Stem Cells: The New Therapeutics Era

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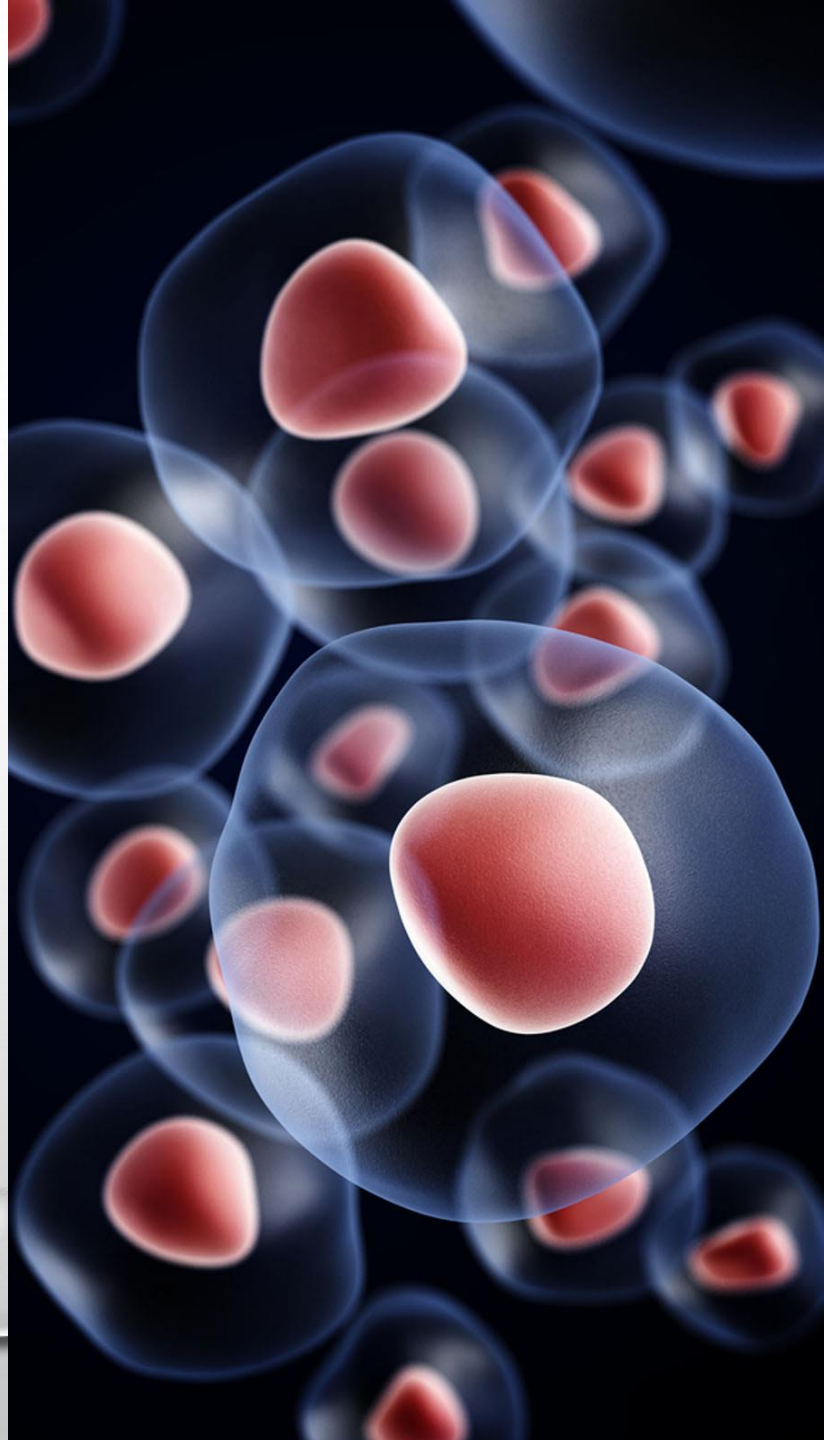
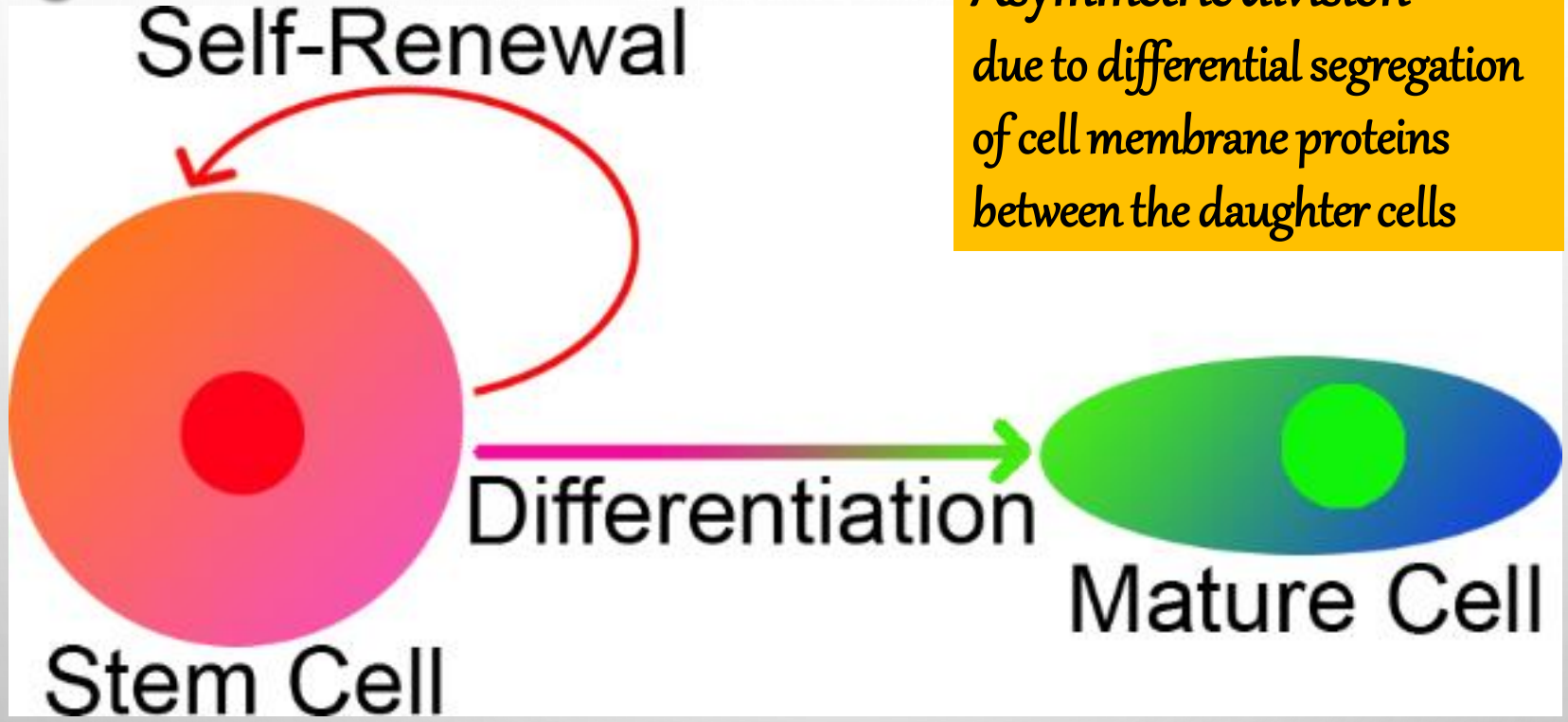
Central Nervous System



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



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

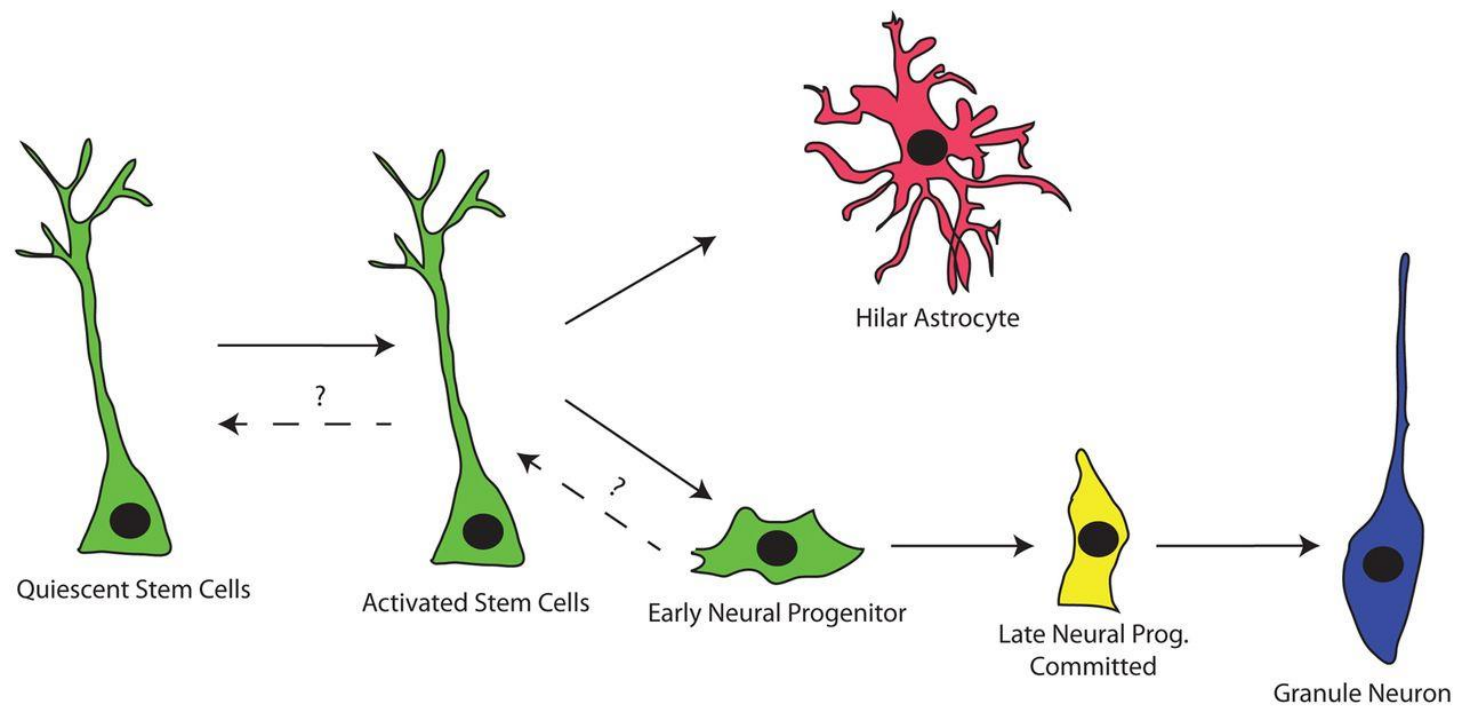
Self-renewal: The ability to go through numerous cycles of cell division while maintaining the undifferentiated state.

