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).

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.

e.g PD- symptomatic 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

another point to look at

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

another point

- 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

=> Is it just replacement of neurons or due to reconstruction of neuronal circuitry?
- Is it by inducing or activating neurological repair in the site by 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.

- Do we need to immuno-suppresion during befor the therapy.
- what are the potential SE associated with
- Are they safe to be administered by this pereint
- Are they going to cause problems later on. that might be more denegerous than the disease itself.
- what types of studies do we need to consider the (placebo) ideal point

- what are the expectations ?

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 (To replace the lost dopamine)

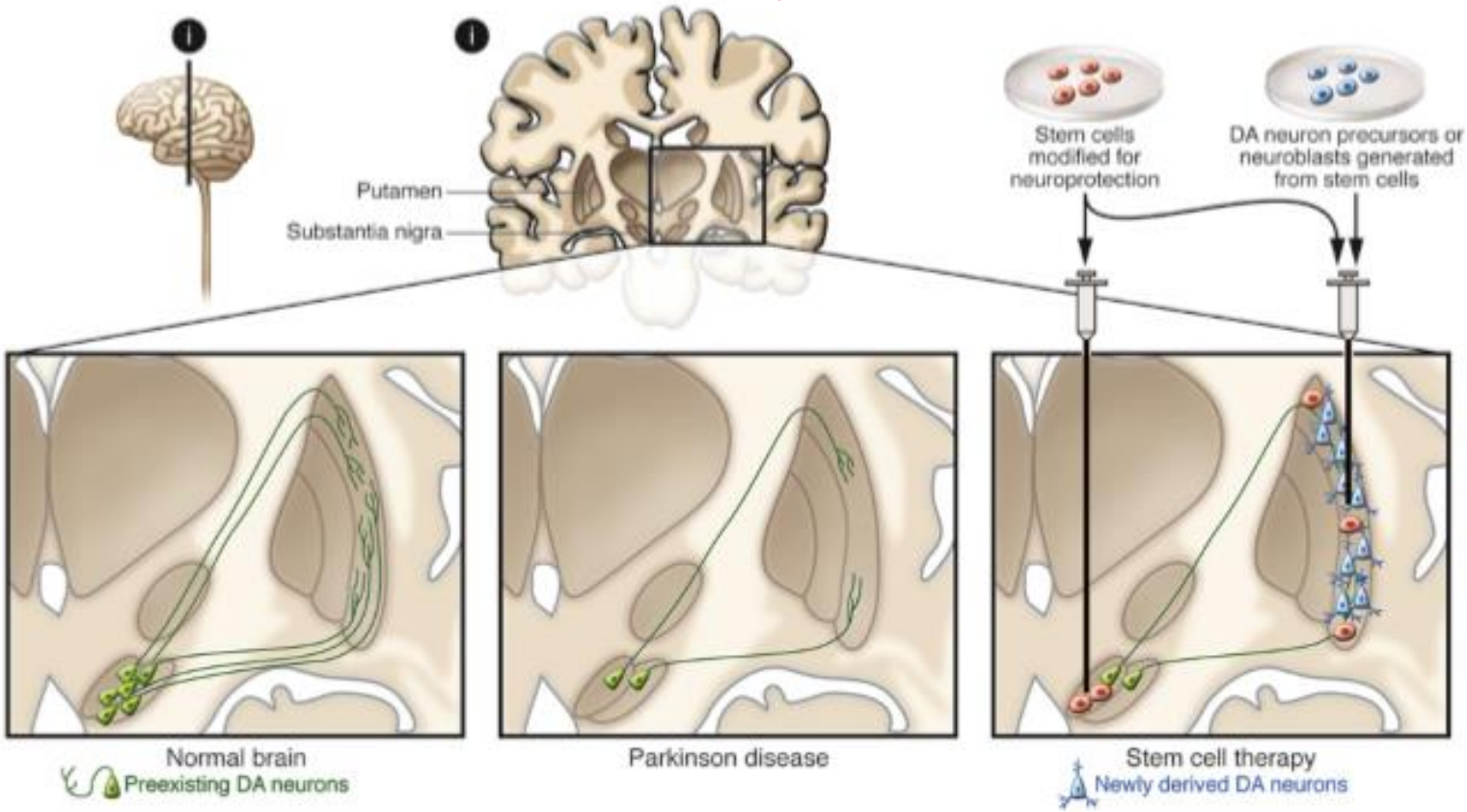
No Tx for dementia

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).

