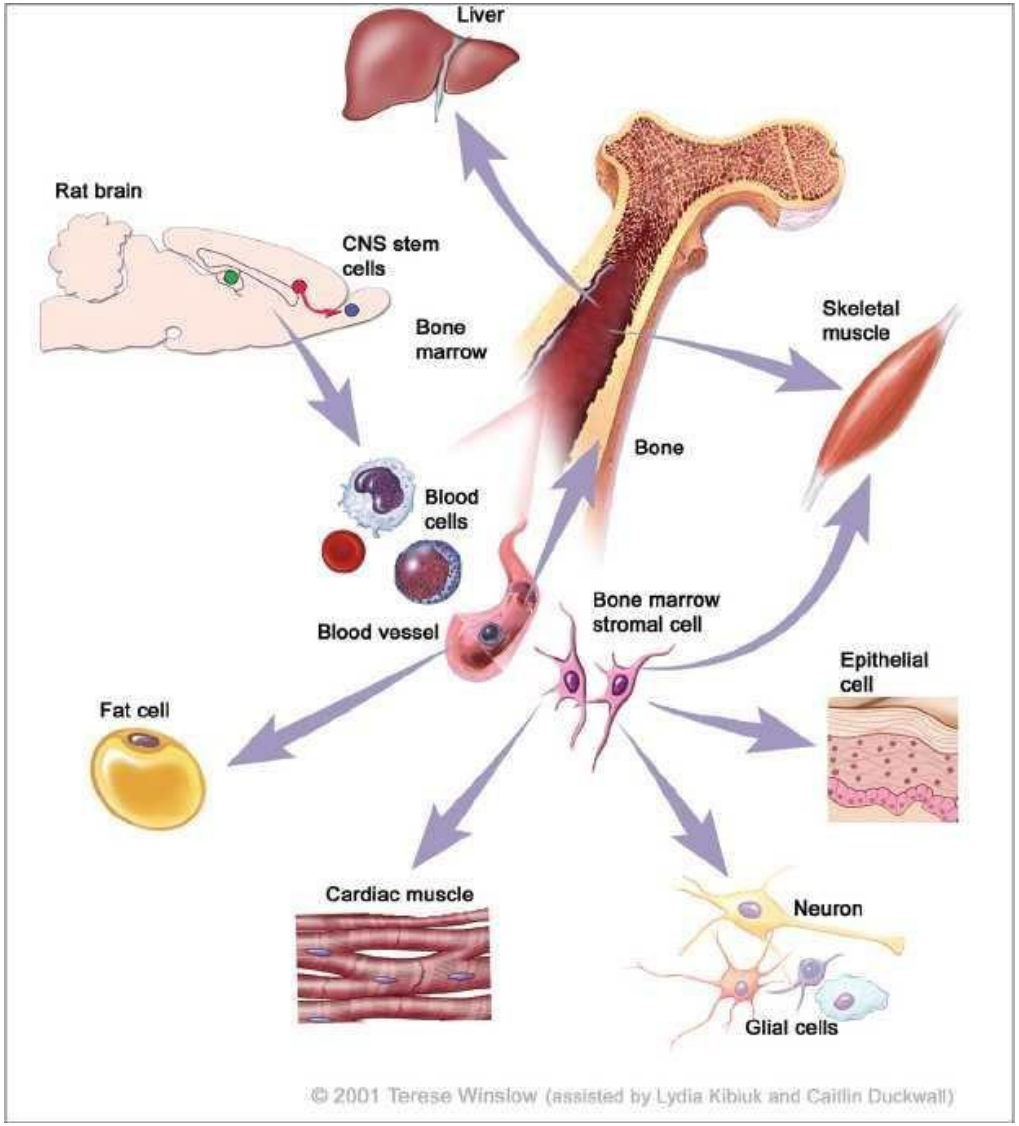
A. Hematopoietic stem cells.
Can raise to all types of **blood cells**.



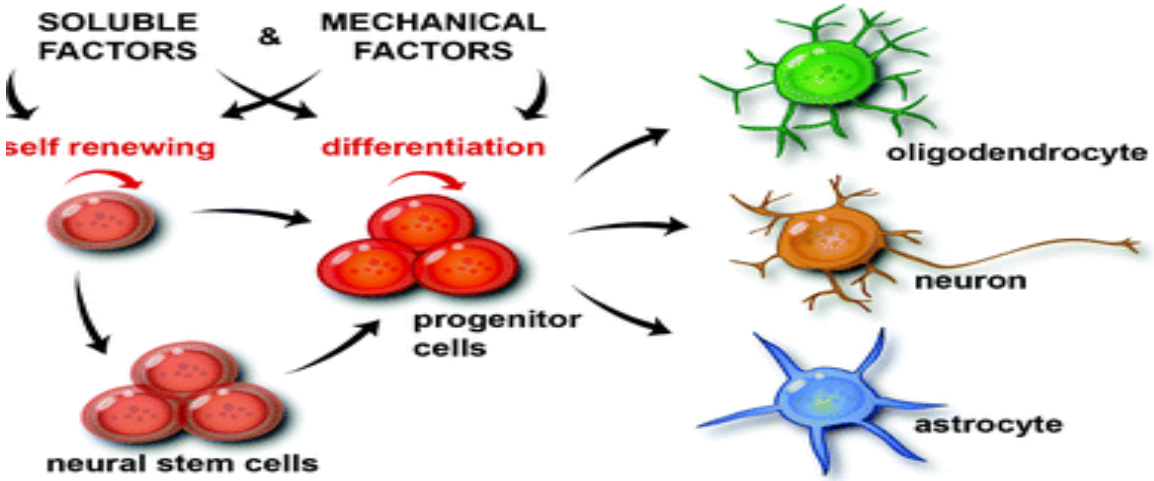
Types of adult stem cells

B. Somatic stem cells

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



Types of adult stem cells



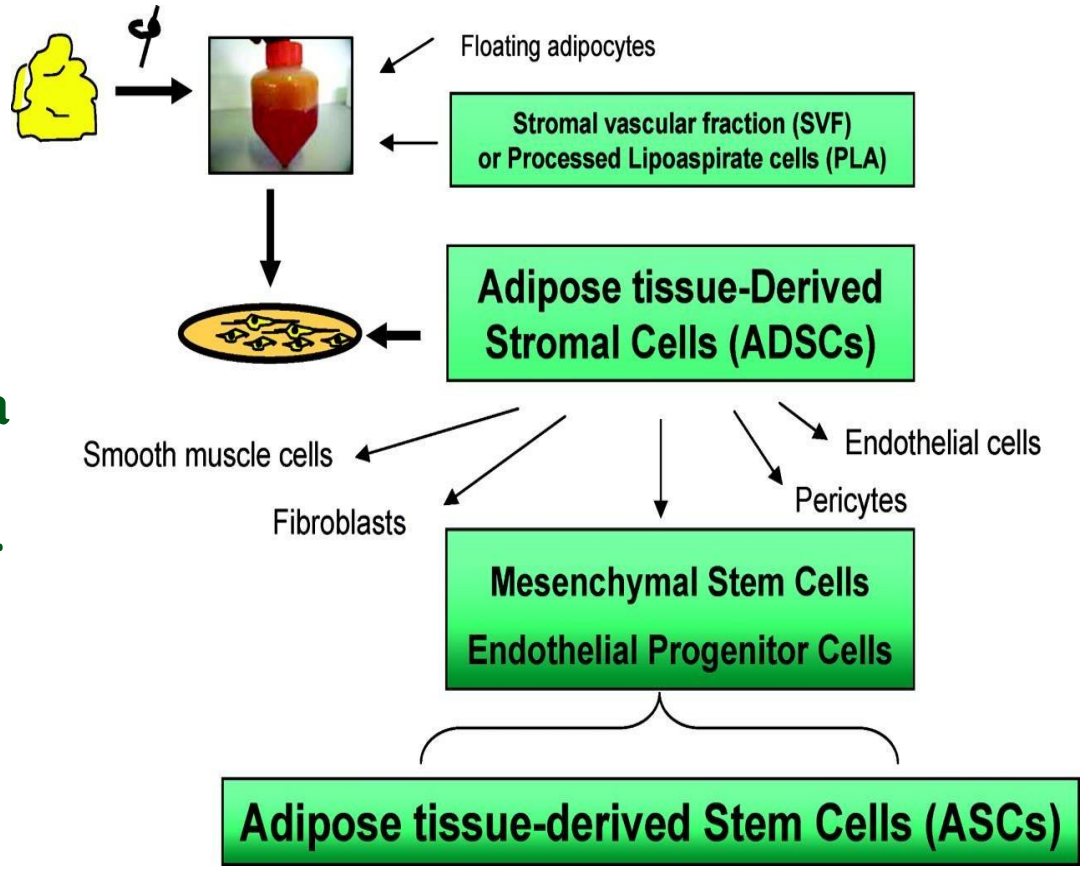
2. Neural stem cells: neurospheres – floating heterogenous aggregates of cells, containing a large proportion of stem cells responsible for adult neurogenesis in **subventriculare zone**, which lines the **lateral ventricles** of the brain, and **the dentate gyrus of the hippocampal formations.**

- They are neuronal cells, and they **can generate** some types of neurons.