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?

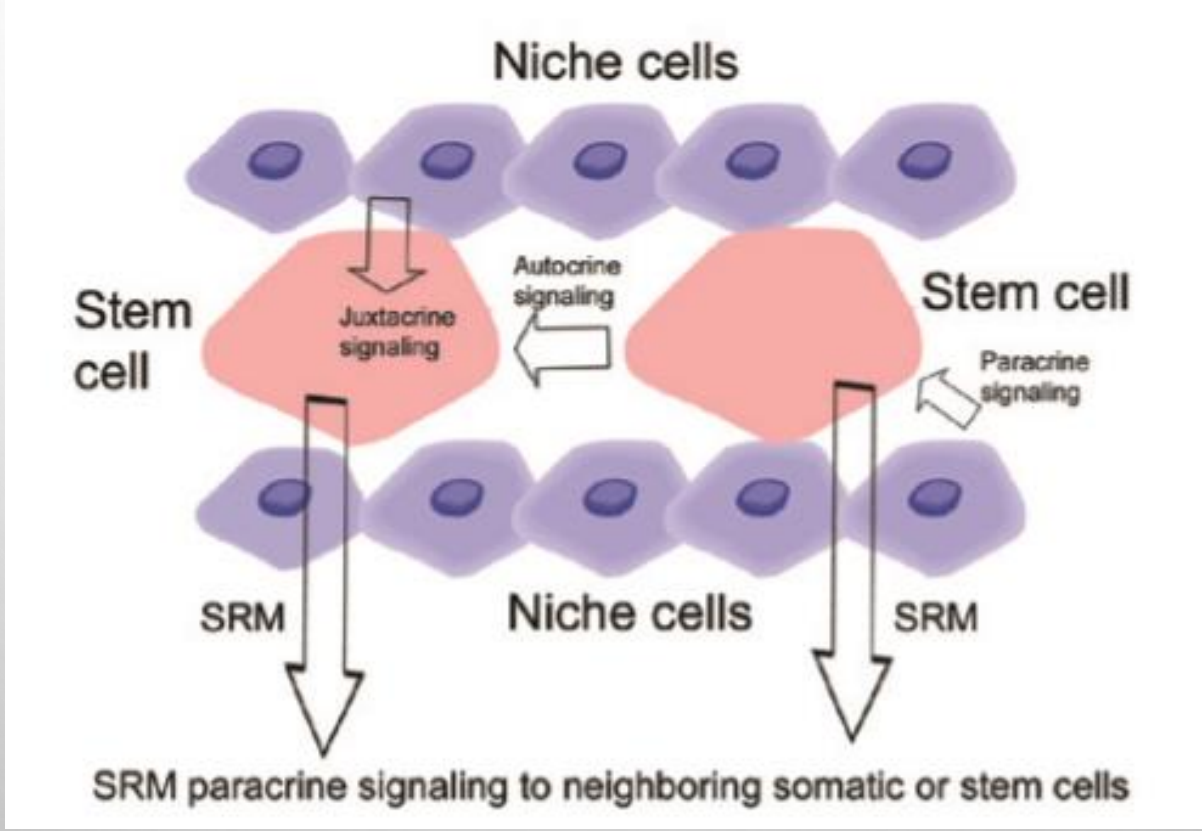
- **PROGENITOR CELL** :STEM CELLS GENERATE AN INTERMEDIATE CELL TYPE OR TYPES BEFORE THEY ACHIEVE THEIR FULLY DIFFERENTIATED STATE.



Venere et al 2012

Stem cell niche

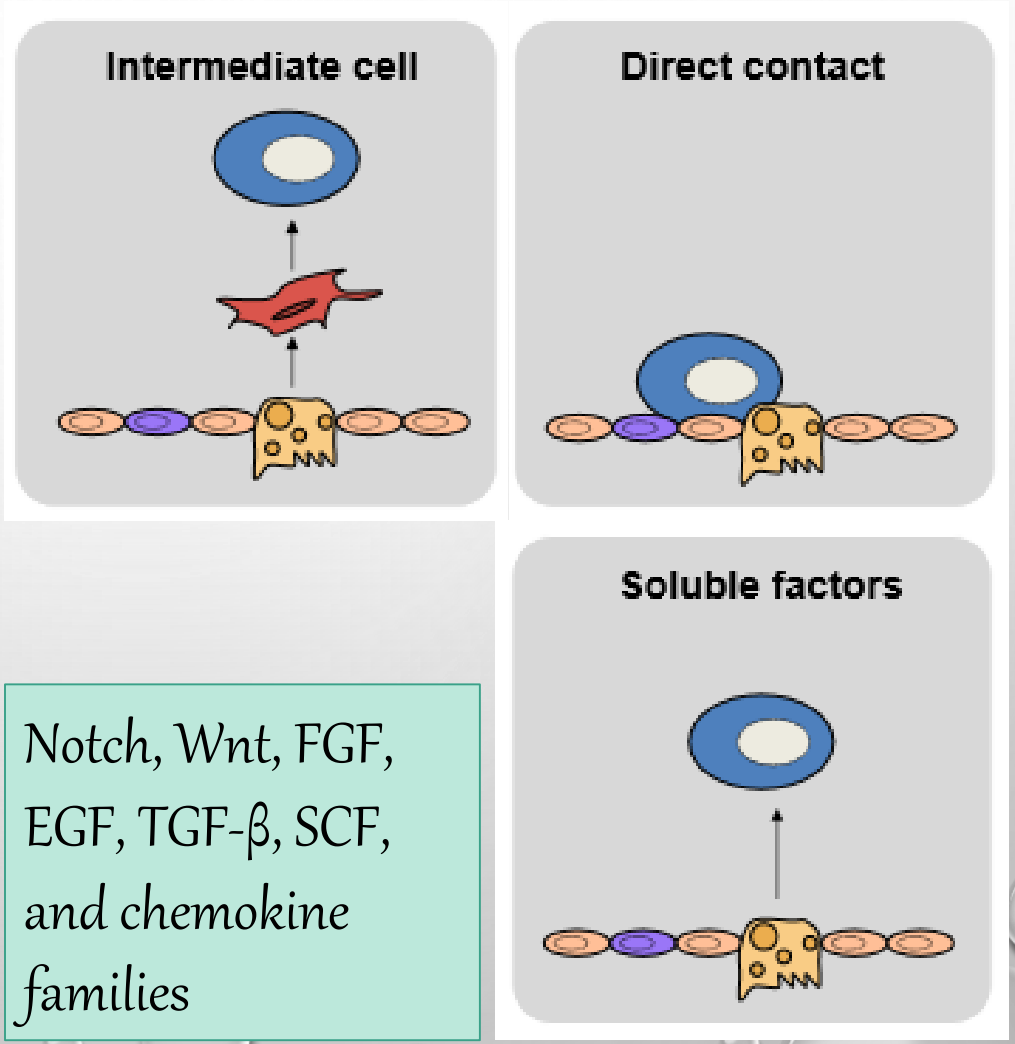
A specialized cellular environment that provides stem cells with the support needed for self-renewal (keeping stemness).



Stem cell niche-composition

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 (extracellular matrix)

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

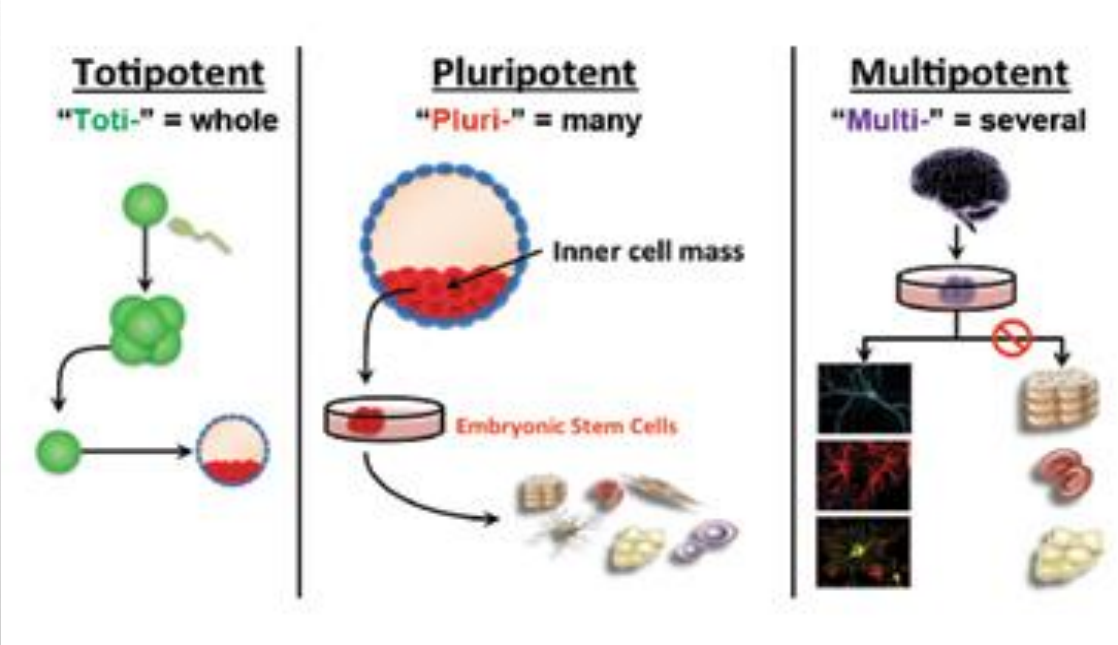
TYPE OF POTENCY :

1-TOTIPOTENT (GIVES ALL CELLS OF THE BODY IN THE 3 GERM LAYERS AND EXTRAEMBRYONIC TISSUES)

2-PLEURIPOTENT (GIVES ALL CELLS OF THE BODY)

3-MULTIPOTENT (GIVES A FEW NUMBER OF CELL TYPES)