(dopaminergic)



Stem cell–based therapies for PD

↳ have advantages and dis.

Pros (Adv.)	Cons (Dis.)
-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). which means either the disease become transferred to them and become diseased neurons. - 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. (some patients improve in great amount and other didn't show good improvement).
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 and their limited amount.

Stem cell–based therapies for PD

Other sources of DA neurons:

- ✓ ES cells (embryonic stem)
- ✓ 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:

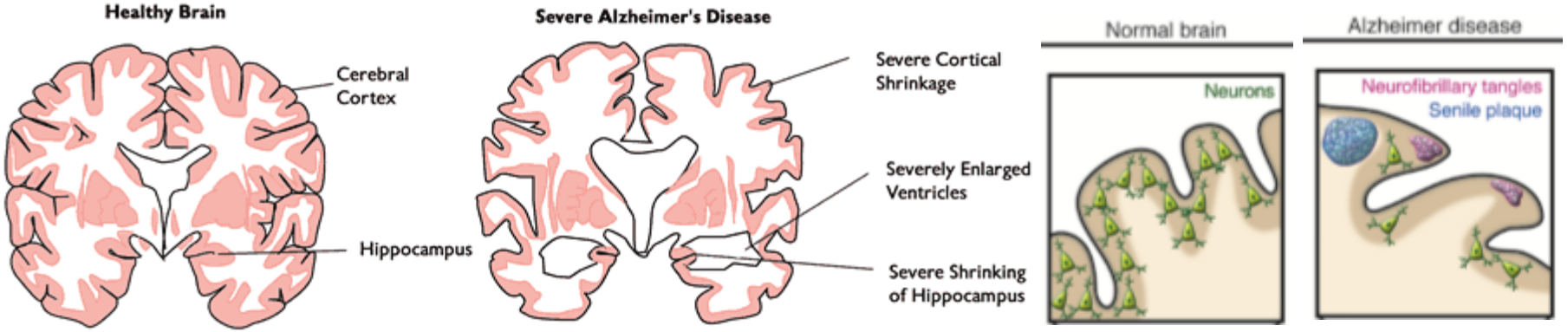
- ✓ PD is a **multisystem disorder**, if **nondopaminergic** systems are affected, they will not improve by intrastriatal DA grafts.
- ✓ **Substantial re-innervation** of striatum has not been demonstrated.
- ✓ **Restoration of DA release** in vivo has not been demonstrated.
- ✓ **Marked improvement** (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.** and this might be hard on the practical.

Clinical trials

- By International Stem Cell Corporation (ISCO)
- 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.

Alzheimer's disease (AD)



