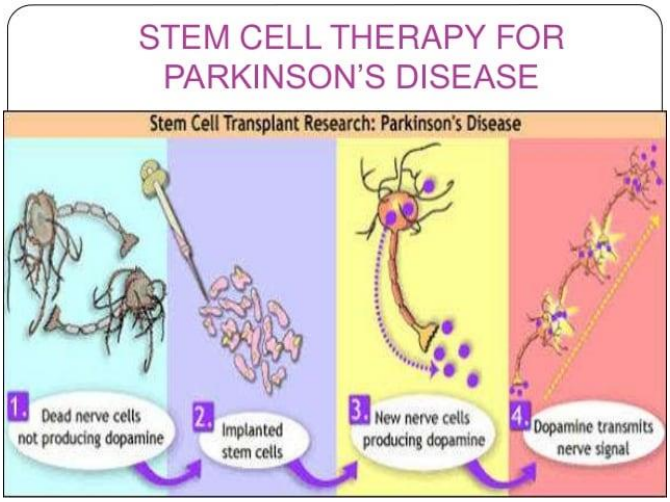


STEM CELL THERAPY IN PARKINSON'S DISEASE

CONTENTS

Development

Function

Current research

OVERVIEW

Stem cell biology is a rapidly expanding field.

- In vitro as research tools for modeling human neurological diseases and drug screening.
- In vivo in regenerative medicine has a complex pathophysiology that is by no means fully understood and involves multiple brain structures and signaling pathways.
- There are three broad approaches to selection of a therapeutic target
  - 1. Restoration of DA synthesis in the dorsal striatum;
  - 2. Modulation of activity in the basal ganglia downstream of the
  - striatum; and
  - 3. Modification of disease progression by neuroprotection.

A BRIEF HISTORY

- Discovered ways to derive embryonic stem cells from early mouse embryos nearly 30 years ago, in 1981.
- The detailed study of the biology of mouse stem cells led to the discovery, in 1998, of a method to derive stem cells from human embryos and grow the cells in the laboratory. These cells are called human embryonic stem cells.
- The embryos used in these studies were created for reproductive purposes through in vitro fertilization procedures. When they were no longer needed for that purpose, they were donated for research with the informed consent of the donor.
- In 2006, researchers made another breakthrough by identifying conditions that would allow some specialized adult cells to be "reprogrammed" genetically to assume a stem cell-like state. This new type of stem cell is now known as induced pluripotent stem cells (iPSCs). *iPSCs has initially produced by Shinya Yamanaka at Kyoto University in 2006 .*

- Stem cells have two essential properties:
  - Self-renewal
  - Multipotentiality/pluripotency.

- ESSENTIAL PROPERTIES OF STEM CELLS
- FOR USE IN CLINICAL TRANSPLANTATION
  - Capable of clonal propagation in vitro
  - Genetic stability at high passage
  - Integration within the host brain following
  - transplantation
  - Migration and engraftment at sites of damage
  - Correct differentiation into appropriate neural cell
  - types
  - Functional benefits
  - Lack of side effects

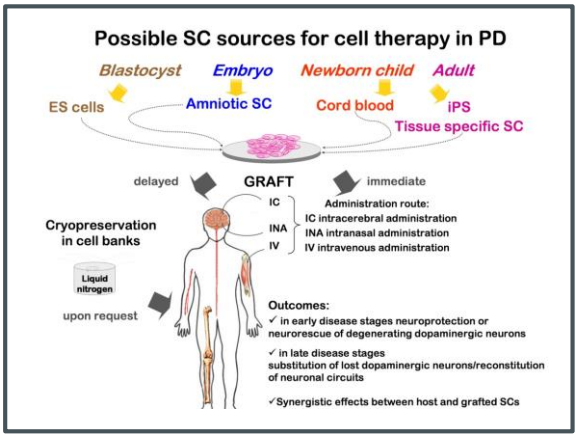
TYPES

- Totipotent cells- can form an entire organism autonomously. (e.g., zygote.)
- Pluripotent cells- can form almost all of the body's cell lineages (endoderm, mesoderm, and ectoderm), including germ cells(e.g., ESCs) .
- Multipotent cells- can form multiple cell lineages(e.g., HSCs)
- Oligopotent cells- can form more than one cell lineage but are more restricted than multipotent
- cells(e.g.,NS cells)
- Unipotent cells or monopotent cells- can form a single differentiated cell (e.g. spermatogonial stem [SS] cells)

SOURCES OF STEM CELLS	Human embryonic stem cells (ESC)	Human umbilical cord blood cells (UCB)	Immortalised cell lines
Foetal neural stem cells	Adult neural stem cells (NSC)	Bone marrow derived cells	Induced pluripotent cells (iPS)