4-UNIPOTENT (GIVES ONE CELL TYPE)



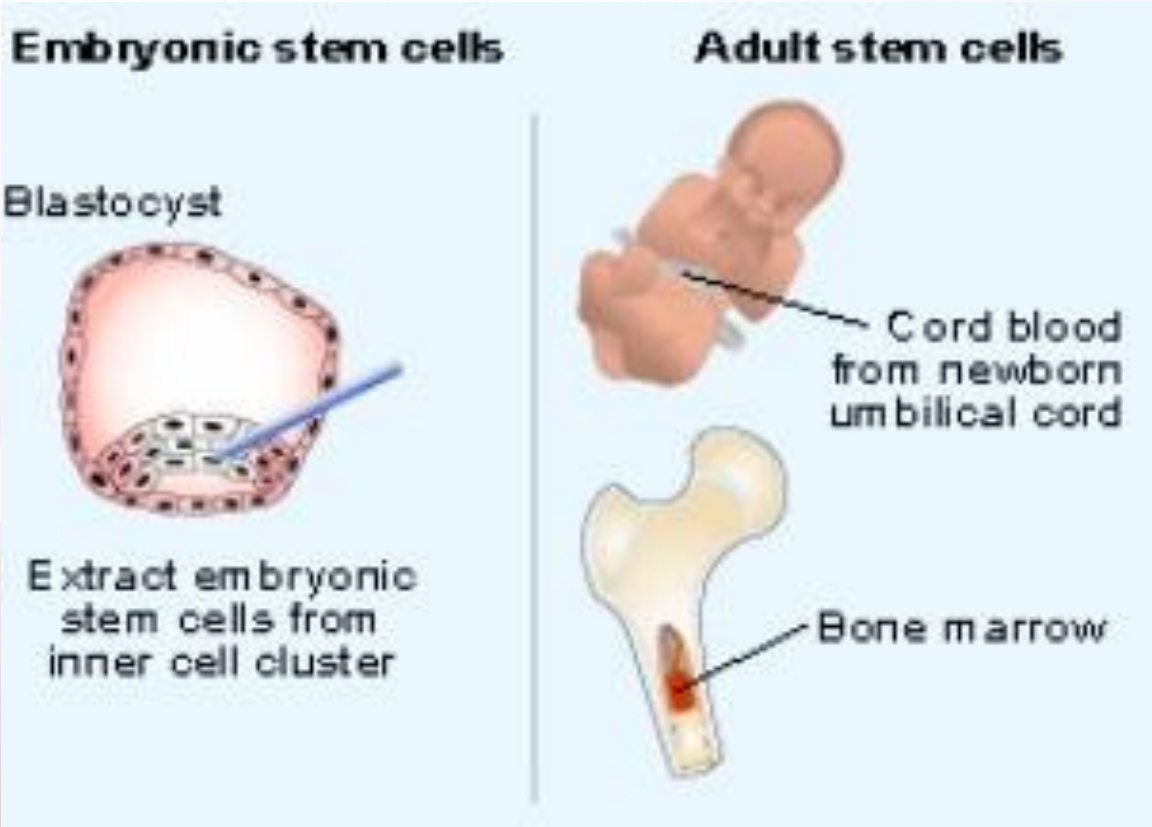
Types of stem cells

Embryonic stem cells

- Are able to differentiate into all the specialized embryonic tissue

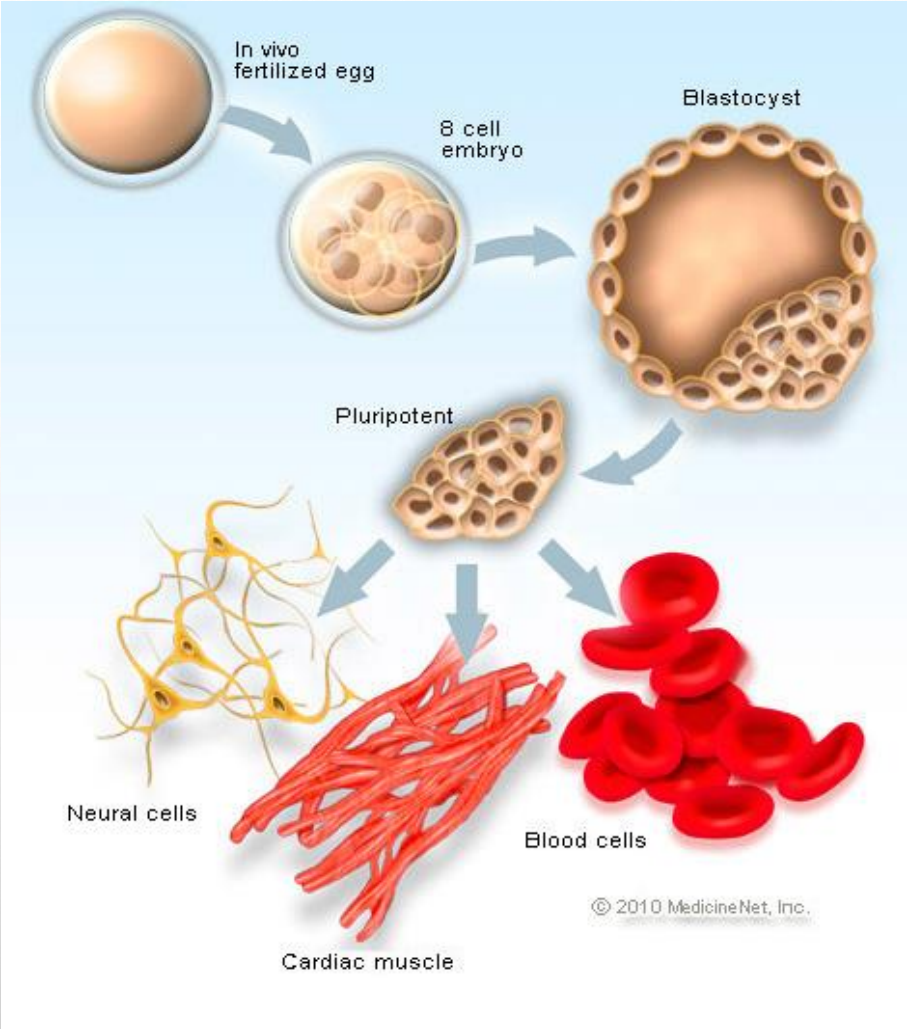
Adult stem cells

- 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

What makes embryonic stem cells pluripotent?

Pluripotency transcription factors (TFs):

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

The Ethical Dilemma of ESCs

To use ESCs, you have to kill embryos and take their cells, is this ethical?

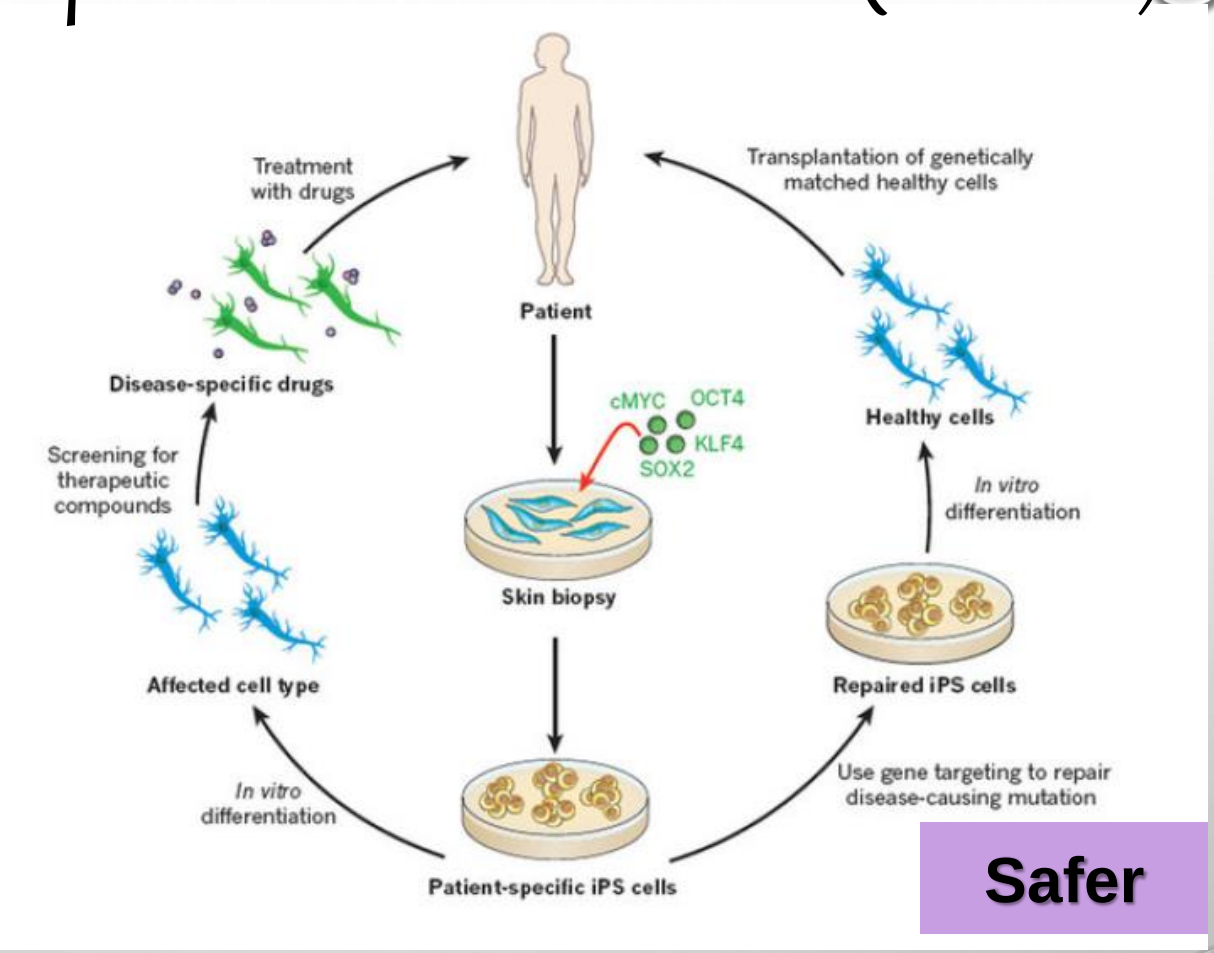
Prevention or alleviation of suffering

Respect the value of human life

Morals and religion

Induced Pluripotent Stem Cells (iPSCs)