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

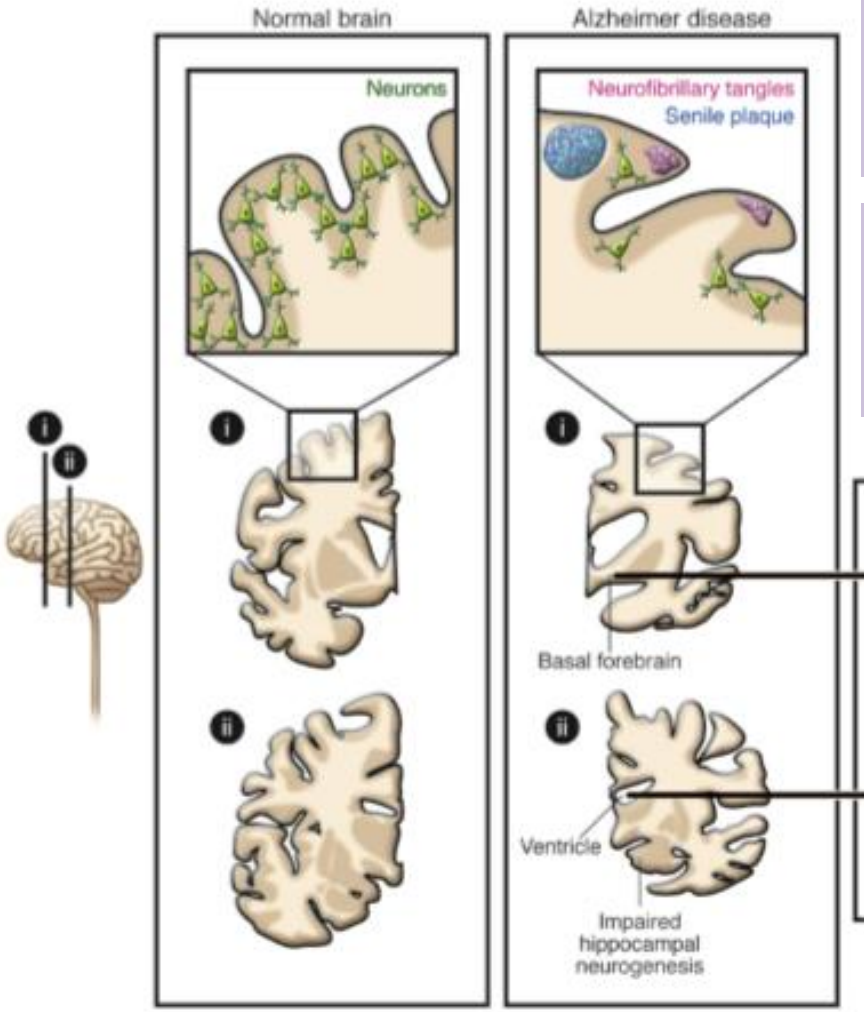
Neuronal and synaptic loss, neurofibrillary tangles, and deposits of β-amyloid protein involve the basal forebrain cholinergic system, amygdala, hippocampus, and cortical areas.

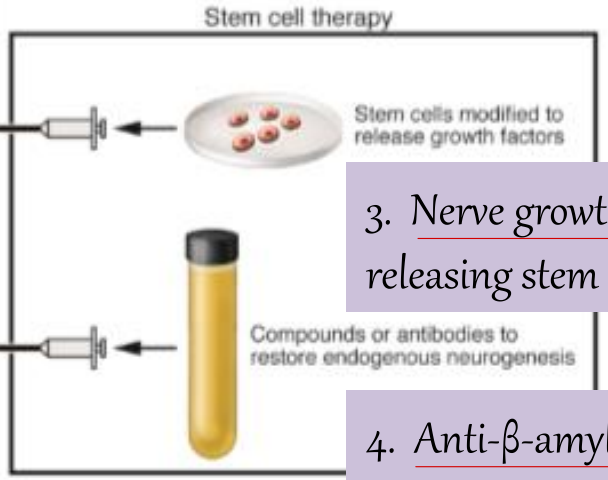
Stem cell–based therapies for AD

↳ Different ways tried to treat AD.

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

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.

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:

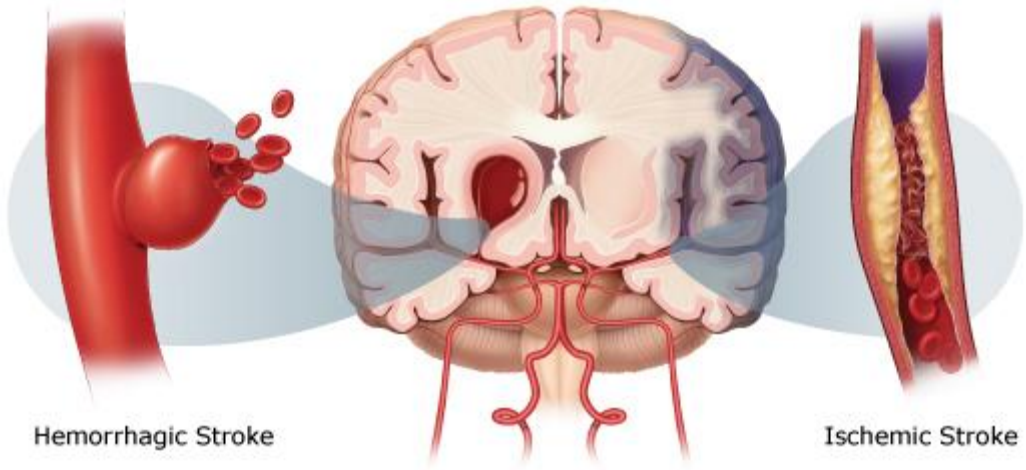
- ✓ Stem cells have to be pre-differentiated in vitro to **many different types of neuroblasts** for subsequent implantation in **many brain areas.**
- ✓ **For a long-lasting symptomatic benefit, cholinergic cell replacement requires intact target cells** (host neurons that the new cholinergic neurons can act on) that are damaged in AD.
- ✓ Stem cell–based cell replacement strategies are very far from clinical application in AD

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

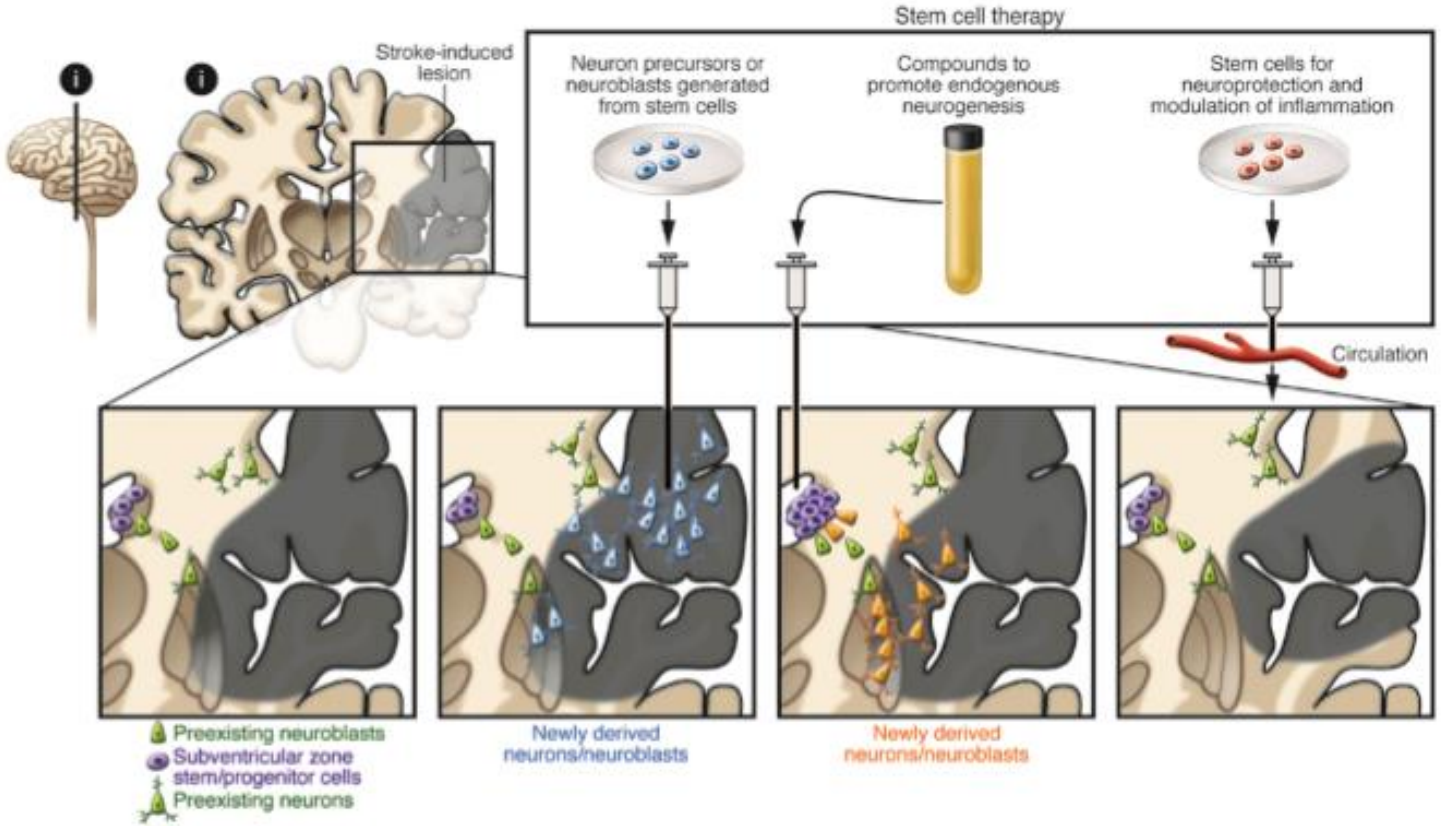
Ischemic stroke, caused by occlusion of a cerebral artery, leads to focal death of multiple neuron types, as well as oligodendrocytes, astrocytes, and endothelial cells.