SOURCE OF STEM CELLS

PARKINSON'S DISEASE



- Embryonic stem cells (ESCs) are derived from the inner cell mass of blastocysts, can differentiate into three germ layers,and can develop into several cell types (Fuet al., 2015). Issues that arise with this cell type include ethical concerns, immune system complications, and potential tumor formation.
- Induced pluripotent stem cells (iPSCs) are unique because we can obtain their embryonic state by reprogramming adult cells with the addition of transcription factors. Fibroblasts are most used because they are easy to obtain (Duncan & Valenzuela, 2017).
- Mesenchymal stem cells (MSCs) are multipotent cells that can be harvested from various tissues such as umbilical cord blood or Wharton's jelly (gelatinous substance within the umbilical cord), bone marrow (BM-MSCs), and adipose tissue (Duncan & Valenzuela, 2017). MSCs cannot differentiate into neural cells but rather induce neural recovery by producing trophic factors that in turn stimulate repair, endogenous neurogenesis, and modulation of inflammation (Liang et al.,2014).

ESSENTIAL FUNCTION

- For a stem cell therapy to be successful, it must restore DA in lacking neurons of the SN and consequently alleviate the motor symptoms associated with PD.
- The therapy should enable 100,000 or more DA neurons to survive long term, and the grafted cells should re-establish a dense terminal network throughout the striatum to functionally integrate into the host's neural circuits (Fu et al., 2015).

Table 1 | **Functional outcome after bilateral intrastriatal nigral grafts in clinical trials***

Surgical centre	Trial design	No. of cases	No. of ventral mesencephalon per putamen	Graft placement	[18F]-DOPA uptake (%increase/ %normal)	UPDRS motor score (% change)	Time in 'off' (% change#)	L-DOPA doses (% change#)	References
Lund‡	OL	4	4.9	Put	60/52	–30	–59	–37	33
	OL	2	2.5	C + Put	87/68	–50 (total)	–50, NR	0, –70	35
	OL	5	2.8 (+L)	C + Put	55/48	–40	–43	–45	34,48
Tampa	OL	6	3.0–4.0	P Put	61/55	–30	–43	–16	49
Créteil	OL	3	1.0–1.5	Put	NR§	–6	15	NR	50
		6	3.0			–33	–66		
Halifax	OL	2	3.25 (+G)	P Put	107/62	–32 (total)	–50	NR	51
Denver	DBPC	19	2.0	Put	40/NR	–18‖	NR	No change	1

INITIAL STEM CELL TRIALS

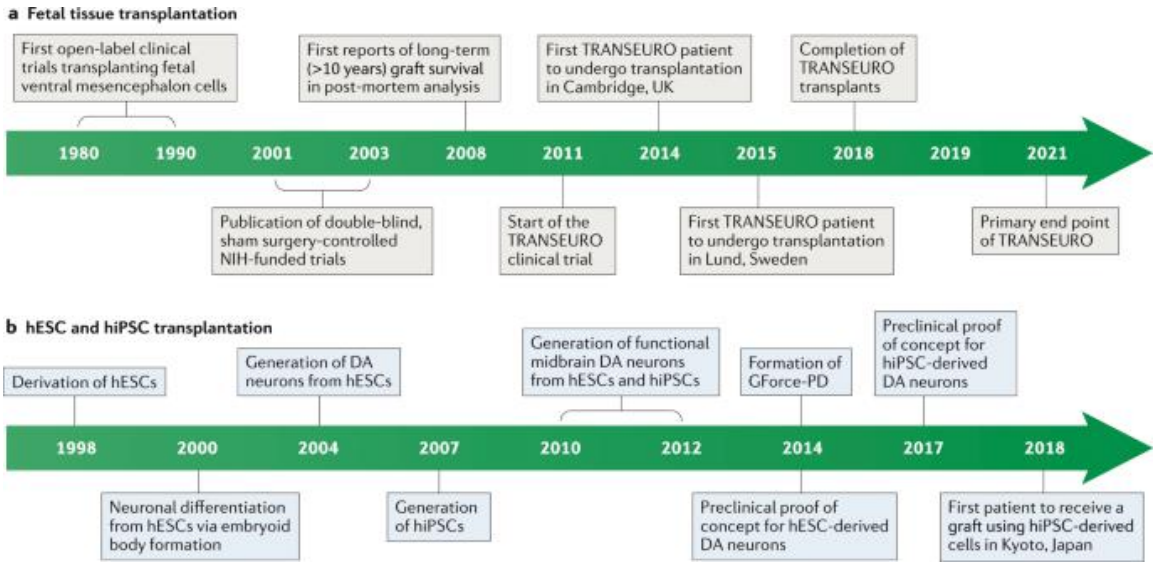
DIFFICULTIES WITH THE EARLY STEM CELL TRIALS

- The two patients reported on now fell into the former category. Both men now have a better UPDRS motor score than their original baseline. It gradually improved after transplantation and then leveled off.
- Both men tapered off their oral levodopa use, and neither has developed dementia.
- Some graft-induced dyskinesias did occur after surgery, but the benefits outweigh that side effect, wrote the authors.
- Postmortem data from other graft recipients showed Lewy bodies in some transplanted cells
- **MIXED RESULTS !**

2 KEY TRIALS

In (July 30), researchers at Kyoto University in Japan announced that they were launching a clinical trial to treat Parkinson's disease using reprogrammed adult stem cells.