Cells that resemble ESCs but they were made by converting differentiated cells (as fibroblasts) back into stem cells



Ethical

Safer

Autologous

Patient-specific

Generation of iPSCs

- **iPS cells were obtained by transducing embryonic and adult fibroblasts with defined transcription factors.**
  - **OCT3/4, SOX2, c-Myc, KLF4**
  - ✓**Different sets of TFs were used to generate iPSCs**

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

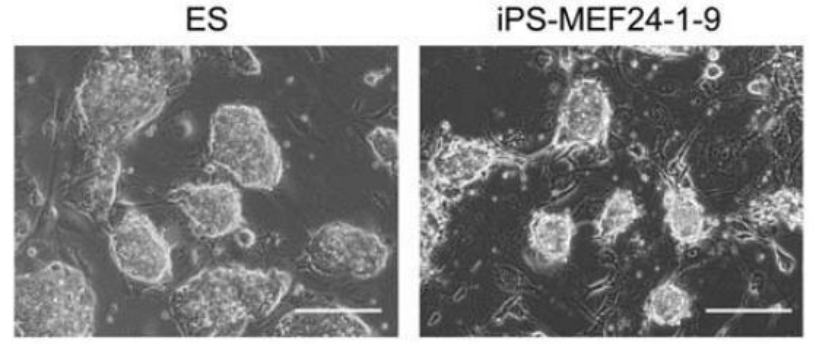
iPSCs were compared to embryonic stem cells in many aspects like:

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

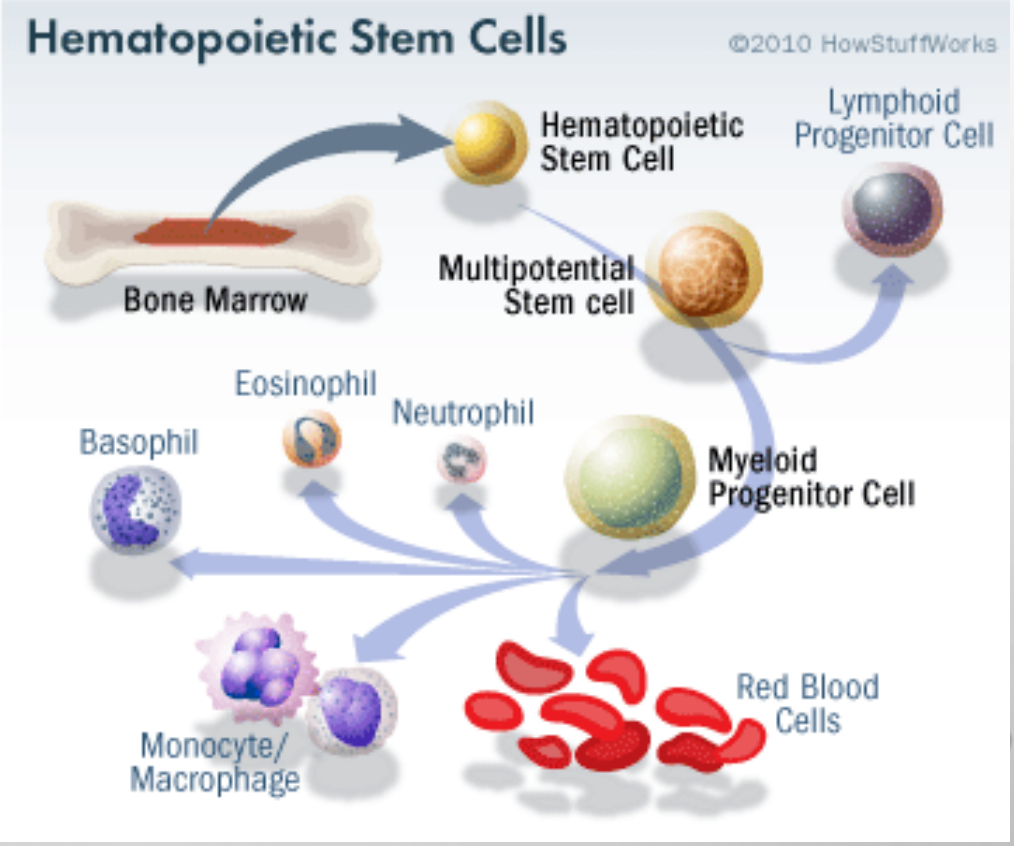
Undifferentiated cells found through out the body.

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

Types of adult stem cells

1. Bone marrow stem cells

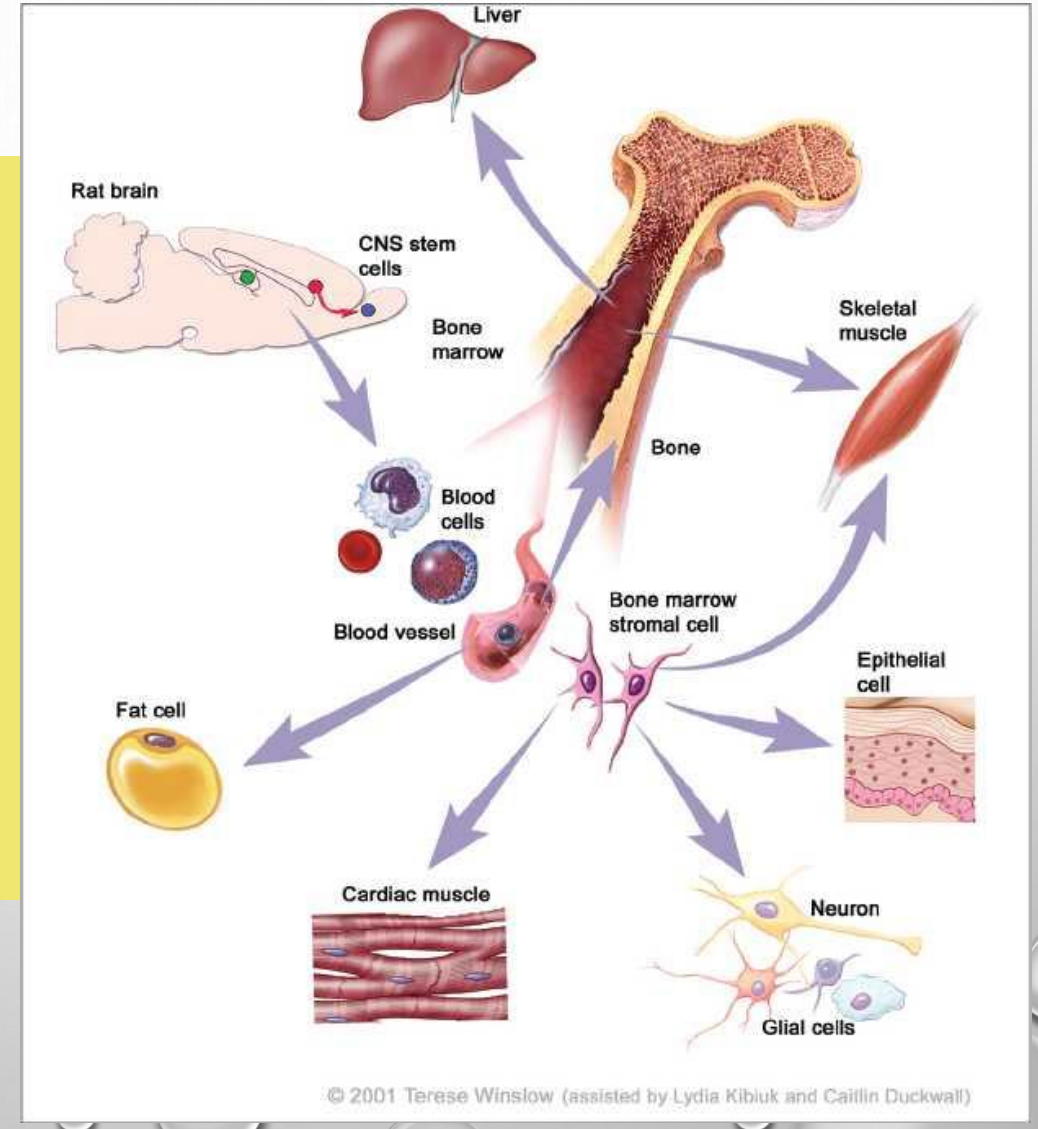
A. Hematopoietic stem cells that give different cells of the blood



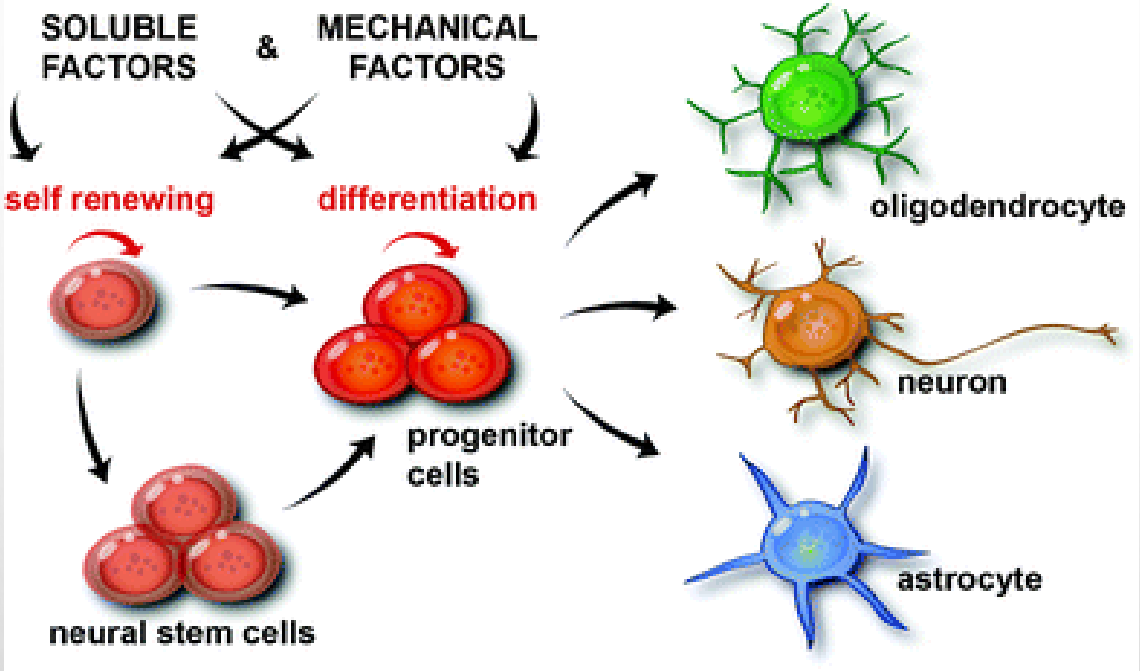
Types of adult stem cells

1. **Bone marrow stem cells**

B. Somatic stem cells *such as mammary stem cells and mesenchymal stem cells that give 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 important for neural tissue regeneration.