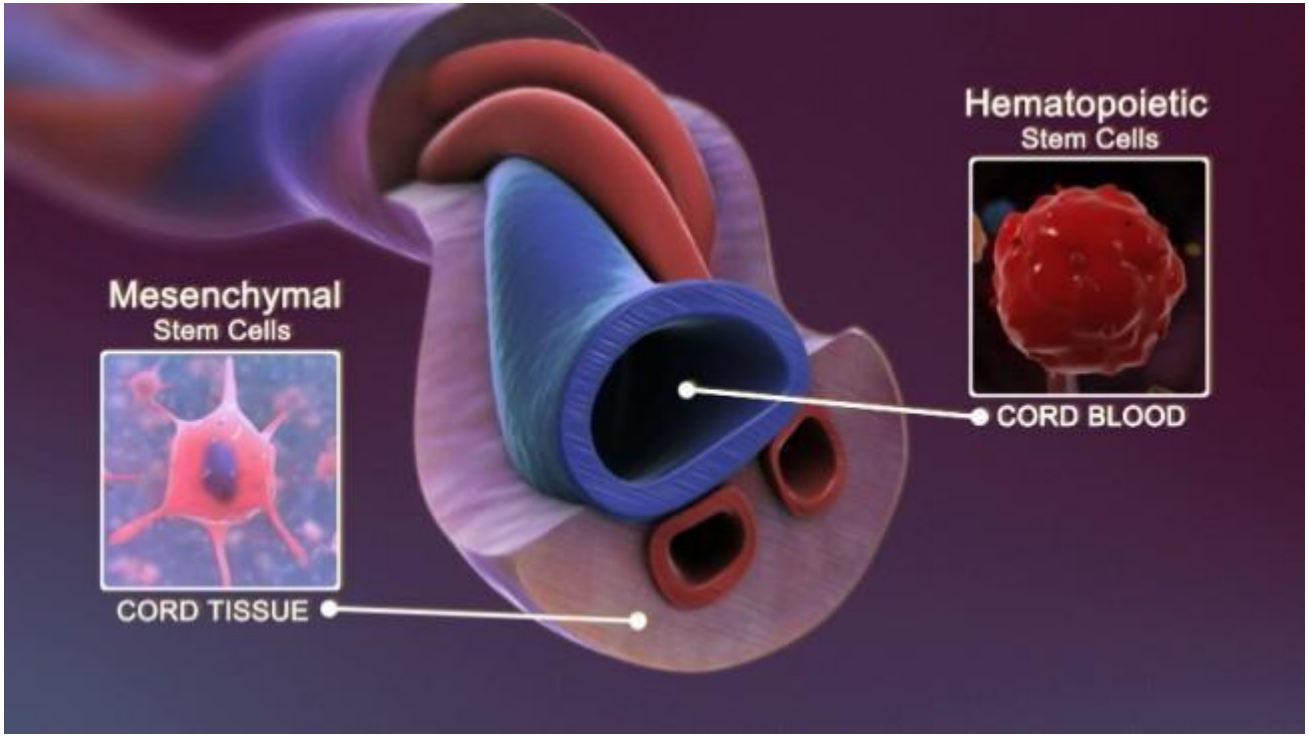
Types of adult stem cells

3. Adipose stem cells (ASCs).

- Found in adipose tissue, these are mesenchymal stem cells. They can be obtained after **liposuction procedures**, where adipose tissue is removed.
- Some of these cells can differentiate into **fibroblasts, pericytes, endothelial cells, and other cell types**.



Types of adult stem cells



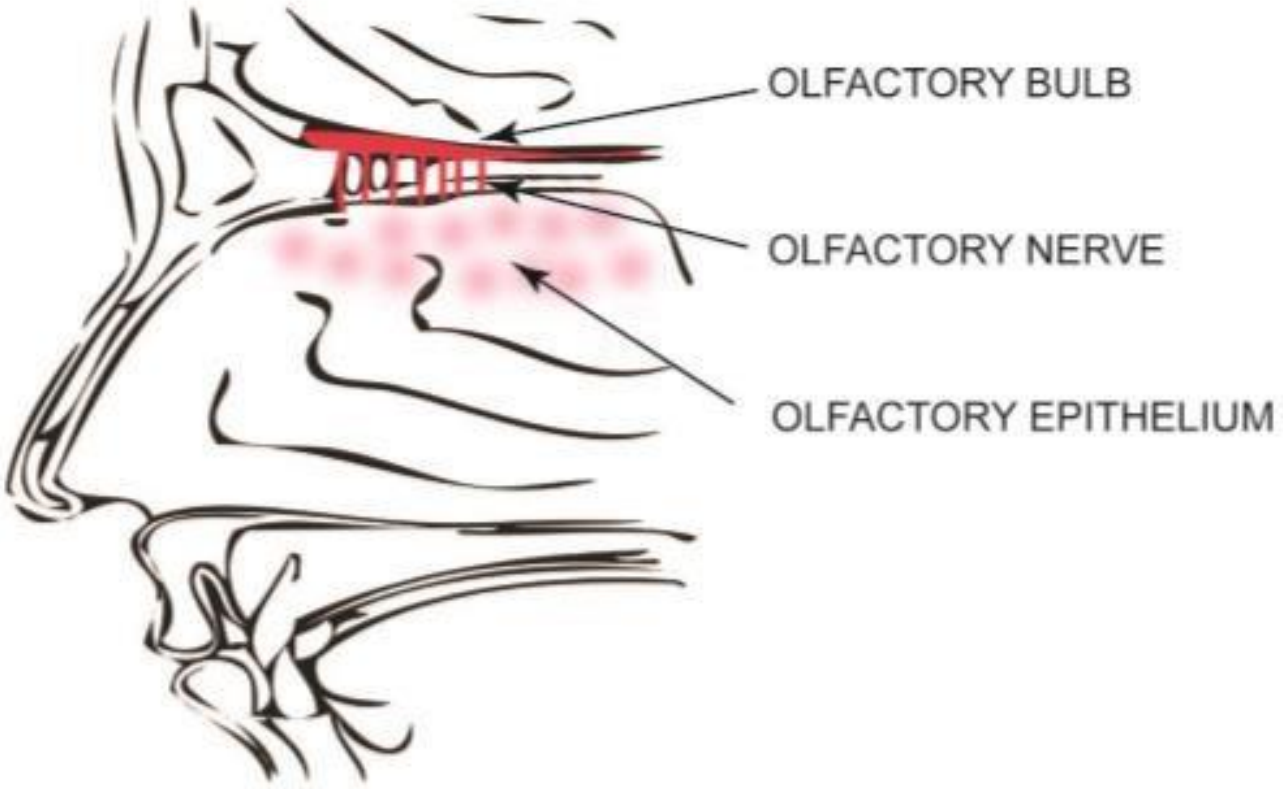
4. Umbilical cord stem cells

- Umbilical cords contain **two types** of stem cells.
- ✓ The blood of the cord contains **hematopoietic stem cells**, while the cord tissue itself contains **mesenchymal stem cells**. In Jordan, there is a center that stores these stem cells from newborn babies.