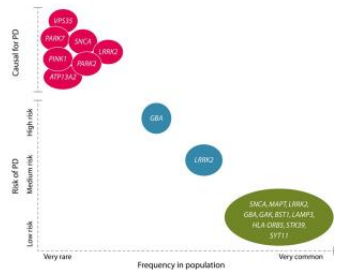
TRANSNEURO (European consortium) :a European Union–funded multicenter clinical trial of fetal nigral cell transplantation.



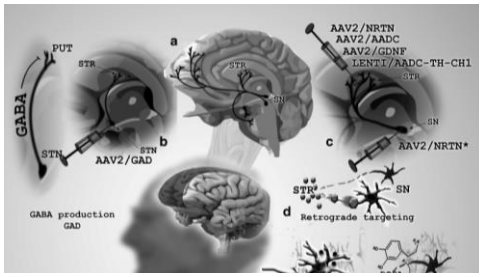
Terminated	Autologous Mesenchymal Stem Cell Transplant for Parkinson's Disease	•Parkinson's Disease	•Procedure: Autologous Bone marrow derived stem cellstransplant	•Jaslok Hospital And Research Centre Mumbai, Maharashtra, India	
2	Unknown †	A Study To Evaluate the Safety and Efficacy of Human Neural Stem Cells for Parkinson's Disease Patient	•Parkinson Disease	•Biological: human neural **stem cell**	•Department of Neurology, Second Affiliated Hospital of Soochow University Suzhou, Jiangsu, China
3	Enrolling by invitation	Umbilical Cord Derived Mesenchymal Stem Cells Therapy in Parkinson's Disease	•Parkinson's Disease	•Biological: mesenchymal **stem cells**	•Hebei Newtherapy Bio-Pharma Technology Co., Ltd Shijiazhuang, Hebei, China
4	Recruiting	Use of Mesenchymal Stem Cells (MSCs) Differentiated Into Neural Stem Cells (NSCs) in People With Parkinson's (PD).	•Parkinson Disease	•Biological: Injection of Umbilical cord derived MSCs	•**Cell** Therapy Center, University of Jordan Amman, Jordan
5	Unknown †	Mesenchymal Stem Cells Transplantation to Patients With Parkinson's Disease	•Parkinson's Disease	•Biological: bone marrow derived mesenchymal **stem cells**	•Guangzhou General Hospital of Guangzhou Military Command Guangzhou, Guangdong, China
6	Unknown †	Parkinsonian Brain Repair Using Human Stem Cells	•Idiopathic Parkinson Disease	•Drug: Human **Stem Cells**	•Hospital Angeles del Pedregal Mexico City, Mexico
7	No longer available	Individual Patient Expanded Access IND of Hope Biosciences Autologous Adipose-derived Mesenchymal Stem Cells for Parkinson's Disease	•Parkinson Disease	•Biological: HB-adMSCs	•Hope Biosciences **Stem Cell** Research Foundation Sugar Land, Texas, United States
8	Completed	Allogeneic Bone Marrow-Derived Mesenchymal Stem Cell Therapy for Idiopathic Parkinson's Disease	•Parkinson's Disease	•Biological: Allogeneic bone marrow-derived MSCs (1 x 10 6 MSC/kg) •Biological: Allogeneic bone marrow-derived MSCs (3 x 10 6 MSC/kg) •Biological: Allogeneic bone marrow-derived MSCs (6 x 10 6 MSC/kg) •Biological: Allogeneic bone marrow-derived MSCs (10 x 10 6 MSC/kg)	•The University of Texas Health Science Center at Houston Houston, Texas, United States

CURRENT TRIALS VIA CLINICAL TRIALS .GOV

GENETIC AND GENE RELATED THERAPIES



GENE THERAPIES



GENE THERAPY

A GENE THERAPY that makes an **enzyme allowing better communication between cells in the nervous system**, was found in early stage clinical trials to REDUCE THE AMOUNT OF LEVODOPA the subject needed to take — **up to 42% less** in the highest dose group (Christine et al. 2019)

A **GENE THERAPY** that **encodes for the three critical enzymes required for dopamine production**, was found in early stage clinical trials to produce a **42% improvement in UPDRS OFF scores and improvements in activities of daily living**, 3 months after treatment (Lopes 2019)