Types of adult stem cells

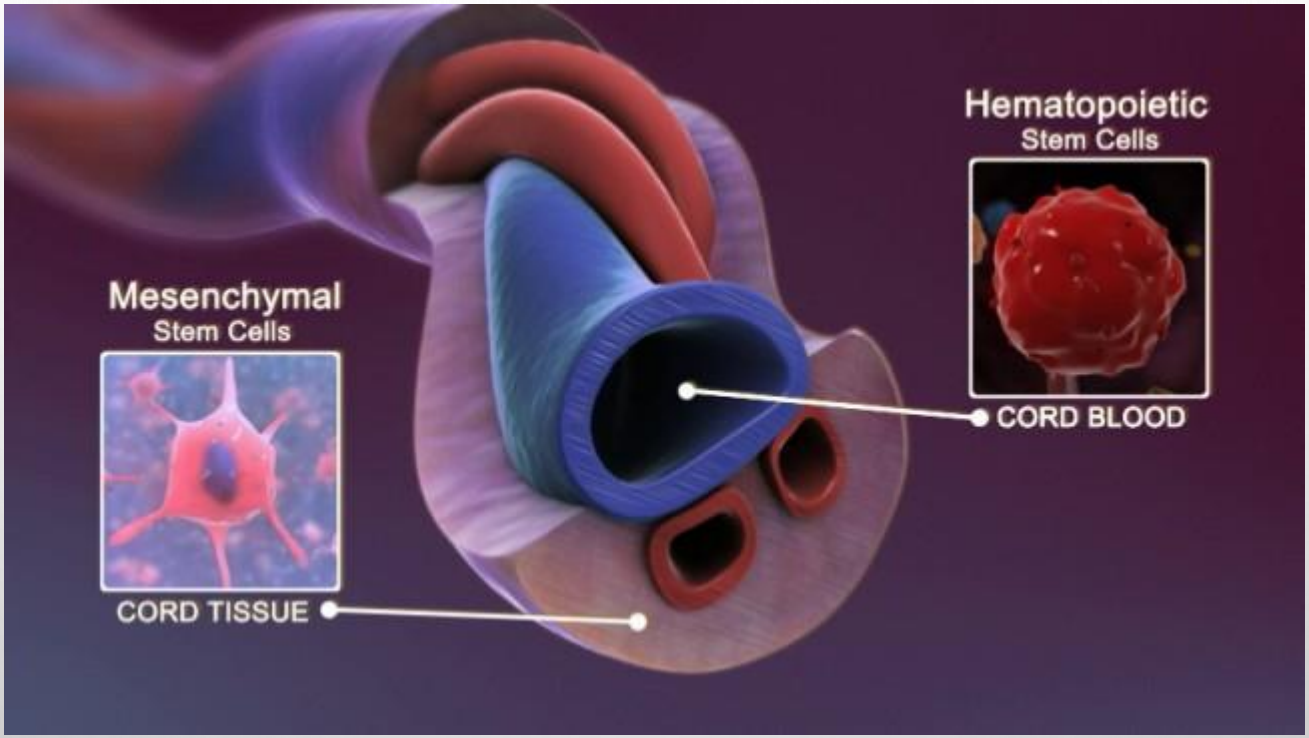
3. Adipose tissue-derived stem cells (ASCs).

Present in adipose tissue.

Can be obtained by liposuction.

It can differentiate to several cell types

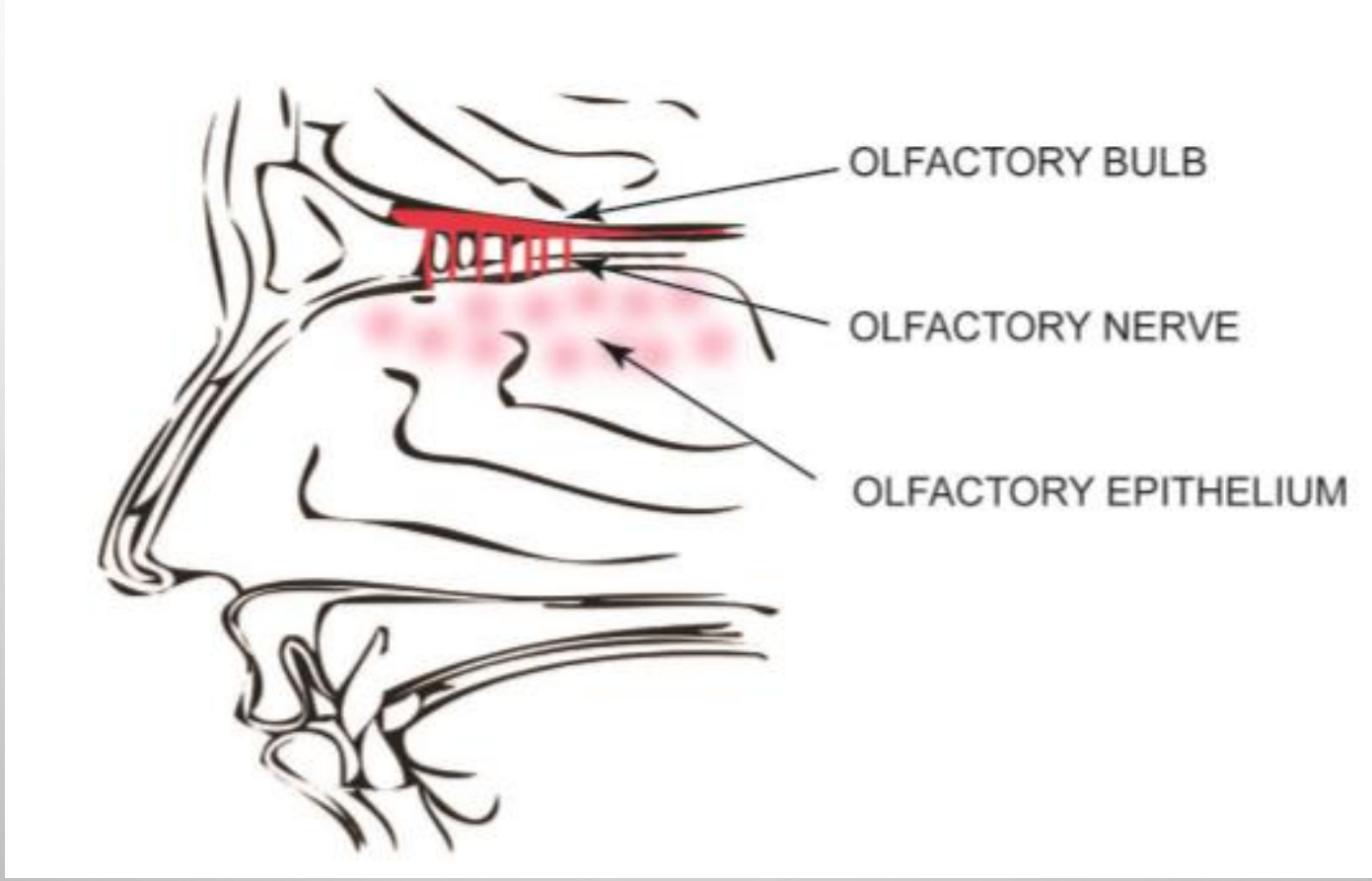
Types of adult stem cells



4. Umbilical cord stem cells.
Are mesenchymal stem cells and can differentiate to several cell types

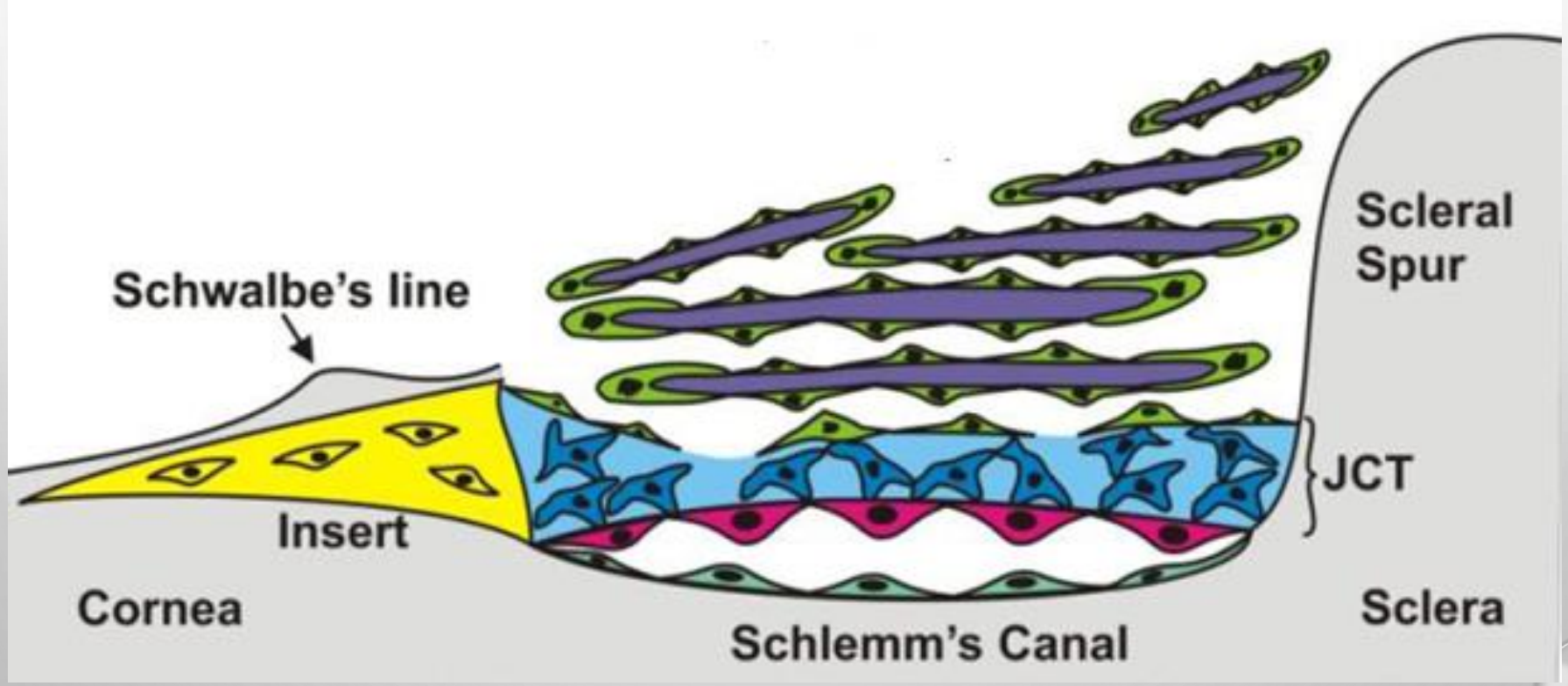
Types of adult stem cells

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



Types of adult stem cells

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



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

- ✓ 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

Why stem cell research is important?