Types of adult stem cells

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

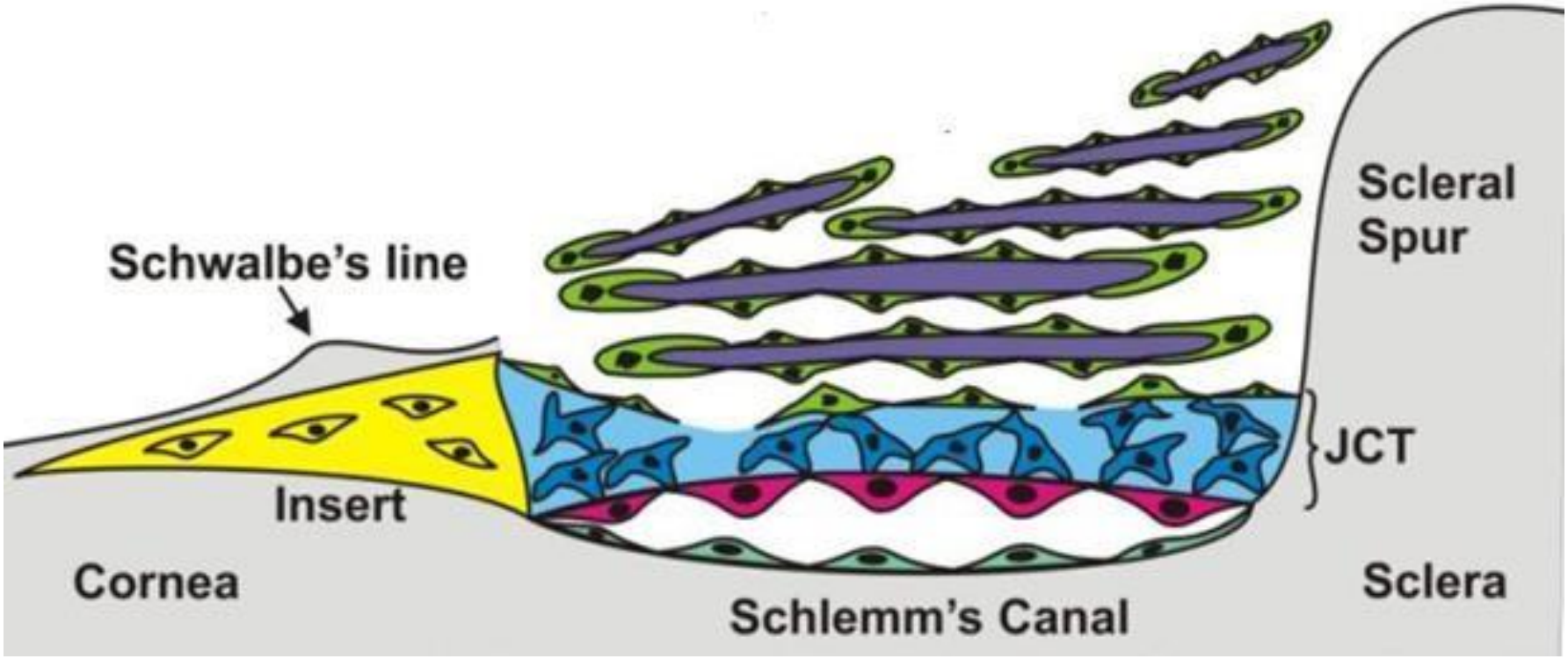
- They are responsible for the **regeneration of sensory cells**, as these cells are easily damaged by certain chemicals and odorants.

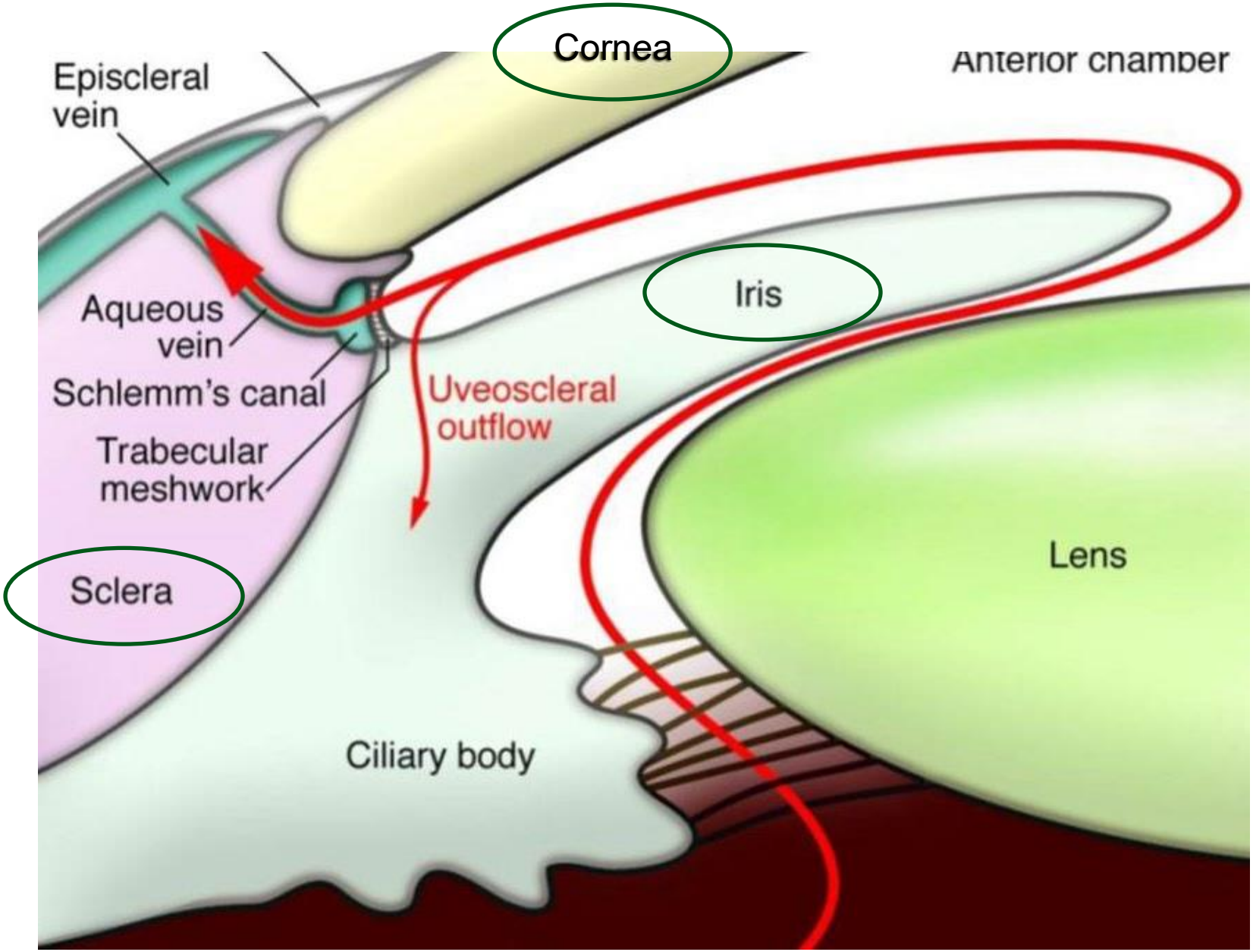


Types of adult stem cells

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

- They are a small population of stem cells located between the cornea and iris at the anterior chamber angle, responsible for **regulating intraocular pressure** in a very small region just beneath Schlemm's canal.





Extra figure

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

if we want to test a certain drug to work on hepatocytes, we can use stem cells and differentiate them into hepatocytes and test the drug on these liver cells to check whether they are effective or not, and we can also choose that this certain cell has a certain genetic makeup to see if a certain drug will work better including this genetic makeup or not, which will of course simulate how drugs work in real life in which sometimes they are more effective in certain individuals with certain genetic makeup and they are less effective in others

Stem Cell Therapy Limitations

✓Stem cell therapy has disadvantages such as:

- Carcinogenicity — If you transplant them as stem cells not as differentiated form, Since they have the ability to divide.
- Immune rejection — If it is not autograph transplantation
- Infection

✓These factors make the usage of stem cells limited.

Limitations of Using Adult Stem Cells (ASCs)

1. Lack of stem cell makers resulting in difficulties to separate and identify cells.
2. In vitro systems for manipulating adult stem cell populations (**to maintain their stemness**) are often not well defined.
3. In vivo: our understanding of how adult stem cells regulate within their niche is in its infancy.
4. Multi potency of ASCs, **limited differentiation ability compared to pluripotent cells.**

Past papers:

1- The statement that describes stem cells is:
a. Changes in the niche have no effect on the behavior of stem cells.
b. They can be used for cell- based therapy and modelling human diseases.
c. Their niche drive their differentiation and does not keep their stemness
d. They have a limited ability to asymmetrically divide.
e. We can use them as a cell- based therapy directly after we test them in tissue culture disease models and they show an improvement of the disease.

2- You have recently heard that stem cells may have a potential in regenerating damaged lung tissue caused by SARS-CoV-2 in COVID-19. Before they can be used in clinic, the following has/have to be checked:
a. Carcinogenicity specifically if pluripotent stem cells are used.
b. The mechanism by which stem cells repair the lost pulmonary function.
c. All experimental stages starting with ex vivo experiments, animal stage, clinical trials of 3 stages.
d. Food and drug administration approval in the country of practice.
e. All points have to be verified before stem cell can be used as a treatment for COVID.