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

Clinical trials

induced pluripotent

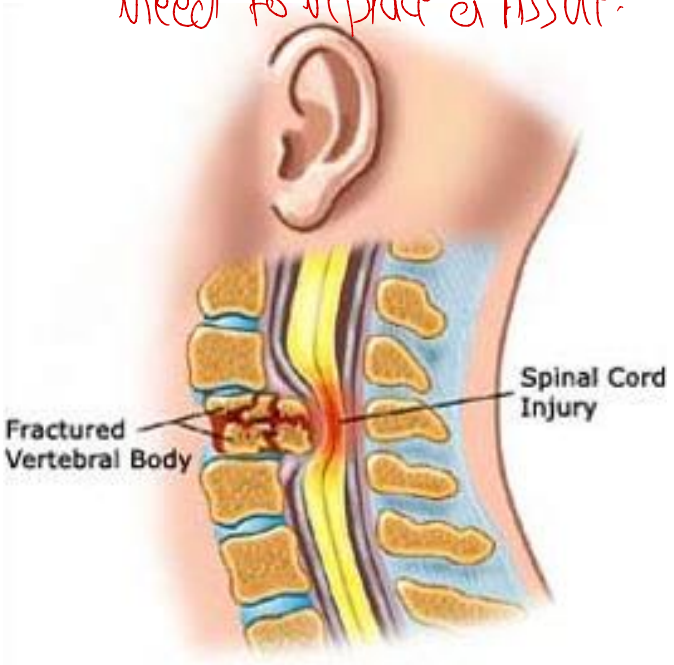
- Transplanted ESCs, iPSCs, and NSCs can replace the missing brain cells in the infarcted area
- Non-neuronal adult stem cells, such as MSCs provide trophic support to enhance self-repair systems such as endogenous neurogenesis

Spinal cord injuries

*here we loss tissues rather than cells, so we need to replace a tissue.