- **Functional genomic studies** to understand human embryonic gene expression, genomic data mining, and bioinformatics.

- To study biological processes to understand **human developmental disorders** like birth defects, cancers, etc.

- Creating **human disease models** for drug discovery and development.

- **Cell-based therapy and regenerative medicine**.

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).

Neurodegenerative Diseases & Stem Cell Therapy

- 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.
- Ethical, regulatory, societal, and economical issues need to be addressed.

Main considerations when we use stem cells to treat neurodegenerative diseases

- What is required for the stem cell–based approach to be clinically competitive
- **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.
- The **variability** between neurodegenerative diseases in the **degree of disability** that they cause and in the therapeutic options that are available.

PD- symptomatic treatment

ALS- No efficient treatment

Main considerations when we use stem cells to treat neurodegenerative diseases

- The **cell type** to be regenerated and transplanted.

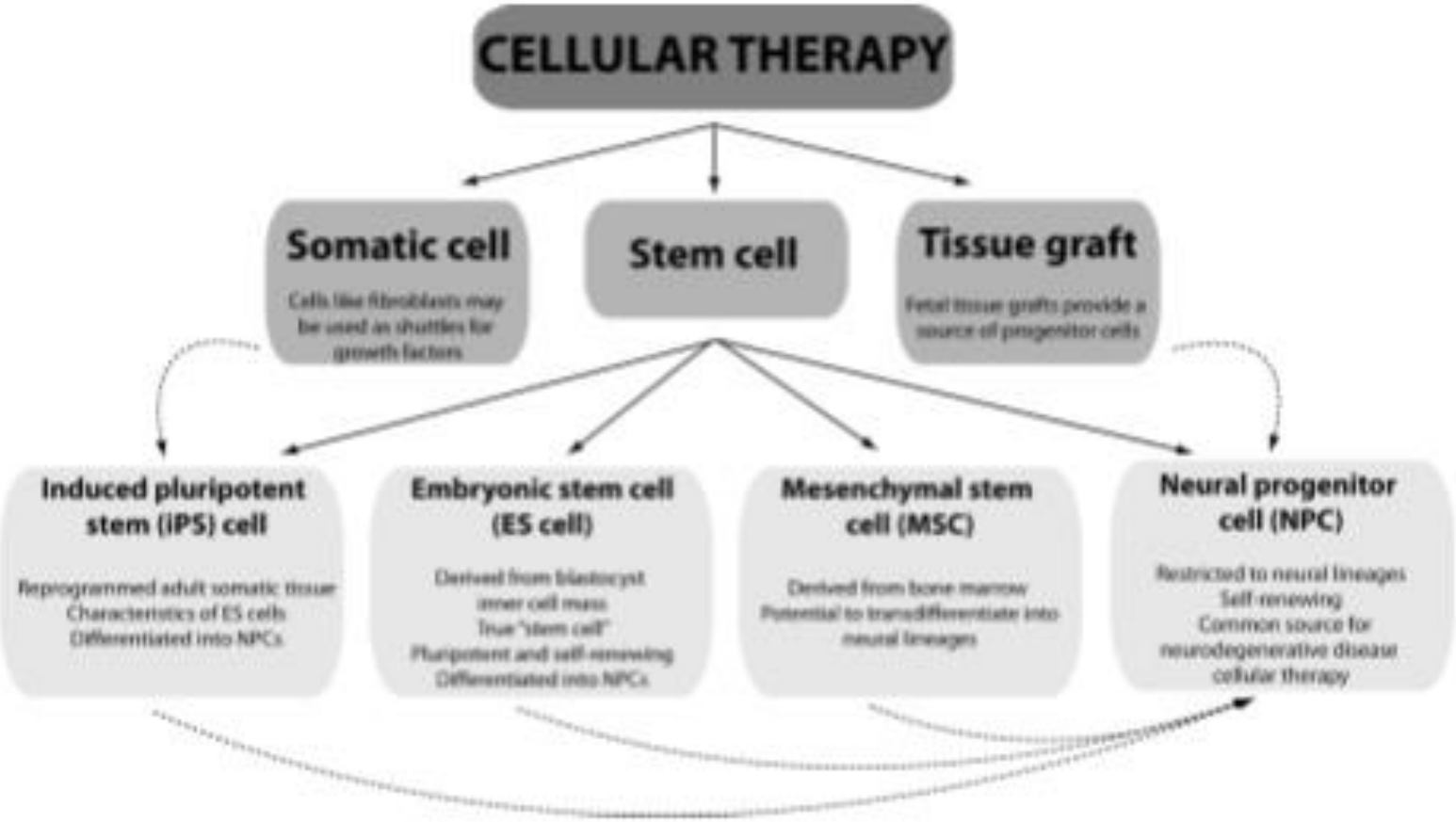
PD- dopamine neurons

ALS – motor neurons

Stroke and Alzheimer's disease-several cell types

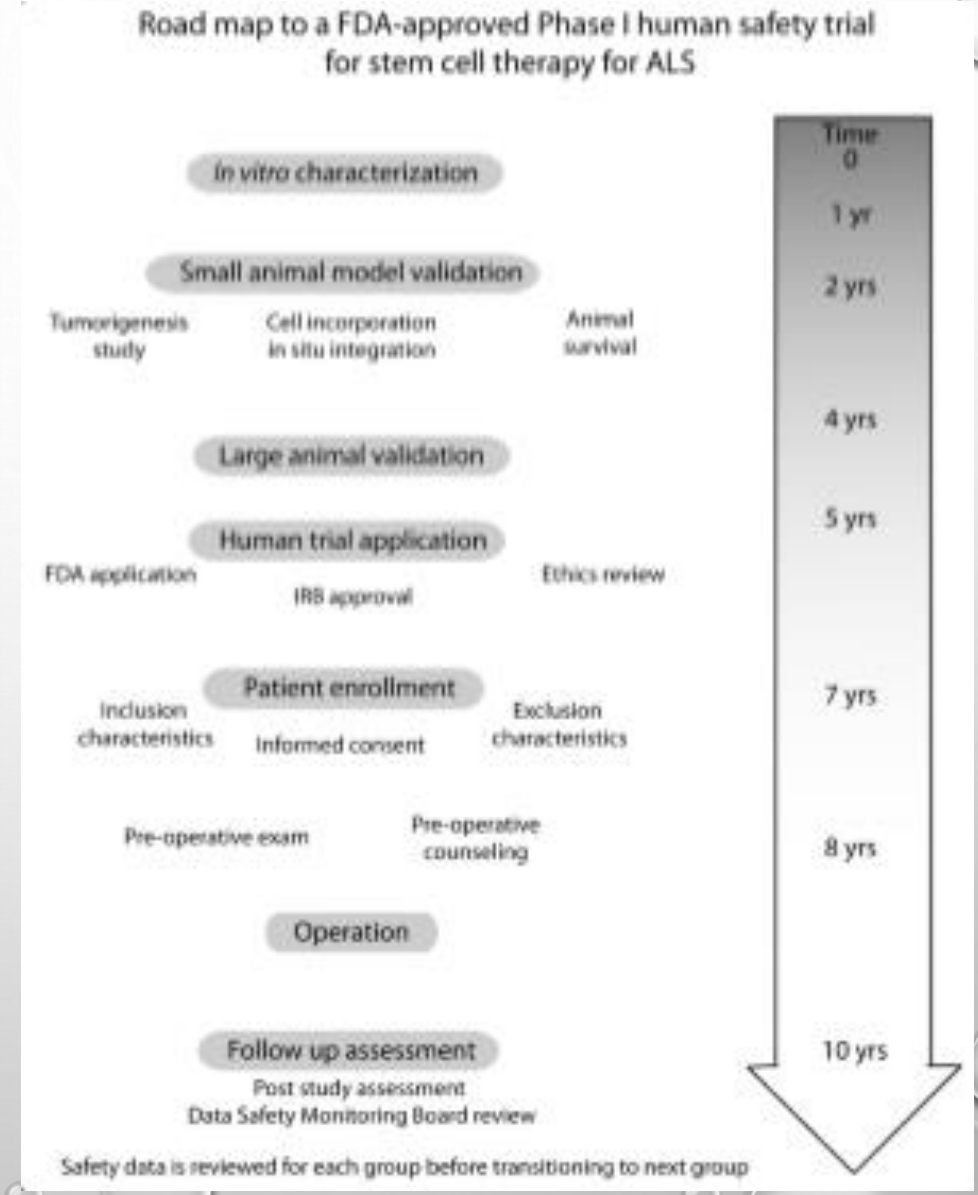
- The stem cell–based approach should show **substantial improvement** of functional deficits in animal models before their use in clinical application.
- To determine the **biological mechanism** underlying the observed effects of a stem cell–based treatment in an animal model. E.g. reconstruction of neuronal circuitry

Stem cell technology and cellular therapy classifications



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

- Research and medical ethics must be considered.
- Trials begin with cells in the dish, then small animal models, followed by large anima models and ending with clinical trials.
- No treatment with stem cells should be applied until it is approved by the Food and Drug Administration (FDA)



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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.