3-Which stem cell is the most potent, genetically engineered and causes no immune reaction:
a. iPS
b. embryonic
c. adult neural

4- True about stem cells
embryonal stem cells have more potency that adult

Answers: B, E, A

Stem Cells & neurodegenerative diseases

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Neurodegenerative Diseases

- A wide range of acute and chronic conditions in which neurons and glial cells in the brain and spinal cord are lost.
- Acute : ischemic stroke or spinal cord injury
- Chronic: Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), or Alzheimer disease (AD).

- The type of neurodegenerative condition –whether acute or chronic– and whether it affects a single cell type or multiple cell types determines the **extent of cellular damage and functional loss**. This variation would affect the use of stem cells as a treatment modality for these diseases.

Main considerations when we use stem cells to treat neurodegenerative diseases

- What is required for the stem cell–based approach to be clinically competitive?
  - Stem cells as a treatment modality must be **competitive** with existing treatment modalities available in the clinics for different neurodegenerative diseases. They should provide significant improvement in the patient's condition and quality of life, effectively treat the disease, and avoid causing additional or more serious complications. In this way you can convince yourself first then your patient to consider using stem cells therapy instead of other treatments that might be even cheaper.

- Risks to the patient that are acceptable, depending on disease severity. Animal models may not fully predict their toxicity, occurrence of immune and other biologic responses, and risk for tumor formation after implantation in patients.

  - Side effects of using stem cells may include carcinogenicity, toxicity, immunological problems and infection etc.

Main considerations when we use stem cells to treat neurodegenerative diseases

- The variability between neurodegenerative diseases in the degree of disability that they cause and in the therapeutic options that are available.

e.g PD- symptomatic treatment

- Another point to consider is the variability among neurodegenerative diseases in the degree of disability they cause. Some diseases are highly disabling, where even a small reduction in disability would be acceptable and convincing to the patient. In other diseases, available treatments mainly treat the symptoms, and patients may already be satisfied with their current management. Therefore, when using stem cells, there should be a significant improvement in the patient's quality of life, along with reduction in the degree of disability associated with these diseases.

Main considerations when we use stem cells to treat neurodegenerative diseases

- The cell type to be regenerated and transplanted.

PD- dopamine neurons

ALS – motor neurons

Stroke and Alzheimer's disease-several cell types

- **The next point to consider is the specific cell type that needs to be replaced or regenerated in each neurodegenerative disease.**

- ✓ **For example, in Parkinson's disease, where there is dopaminergic loss, dopaminergic neurons need to be replaced. In conditions such as Alzheimer's disease, stroke, and spinal cord injury, multiple cell types may need to be replaced. This may include restoring myelin, re-establishing synapses, and remyelinating axons.**

- **Therefore, several changes occur in the tissue that need to be repaired.**

Main considerations when we use stem cells to treat neurodegenerative diseases

- The stem cell–based approach should show substantial improvement of functional deficits in animal models before their use in clinical application.

  - Another point to look at is the amount of improvement the patient is expecting. A patient with Parkinson's disease, for example, can live with it with the available treatments right now, so they need a **great amount of improvement** to consider stem cells as a treatment option. But for a spinal cord injury with a high degree of disability, even a **small percentage of improvement would be acceptable** for the patient. So it depends on the disease and the amount of disability associated with it.

- To determine the biological mechanism underlying the observed effects of a stem cell–based treatment in an animal model.

- e.g. reconstruction of neuronal circuitry

  - We also need to determine the **biological mechanism** by which the repair happens. Is it due to the simple replacement of lost neurons, or due to the reconstruction of neuronal circuitry? Is it through inducing or activating neural repair at the site by the transplanted stem cells, etc.?

Common considerations when translating stem cell therapies to neurodegenerative disease patients

Inclusion/exclusion criteria	Enrolling late-stage patients may prevent loss of quality of life Late-stage patients may mask any positive effects due to the intervention occurring too late in the disease course
Realistic expectation	Informed consent forms must clearly illuminate the goals of the study Safety trials vs. efficacy trials Expectations of therapeutic effects based on disease state at intervention
Controlled study	Ideal study is a double-blind placebo study Late-stage patients may mask any positive effects not observed due to the intervention occurring too late in disease Original PD studies offered control arms treatment after a 1-year follow-up which confuses interpretation of efficacy
Immunosuppression	While the brain remains an immunologically privileged site due to the blood-brain-barrier, there is evidence that this barrier can be compromised in disease Studies into cell graft survival demonstrate that immunosuppression increases that survival of graft tissue
Potential side effects	Prevent/minimize potential side effects (i.e. meningitis, fever) Avoid exacerbation of disease and tumor formation Risk vs. quality of life
Safety of cellular therapy administration	Consider CNS accessibility and safety of delivery methods Pros/cons of systemic delivery, lumbar puncture or stereotactic injection are important

Abbreviations: PD, Parkinson's disease; CNS, central nervous system.

Common considerations when translating stem cell therapies to neurodegenerative disease patients

- Other considerations we need to look at include whether we need to immunosuppress the patient before proceeding with any stem cell-based therapy, and what the potential side effects are? Are these therapies safe to be administered? or could they cause problems later that might even be more dangerous than the disease the patient is currently suffering from?

- We also need to consider what types of studies are required, such as double-blind placebo studies, which are the ideal design in which neither the patient nor the operator knows whether the treatment or a placebo is being given.

- In addition, we need to assess whether the patient's expectations are realistic and whether they have been clearly explained. Has informed consent been obtained?

- We also need to define the inclusion and exclusion criteria. Are there specific conditions that must be present in a patient to qualify for this type of treatment, or can any patient with the disease be included?

✓ All of these considerations are important before proceeding with choosing the treatment modality for diseases.

Examples on Neurodegenerative Diseases Targeted by Stem Cell therapy

Parkinson's disease (PD)

Characteristic symptoms are rigidity, hypokinesia, tremor, and postural instability

Degeneration of nigrostriatal DA neurons is the main pathology

Tx: l-DOPA, DA agonists, enzyme inhibitors, and deep brain stimulation

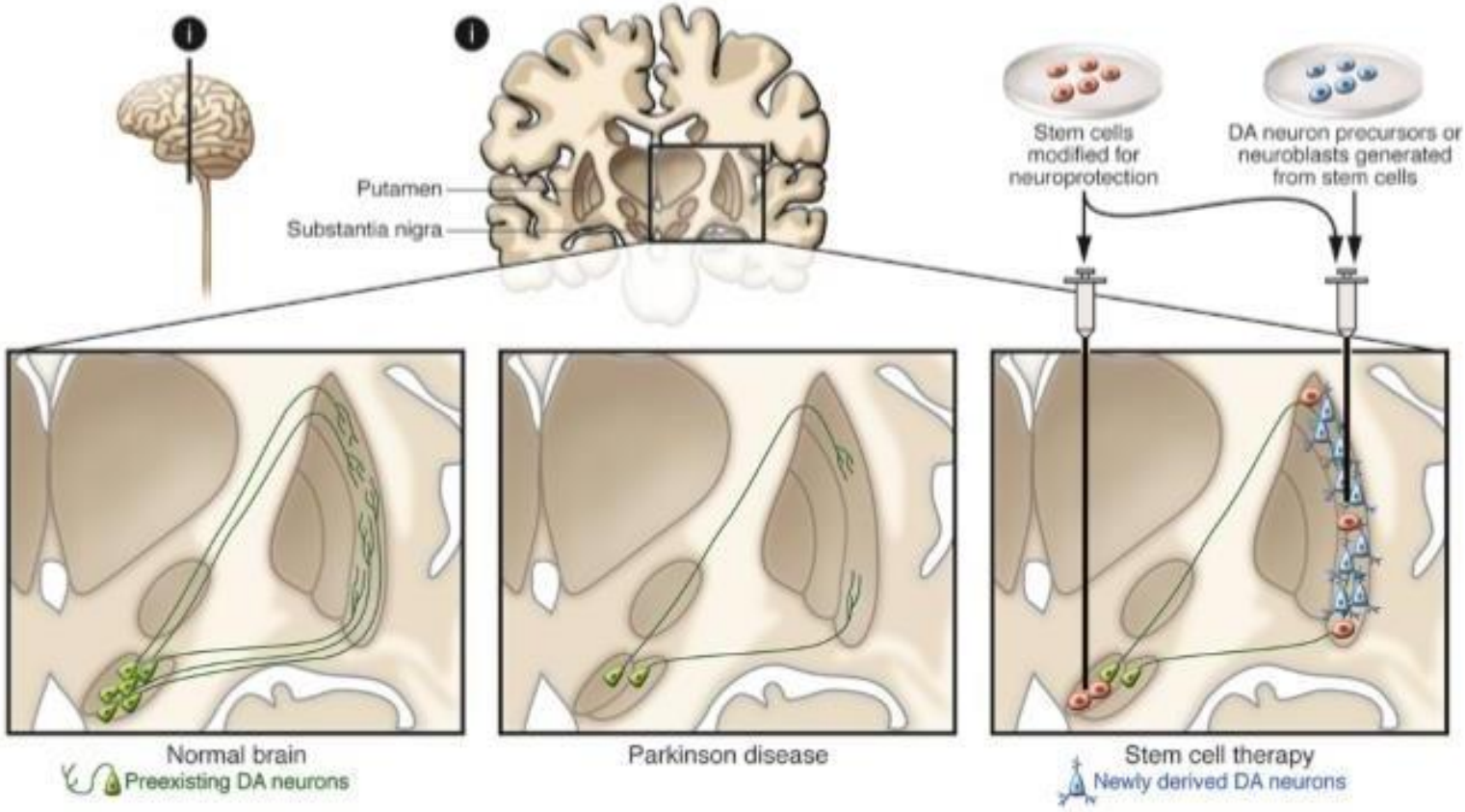
No Tx for dementia

iPSCs for modelling the genetically complex PD

- Different treatment modalities are available, including administration of L-DOPA, dopaminergic agonists, and enzyme inhibitors, etc. The main purpose of these treatments is to **replace the lost dopamine**.