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



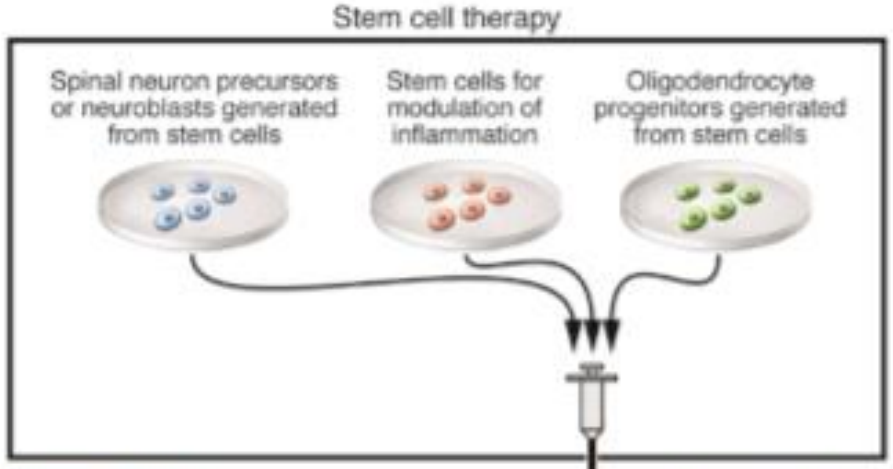
- ✓ Patients experience loss of movement, sensation, and autonomic control below the level of the injured spinal segment.
- ✓ Available treatments are ineffective.
- ✓ Different types of stem cells were tested and improved functional outcome in animal models through **secretion of neurotrophic factors,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

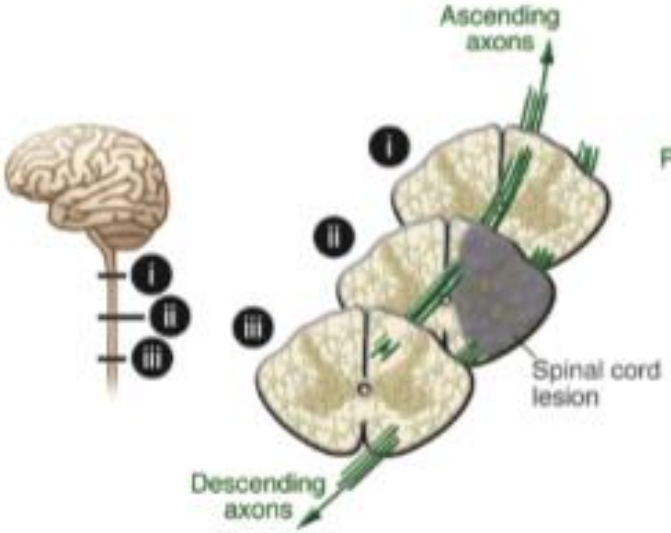
Stem cell–based therapies for spinal cord injuries

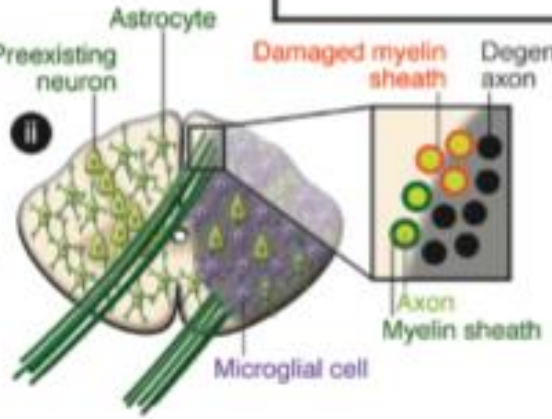
Formation of **neurons, oligodendrocytes, & astrocytes**.

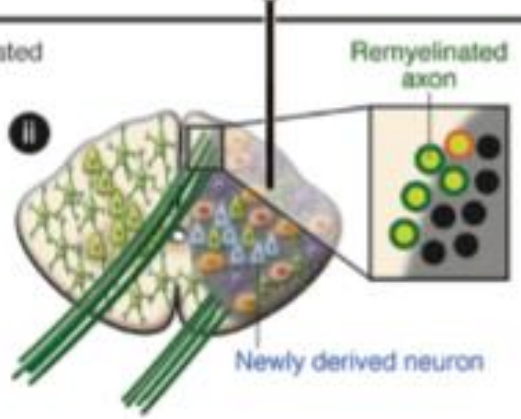
Formation of **synapses and axons**

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:

Determine how to control the proliferation of transplanted stem cells and their progeny Because we need them to stay in certain amount and be able to form certain type of synapses to perform the required function.

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

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. Few of them moved to clinic as a final treatment

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.

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.

* The cost is very high.

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

⇒ It has to move through a lot of studies and animal models.