Parkinson's disease (PD)

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

Degeneration of nigrostriatal DA neurons is the main pathology

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

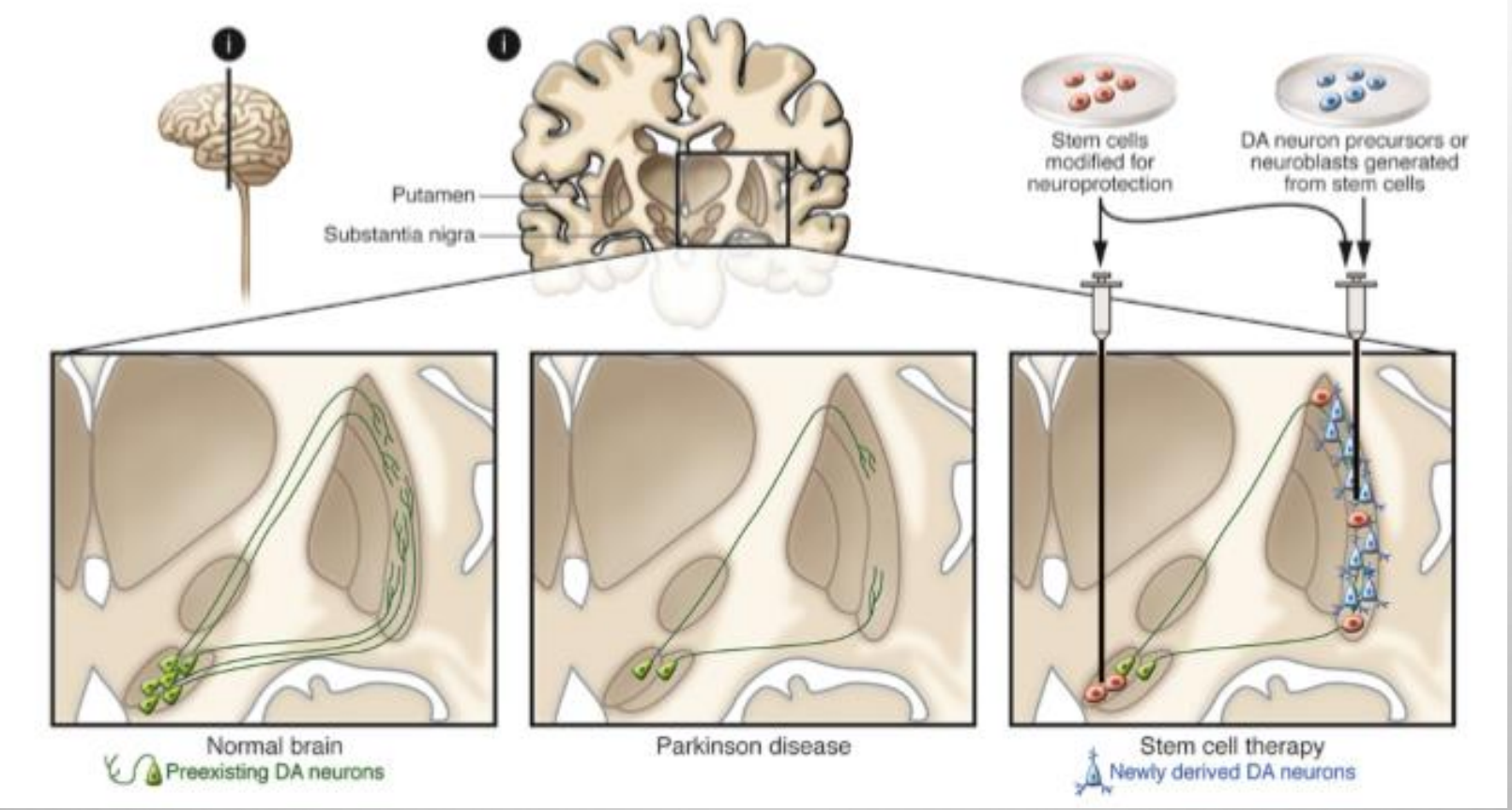
No Tx for dementia

iPSCs for modelling the genetically complex PD

Stem cell–based therapies for PD

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

- Other types of cells were tried for PD treatment but none gave highly improving results



Stem cell–based therapies for PD

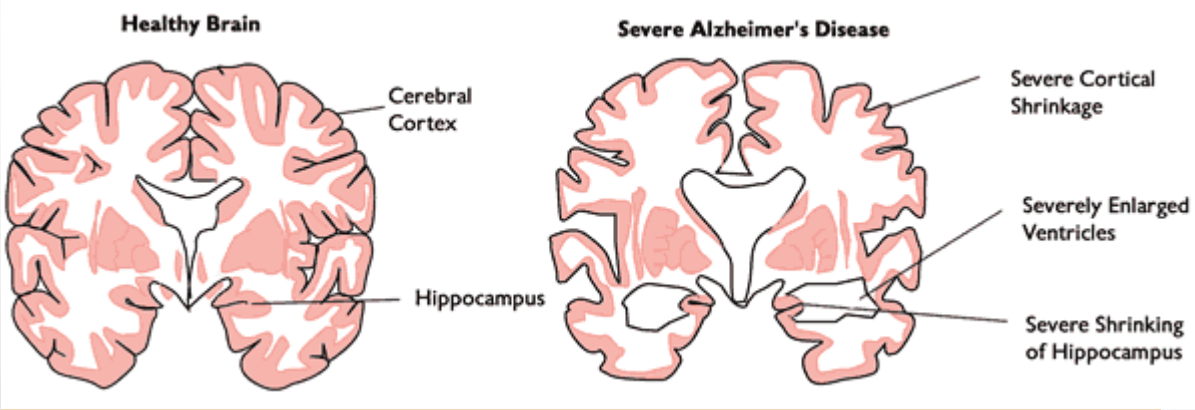
Pros	Cons
-The DA neurons that form from the transplanted tissue reinnervate the denervated striatum and become functionally integrated, restoring striatal DA release and giving rise to clear symptomatic relief in some patients.	-A small fraction of graft-derived DA neurons contain Lewy bodies (the hallmark of PD). - 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.
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

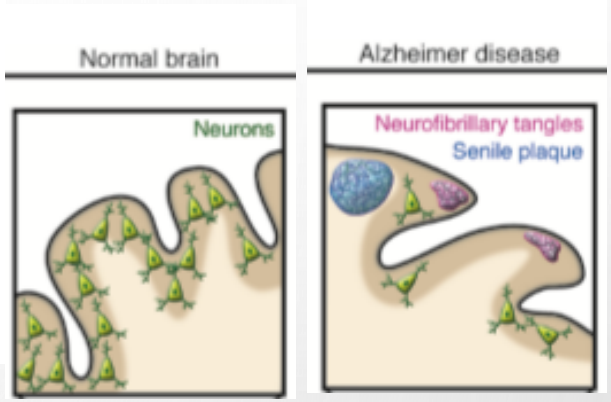
Stem cell–based therapies for PD

- **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.**

Alzheimer's disease (AD)





Memory impairment, cognitive decline, and dementia due to widespread and progressive pathological changes

Loss of several cell types (tissue) adds to the complexity of the disease.
Treatments were tried using cells as well as other approaches such as acetylcholinesterase inhibitors, which enhance cholinergic function, induce some temporary improvement in AD patients. Other approaches include nerve growth factor (NGF) releasing stem cells and anti-β-amyloid antibodies or β-amyloid–degrading protease neprilysin

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

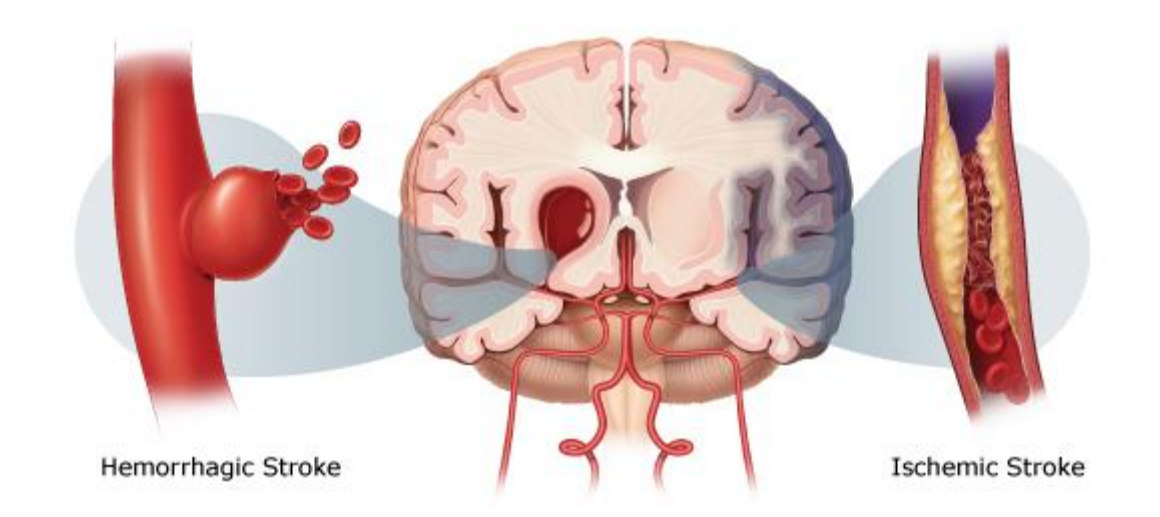
Stem cell–based therapies for AD

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

- ✓ Stem cells have to be pre-differentiated in vitro to **many different types of neuroblasts** for subsequent implantation in **many 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