Stem cell–based therapies for PD

Proof of principle: clinical trials with intrastriatal transplantation of human embryonic mesencephalic tissue (rich in postmitotic DA neuroblasts). DA = Dopaminergic



Stem cell–based therapies for PD

Pros	Cons
-The DA neurons that form from the transplanted tissue reinnervate the denervated striatum and become functionally integrated, restoring striatal DA release and giving rise to clear symptomatic relief in some patients.	-A small fraction of graft-derived DA neurons contain **Lewy bodies** (the hallmark of PD). Suggesting that the disease pathology may have been transferred to the grafted neurons, causing them to become diseased as well. - Availability of human embryonic mesencephalic tissue is limited.
11–16 years after transplantation, cell replacement remains a viable therapy.	Variability of functional outcome after transplantation is high. They show highly variable functional outcomes in terms of restoring lost function, with some patients showing major improvement while others show only minimal benefit. This variability makes it difficult to standardize the treatment.
The progression of pathology in graft-derived neurons is slow, and they are still functional after a decade.	Poor standardization of the transplanted cell material contributes to the high variability

Stem cell–based therapies for PD

Other sources of DA (dopaminergic) neurons:

- ✓ ES cells (Embryonic stem cells)
- ✓ Cloned ES cells
- ✓ NSCs and progenitors of embryonic ventral mesencephalon
- ✓ Adult NSCs from the subventricular zone (SVZ)
- ✓ Bone marrow stem cells
- ✓ Fibroblast-derived iPS cells

Human stem cell–derived DA neuron precursors/neuroblasts can survive in animal models of PD and can be functional after maturation.

Stem cell–based therapies for PD

Hurdles that prevent stem cell therapy for PD from bench to clinic:

- ✓ PD is a **multisystem disorder**, if **nondopaminergic** systems are affected, they will not improve by intrastriatal DA grafts.
- ✓ **Substantial re-innervation** of striatum has not been demonstrated.
- ✓ **Restoration of DA release** in vivo has not been demonstrated.
- ✓ **Marked improvement** (50-70%) in the deficits and symptoms experienced by PD patients has not been demonstrated.
- ✓ Risk of **tumor formation**-even if minor, it is not acceptable.
- ✓ The need to inject cells at **all sites of injury**.

See the next slide

Stem cell–based therapies for PD

- So, the main hurdles that interfered with this approach are that Parkinson's disease is a **multi-system disorder**, meaning that in some systems **non-dopaminergic neurons are also affected**. Therefore, a treatment that only improves dopaminergic release would NOT be a fully effective option in this situation.

- Also, the extent of re-innervation of the striatum was not properly checked or verified in these patients, whether it was substantial or only occurred in a small percentage of the transplanted cells. In addition, restoration of dopaminergic release was **not proven in vivo.**

- Furthermore, the degree of clinical **improvement** in patients was **not sufficiently high**, as it would need to be around **50-70%** to be truly convincing for both clinicians and patients.

- Another concern is the risk of side effects, including **potential cancer formation**, even if the probability is small. This is **not acceptable** in Parkinson's disease, because patients can already live with the condition using available treatments, so exposing them to a therapy that might carry a risk of cancer is not justified.

- Finally, another limitation is that stem cells would need to be **injected into all sites of injury,** which might be hard in practical .

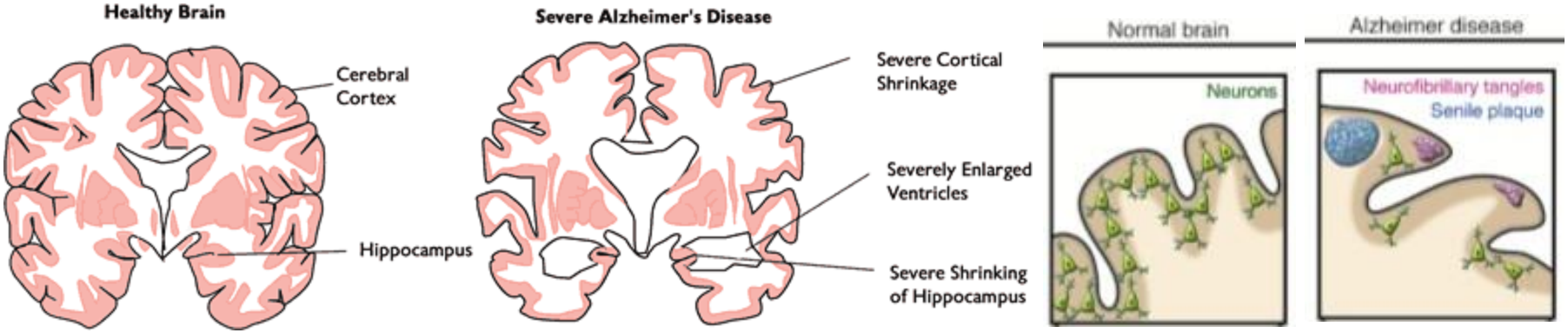
Clinical trials

- By International Stem Cell Corporation (ISCO)
- They tried the Parthemogenetic cells derived of unfertilized oocytes after suppression of the second meiotic division
- Drawbacks:

Used cells are PAX6-positive suggesting that they are of a dorsal neural fate. In contrast authentic midbrain dopaminergic neurons are derived from a PAX6-negative ventral midbrain neural precursor.

- The drawback is that the **transplanted cells are Pax6-positive** (Pax6 is a transcription factor important in development).
- The problem with this marker is that **dopaminergic neurons are normally derived embryologically from Pax6-negative precursors**. Now they are generated from pax positive cells that might have an effect that may appear later on after transplantation in the patient.

Alzheimer's disease (AD)



