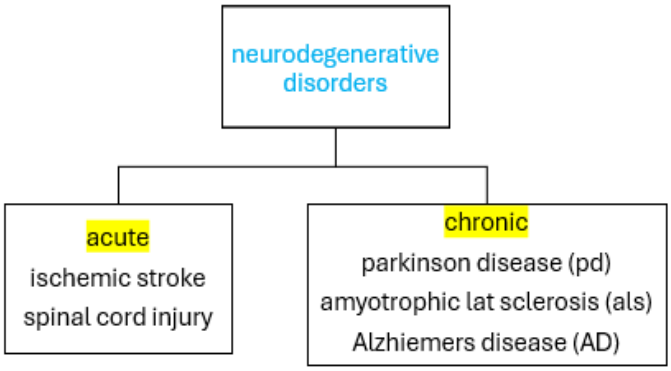
Using stem cells in neurodegenerative disorders

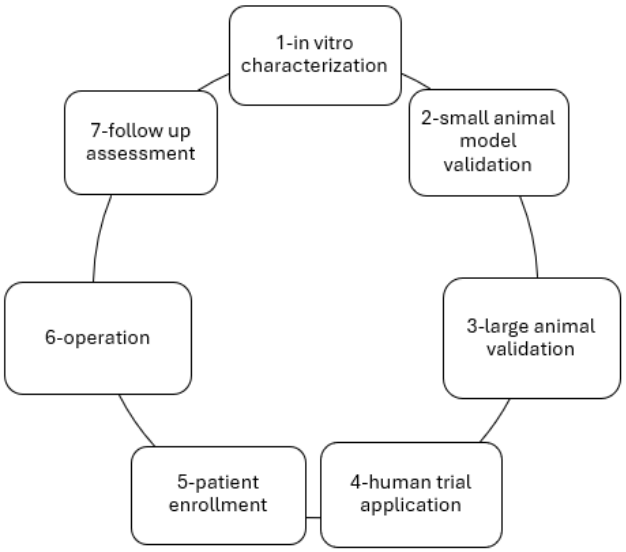


They are conditions in which neurons and glial cells in the brain and spinal cord are lost.

Before using them we should consider some points:

1-their competence with other therapies (are they worth it?)	2-their risks (toxicity,immune response,tumor formation)	3-do they cure disability that the disease causes?or just symptoms?
4-the type of stem cell a certain disease requires to be transplanted	5-do they cause substantial improvement?	6-mechanism of action of stem cell used
7-their inclusion or exclusion criteria	8-do they meet patient and operator's expectation from treatment?	9-type of study to be used (best type of study is double blind placebo)
10-their safety		

In order to translate stem cell therapy from bench to bed we need to use the following steps:



this usually takes 10 years

note: overall neurodegenerative stem cell therapy:

1-clinical trials using it have been initiated

2-it hasn't been proven to be beneficial yet

3-some clinics offer it although it has poor clinical basis

4-its costly

5-it has some ethical, economical and regulatory issues.

Stem cell therapy for Parkinson's disease

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

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). (disease was transferred to the cells). - Availability of human embryonic mesencephalic tissue is limited. (hard to get).
11–16 years after transplantation, cell replacement remains a viable therapy.	Variability of functional outcome after transplantation is high. (some improve, some not)
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

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

Sources of DA neurons: ES 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

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

1-PD is a multisystem disorder that can have other nondopaminergic causes

2-no proof of substantial re-innervation from this therapy

3-Restoration of DA release in vivo has not been demonstrated.

4-Marked improvement (50-70%) hasn't been demonstrated

5-Risk of tumor formation

6- The need to inject cells at all sites of injury.

Clinical trials:

By: International Stem Cell Corporation (ISCO)

Parthenogenetic cells derived of unfertilized oocytes after suppression of the second meiotic division

Drawbacks: used cells are derived from PAX6-positive instead of the normal PAX6-negative (may cause problems in future)

Alzheimer's disease

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

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

note: damage here includes tissues not one cell

modalities used in stem cell based therapies:

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

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

1-stem cells have to be pre-differentiated to many types of neuroblasts that work for the many damaged brain areas included.

2-cholinergic cell replacement requires an intact area as target cells which is hard to find within damaged tissue.

clinical trials:

By: stemedica cell technologies

Stem cells from healthy people to mild to moderate AD patients

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.

Note: 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:

1-Human ES cell–derived NSCs and MSCs, grafted into rat stroke site, Migrated toward the lesion and improve forelimb performance.

2-IV injection of human NSCs induced improvements after hemorrhagic stroke in rats, probably through anti inflammatory actions

what stops us from using them?

1-No substantial clinical improvements were detected

2-studies are still on going about (autologous bone marrow–derived cells & immortalized NCS)

3-80% of neuroblasts and neurons die 2wks post transpla

clinical trials:

1- Transplanted ESCs, iPSCs, and NSCs can replace the missing brain cells in the infarcted area.

2-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

- ✓ 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 cells should be able to :

1-replace: neurons, oligodendrocytes, & astrocytes.

2-re-establish: synapses and axons

3-induce:remyelination from oligodendrocyte progenitor cells (OPC)

what should we determine before we use it clinically:

1-how to control the proliferation of transplanted stem

Cells and their progeny

2-how to enhance the differentiation of the lost cells

By neurons that r already available in site of injury

3-how they can renew lost synaptic contacts

Other stem cell types:

Umbilical cord blood, bone marrow–derived HSCs, and

MSCs.

Problems:

1-poorly characterized (hard to differentiate)

2-lac of efficacy evidence

3-we give physiotherapy with stem cells therapy so

Theres a possible chance improvement was due to phy

4-mechanisms are unclear