Stroke

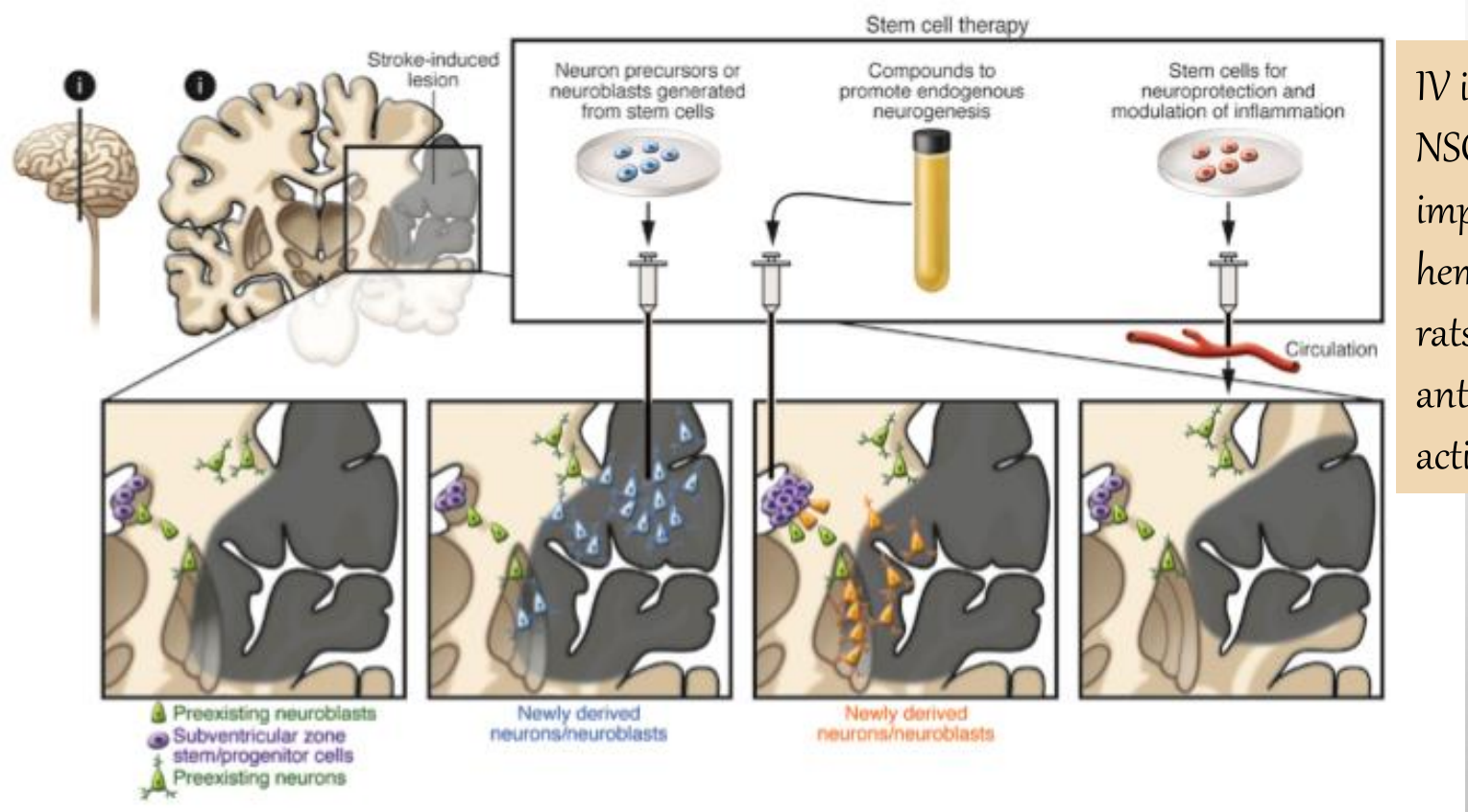
Ischemic stroke, caused by occlusion of a cerebral artery, leads to focal death of multiple neuron types, as well as oligodendrocytes, astrocytes, and endothelial cells.



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

Human ES cell–derived NSCs and 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.
- ✓ A clinical trial in stroke patients involving transplantation of clonal, conditionally immortalized NSCs isolated from human fetal cortex.

Stem cell–based therapies for stroke

80% of neuroblasts and neurons die during the first two weeks after formation at stroke site in rats.

How can we fix this problem?

A. Improvement in c**ell survival** by:

1. Inflammation-modulating agents
2. Caspase inhibitors
3. Neurotrophic factors

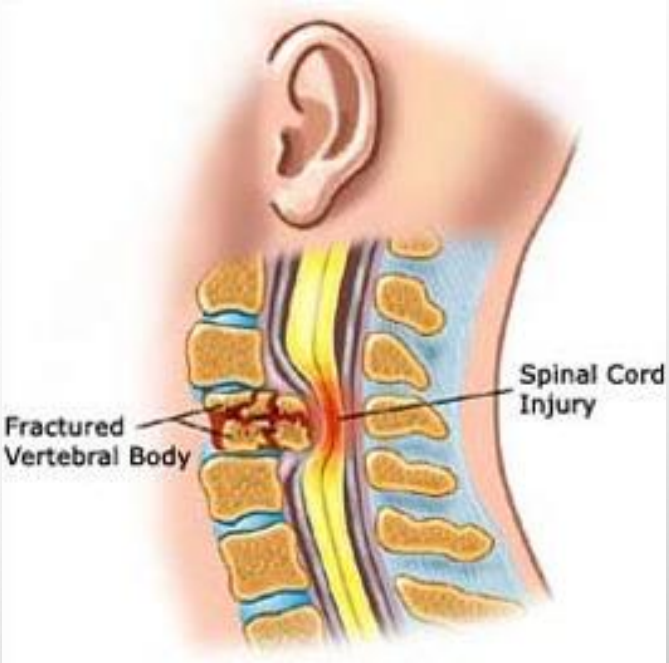
B. Promoting the **migration** of the new neurons to the damaged area by stromal cell–derived factor 1α [SDF-1α], monocyte chemoattractant protein–1, and matrix metalloproteinase–9.

C. Stimulation of the **differentiation of cortical neurons** that form in limited numbers after stroke by growth factor delivery.

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

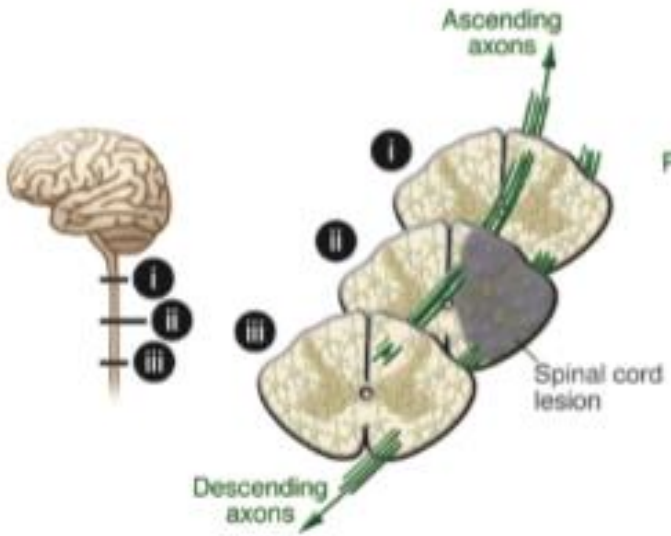


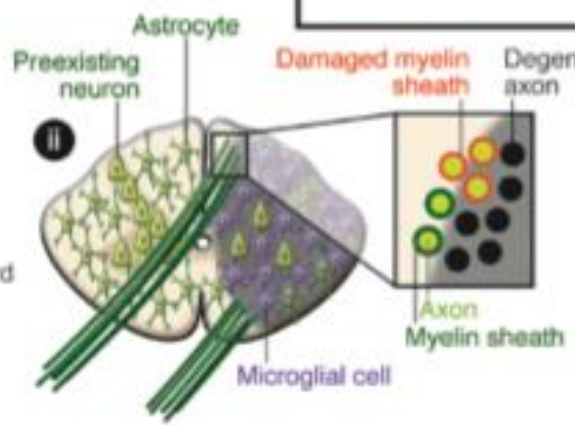
- ✓ Patients experience loss of movement, sensation, and autonomic control below the level of the injured spinal segment.
- ✓ Available treatments are ineffective.
- ✓ Different types of stem cells were tested and improved functional outcome in animal models through secretion of neurotrophic factors,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

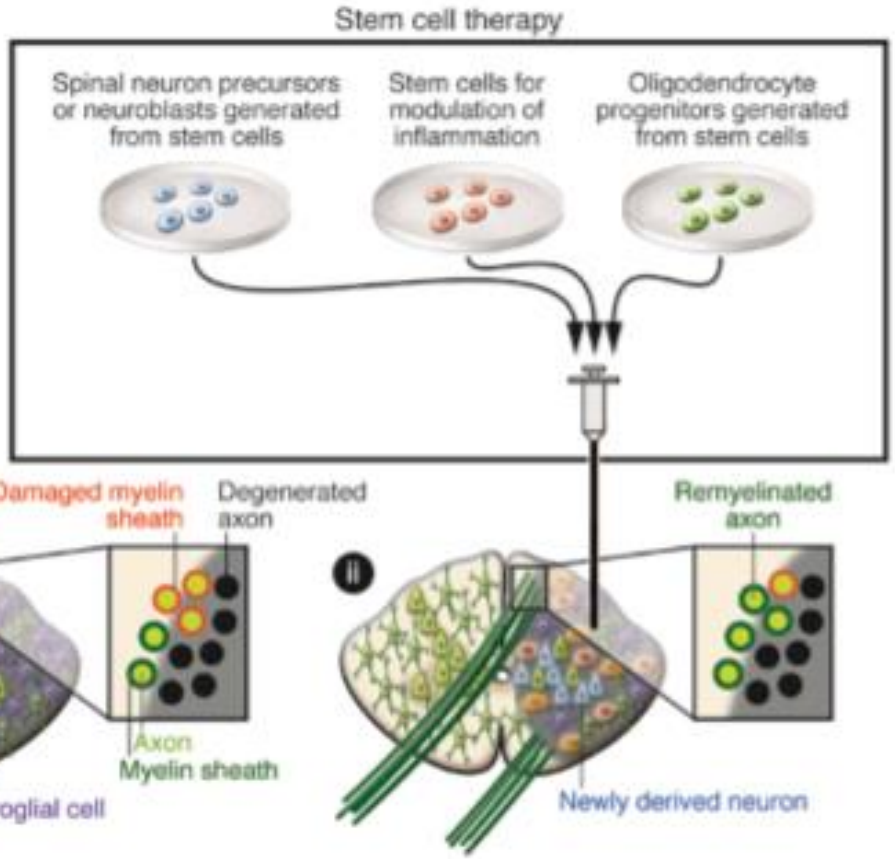
Stem cell–based therapies for spinal cord injuries

Several cell types and synapses were lost due to injury.
Treatment with stem cells should replace:
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)

Several stem cell types were tried







Stem cell–based therapies for spinal cord injuries

Before moving to clinic:

Determine how to control the proliferation of transplanted stem cells and their progeny

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

Stem cell–based therapies for spinal cord injuries

Several stem cell types were tried

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.
4. The mechanisms underlying observed improvements were unclear.

SUMMARY

None of the neurodegenerative disease can be treated safely and effectively by stem cells so far.

Further research has to be done to fine tune the use of stem cells as a therapy

Ethics MUST be considered when treating patients with stem cells. DO NOT CREATE ANOTHER PROBLEM TO THE PATIENT

For the disease we discussed, most of them has reached the stage of clinical trials but none succeeded

Do not be a victim of the propagandas that announce successful treatments everyday. Be aware and check any treatment before you apply it on patients. BE A SAFE DOCTOR.