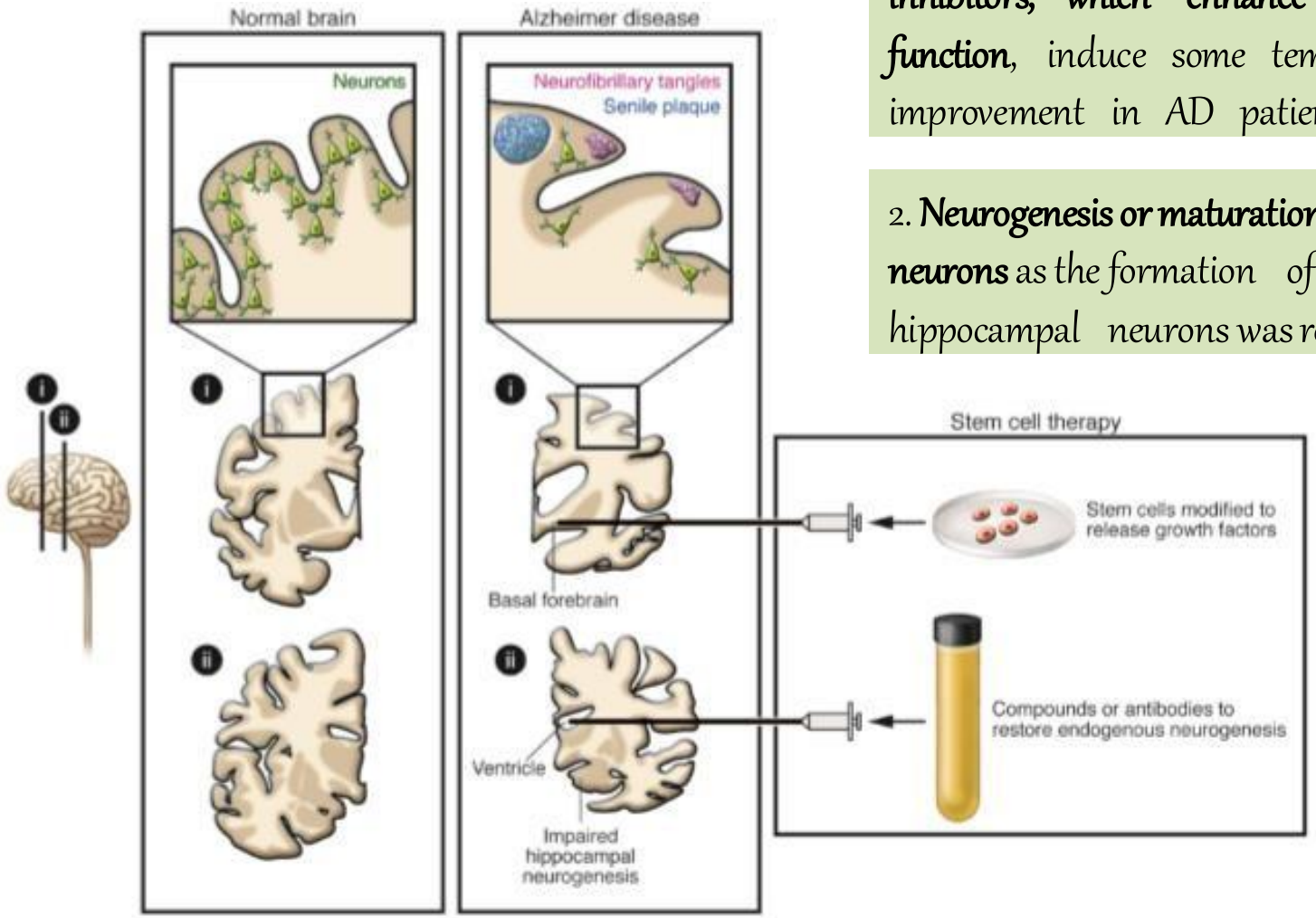
Memory impairment, cognitive decline, and dementia due to **widespread** and **progressive** pathological changes.
The effect is exerted **at the tissue level** rather than at the level of individual cells.

Neuronal and **synaptic loss**, neurofibrillary tangles, and **deposits of β-amyloid protein** involve the basal forebrain cholinergic system, amygdala, hippocampus, and cortical areas.

Stem cell–based **therapies** for AD

1. Cholinergic neurons: **acetylcholinesterase inhibitors, which enhance cholinergic function**, induce some temporary improvement in AD patients

2. **Neurogenesis or maturation of hippocampal neurons** as the formation of immature hippocampal neurons was reported in AD.



3. **Nerve growth factor (NGF) releasing stem cells, that stimulate neurons regeneration and repair**

4. **Anti-β-amyloid antibodies** or β-amyloid–degrading protease neprilysin.

Stem cell–based therapies for AD

Hurdles that prevent stem cell therapy for AD from bench to clinic:

- ✓ Since in AD brain loss many cell types, stem cells have to be **pre-differentiated in vitro to many different types of neuroblasts** for subsequent implantation **in many brain areas,** because there are multiple lesions in different brain areas.

- ✓ **For a long-lasting symptomatic benefit, cholinergic cell replacement requires intact target cells** (host neurons that the new cholinergic neurons can act on) that are damaged in AD.

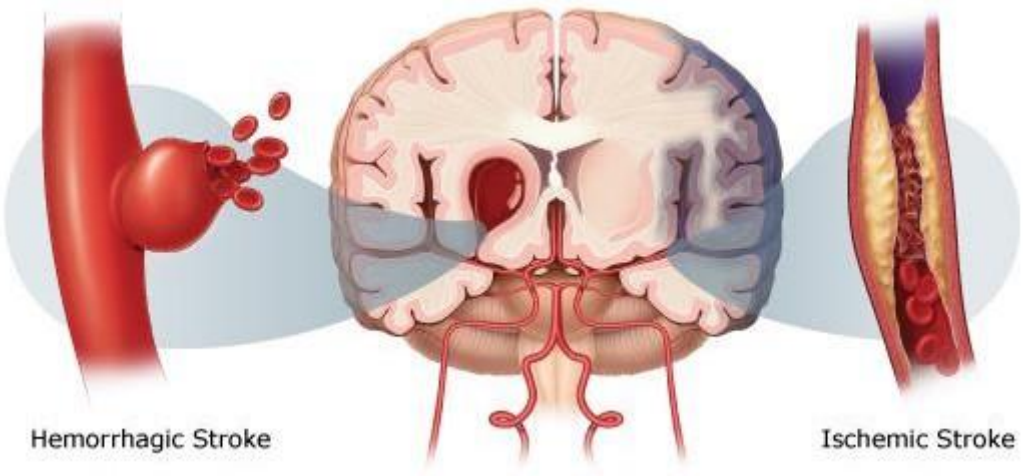
- ✓ Stem cell–based cell replacement strategies are very far from clinical application in AD.

Clinical trials

- By stemedica cell technologies:
- Stem cells from healthy people to mild to moderate AD patients
- To test if stem cells work for AD

Stroke

Ischemic stroke, **caused by occlusion of a cerebral artery**, leads to focal death of multiple neuron types, as well as oligodendrocytes, astrocytes, and endothelial cells, **Depending on the artery that is occluded.**

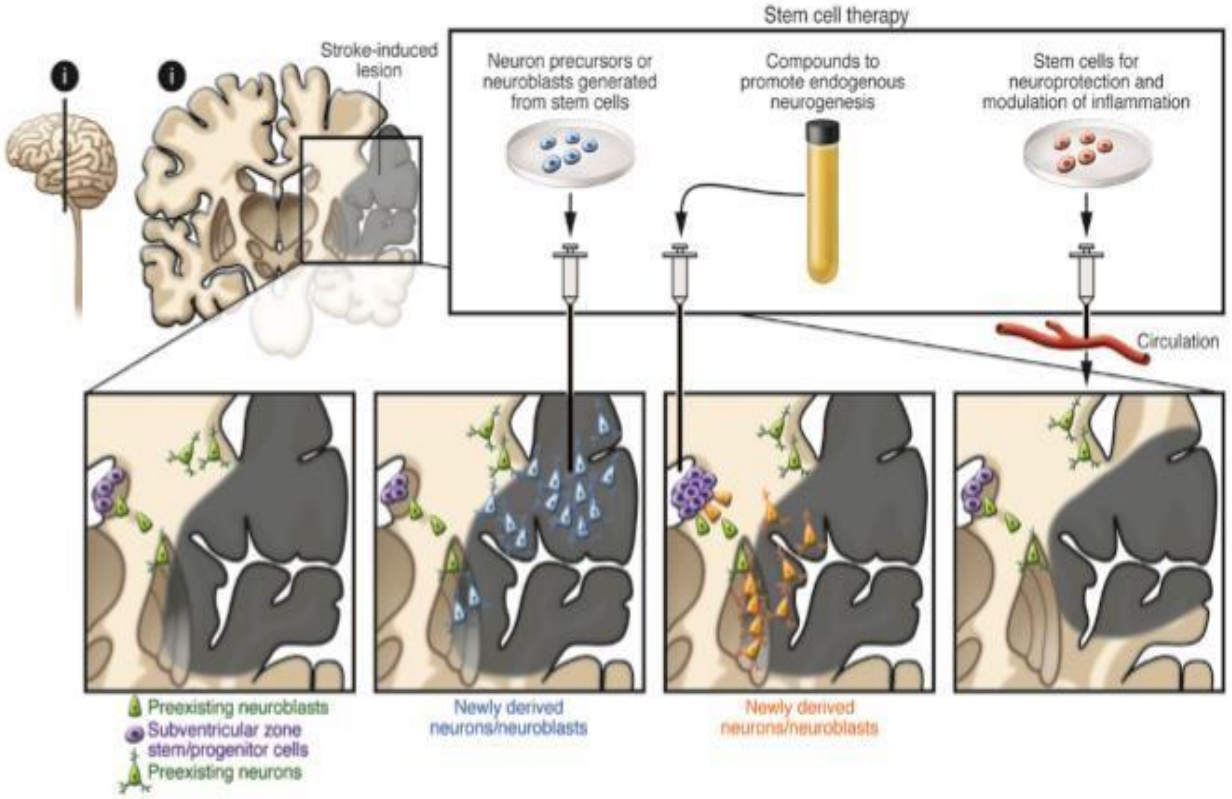


Neuronal plasticity and reorganization of neural circuitries contribute to spontaneous recovery to varying degrees, but most patients exhibit persistent motor, sensory, or cognitive impairments.

Stem cell–based therapies for stroke

✓ Many stem cell types can be used to treat post-stroke brain lesions, such as:

Human Embryonic Stem (ES) cell–derived, Neuronal Stem Cells (NSCs) and Mesenchymal Stem Cells (MSCs), grafted into rat stroke site, migrated toward the lesion and improve forelimb performance.



IV injection of human NSCs induced improvements after hemorrhagic stroke in rats, probably through antiinflammatory actions

Stem cell–based therapies for stroke

- ✓ **No substantial clinical improvements were detected** after IV injection of autologous MSCs in patients with an ischemic lesion in the regions supplied by the middle cerebral artery (MCA).
- ✓ Several clinical studies using intravenous or intraarterial (into damaged territory) infusion of autologous bone marrow–derived stem cells in stroke patients are ongoing, but still **However, none of these studies have yet been established as a final clinical treatment.**
- ✓ A clinical trial in stroke patients involving transplantation of clonal, conditionally immortalized NSCs isolated from human fetal cortex is being tested.
- ✓ **80% of neuroblasts and neurons die during the first two weeks after formation at stroke site in rats.**

Clinical trials, include:

- Transplanted ESCs, Induced Pluripotent Stem Cells (iPSCs), and NSCs can replace the missing brain cells in the infarcted area.

Neuronal stem cells

Mesenchymal stem cells

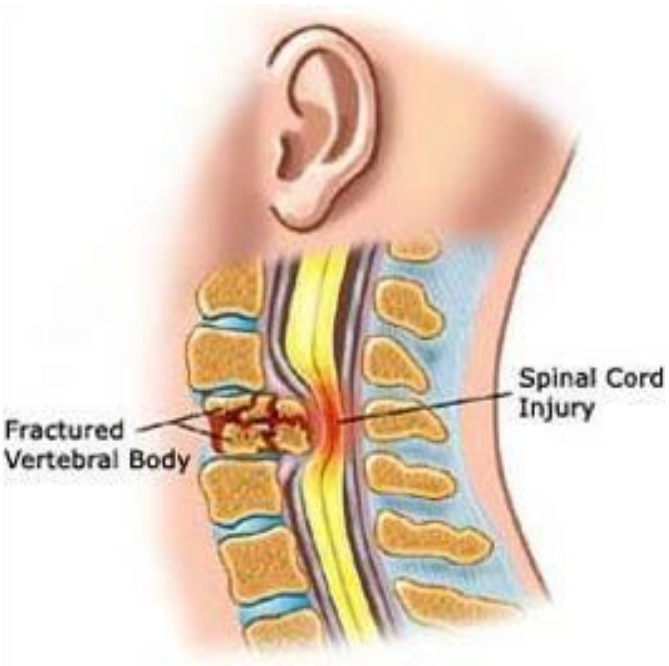
- **Non-neuronal adult stem cells**, such as MSCs **provide trophic support to enhance self-repair systems such as endogenous neurogenesis.**

Spinal cord injuries

Pathological changes after spinal cord injury are complex and include:

1. Interruption of ascending and descending pathways
2. Loss of neurons and glial cells
3. Inflammation
4. Scar formation
5. Demyelination

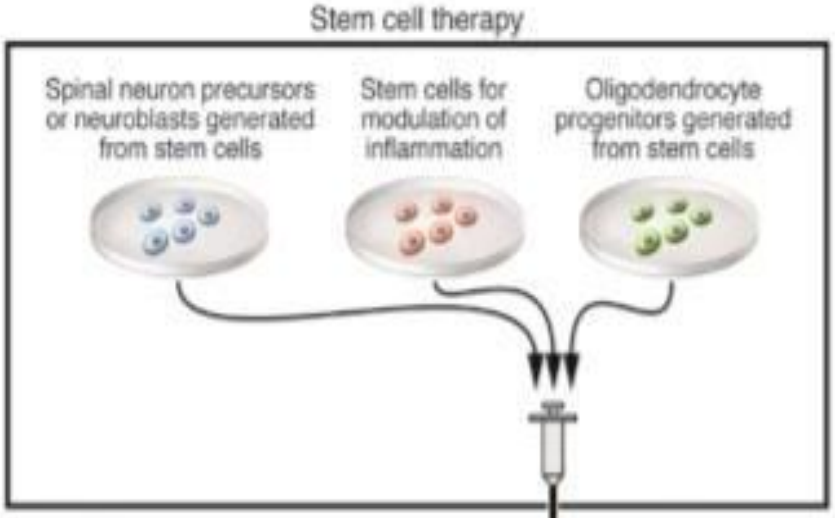
Similar to AD, spinal cord injuries involve tissue-level damage, making stem cell therapy more complex.

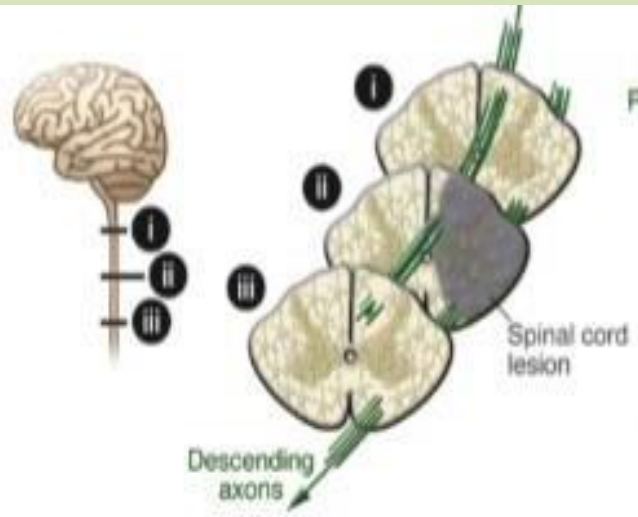


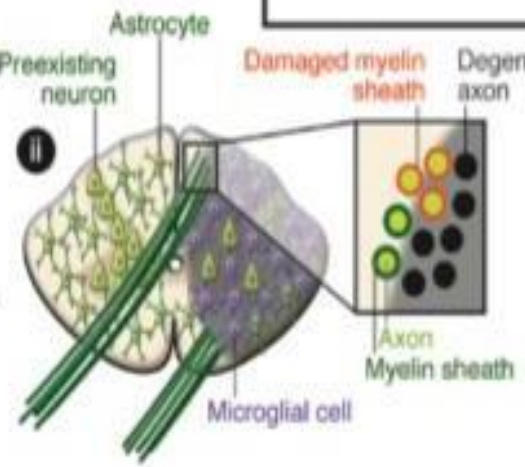
- ✓ Patients experience loss of movement, sensation, and autonomic control below the level of the injured spinal segment.
- ✓ Available treatments are ineffective.
- ✓ Different types of stem cells were tested and improved functional outcome in animal models through secretion of neurotrophic factors, remyelination of spared axons, or modulation of inflammation

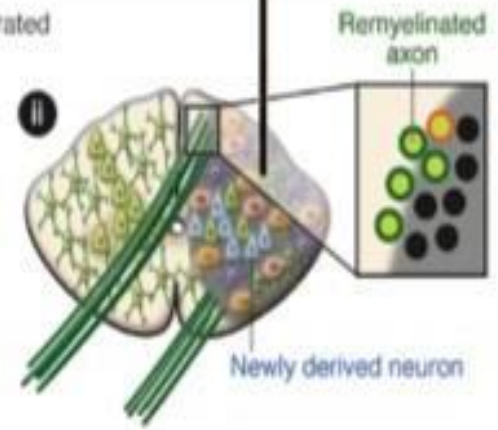
Stem cell–based therapies for spinal cord injuries

Formation of **neurons, oligodendrocytes, & astrocytes.**
Formation of **synapses and axons**
Remylenation : high-purity oligodendrocyte progenitor cells (OPCs) generated from human ES cells in vitro can differentiate into oligodendrocytes (clinical trial)









Stem cell–based therapies for spinal cord injuries

Before moving to clinic, **we should determine the following:**

- Determine **how to control the proliferation** of transplanted stem cells and their Progeny. Because we need them to be in certain amounts and be able to form different types of synapses.

- Determine **how to enhance the differentiation of these cells to the specific types of neurons that have been lost**.

- Determine **how the resulting neurons can be directed to format appropriate synaptic contacts.** To perform the lost function

Stem cell–based therapies for spinal cord injuries

- Other stem cell types:

Umbilical cord blood, bone marrow–derived HSCs, and MSCs have already been applied in patients with spinal cord injury, with claims of partial recovery, **Thus far, these strategies have NOT reached clinical implementation as definitive therapies.**

- Problems in these trials:

1. The implanted cells were often **poorly characterized.**
2. The **preclinical evidence** of efficacy for several of these approaches **was insufficient**.
3. The therapeutic benefit was reported from open-label trials where patients had been subjected to physiotherapy, **Consequently, it remains unclear whether the improvements result from stem cell therapy or physiotherapy!**
4. The mechanisms underlying observed improvements were unclear.

Neurodegenerative Diseases & Stem Cell Therapy: A Summary

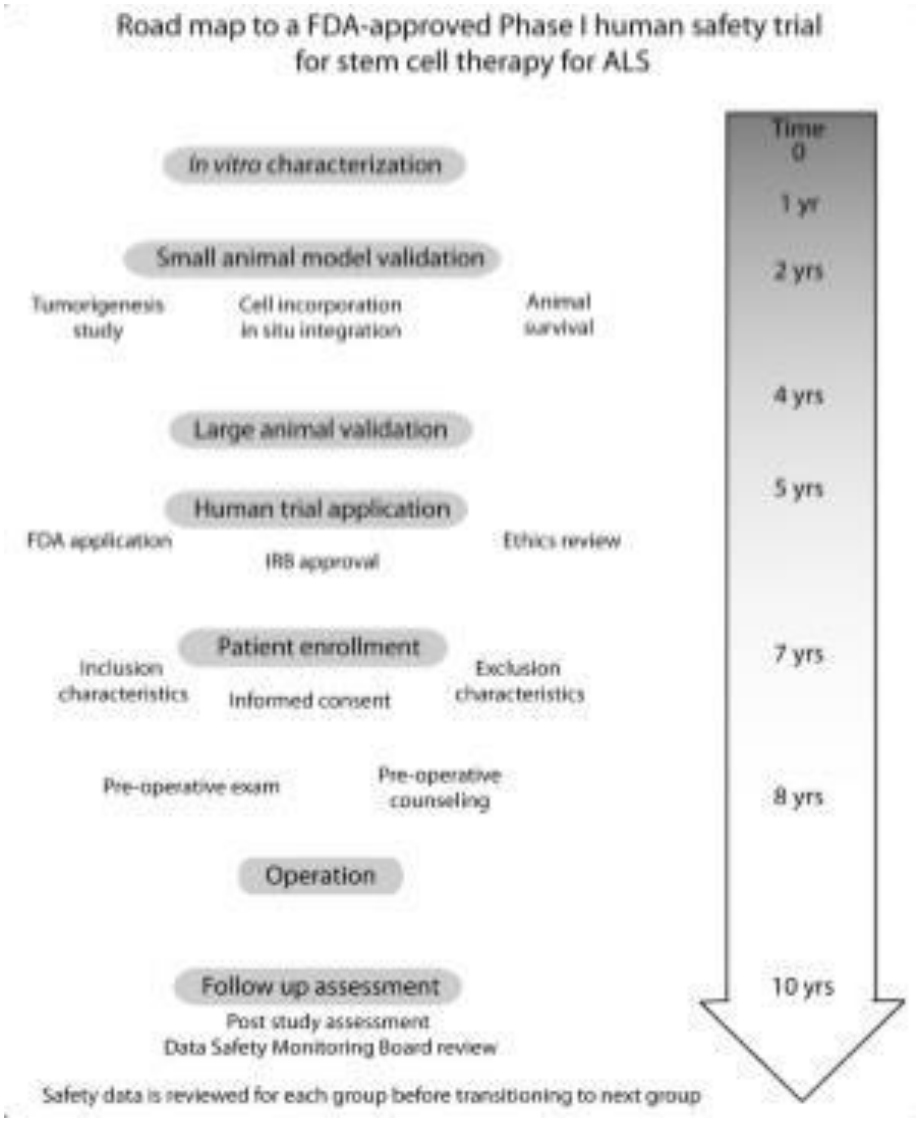
- Clinical trials using stem cells have already been performed or initiated (e.g., for the rare, fatal, autosomal recessive neurodegenerative disorder Batten disease)
- **No stem cell–based therapy has yet been proven beneficial for any neurodegenerative condition.**
- Despite this fact, unproven treatments for several neurodegenerative diseases are offered at "clinics" around the world without rationale and with poor scientific and clinical basis. **So, as a clinician, you should check its approval by the FDA.**
- Ethical, regulatory, societal, and economical issues need to be addressed.

Translating a stem cell-based treatment from the bench to bed,

- Requires a long research pathway:

1. Starting with **in vitro** characterization and studies.
2. Then progresses to **animal model** studies–using small animals first, followed by large animals.
3. After that, it moves to **clinical trials**, which consist of **3** phases. (This stage is the longest, often taking 10 to 20 years of investigation, until we obtain conclusive evidence on the benefits of using this treatment in any neurodegenerative disease or other conditions).

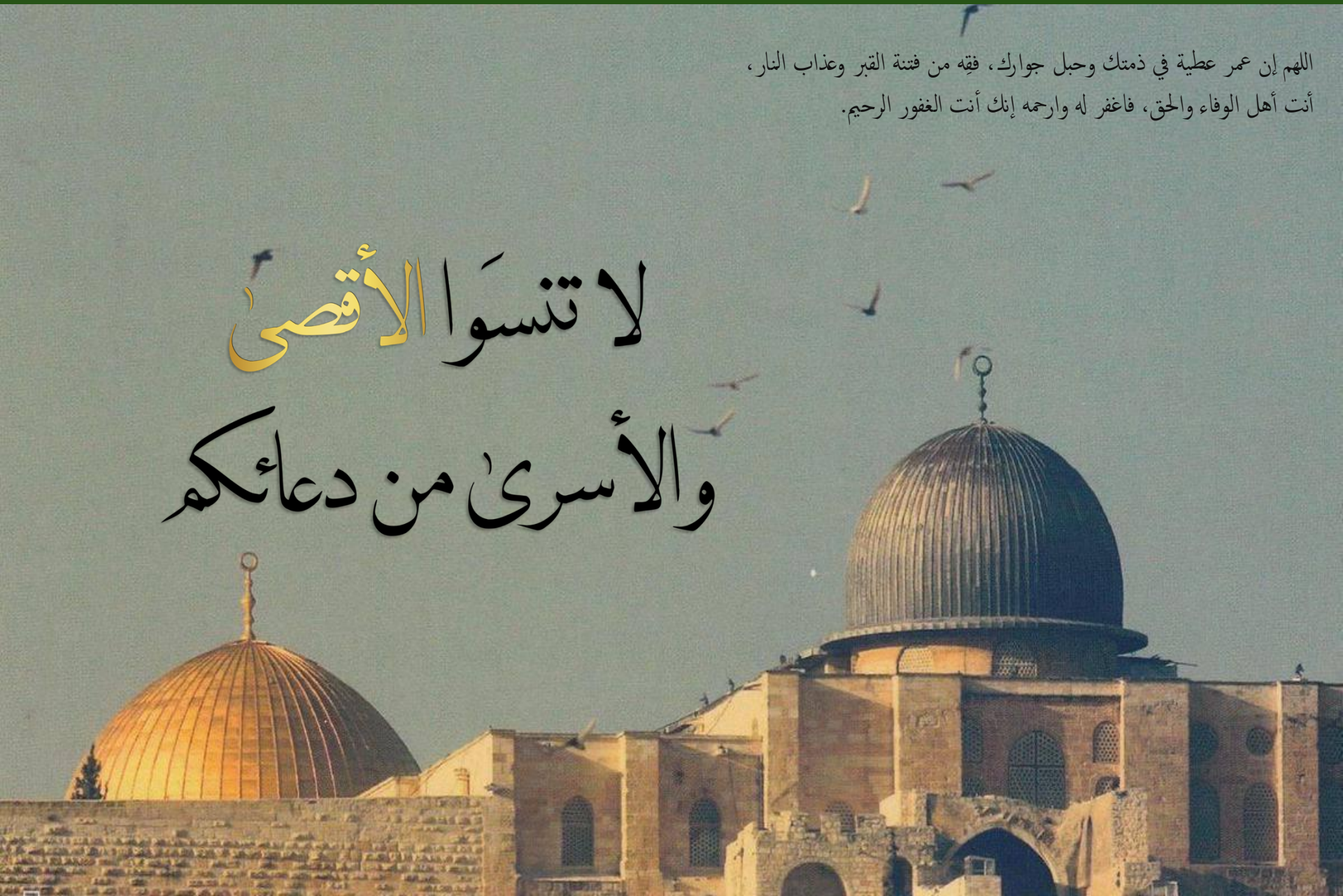
✓ You should help the patient to choose the proper treatment.



BIOCHEMISTRY QUIZ

External Resources

رسالة من الفريق العلمي



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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			