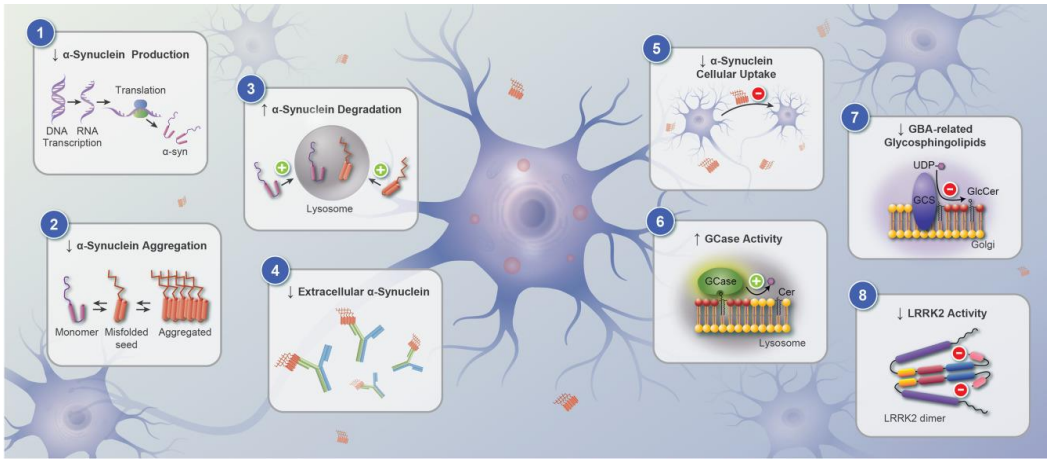
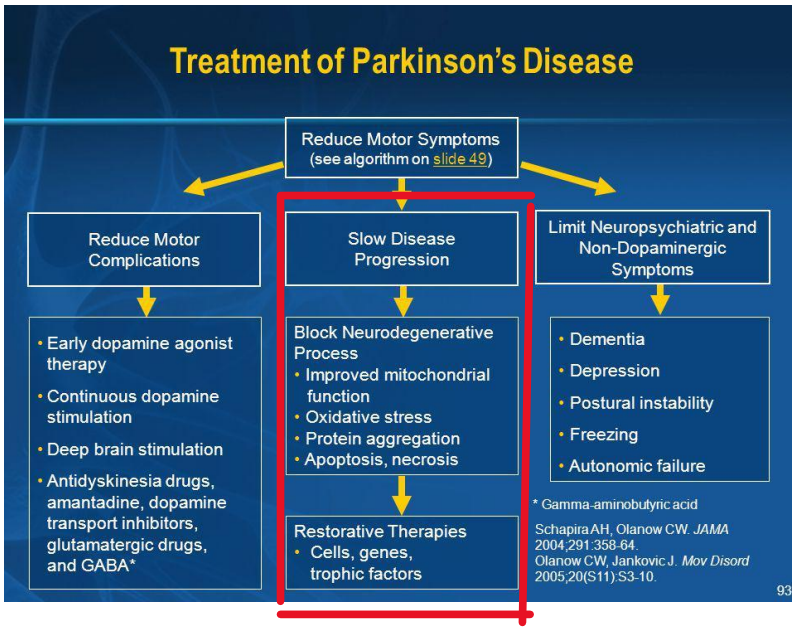


TABLE 1. Genetic-based targeted therapies currently being tested in PD patients[a]

Gene	Targeting mechanism	Drug	Therapeutic modality	Mechanism of action	Target population (n)	Status
SNCA	Decrease α-synuclein aggregation	NPT200-11	Small molecule	Inhibition of α-synuclein misfolding	HV (55)	Phase I
		NPT088	Biologic	Reduction of α-synuclein aggregation	AD (66)[b]	Phase I
	Increase α-synuclein degradation	Nilotinib	Small molecule	Inhibition of c-Abl	Mild PD(75) Early and mild PD (135)	Phase II Phase II
	Decrease extracellular α-synuclein	RO7046015	Biologic	Passive immunization	Early PD (300)	Phase II
		BIIB054	Biologic	Passive immunization	Early PD (311)	Phase II
		MEDI1341	Biologic	Passive immunization	HV (40)	Phase I
		PD01A, PD03A	Biologic	Active immunization	Early PD (36)	Phase I
GBA	GCase activation	Ambroxol	Small molecule	GCase activation	GBA-PD (10) PD (10) PDD (75)	Phase II Phase II
	Reduction of *GBA*-related GSLs	Venglustat	Small molecule	Glucosylceramide synthase inhibitor	GBA-PD (243)	Phase II
LRRK2	LRRK2 kinase inhibition	DNL201	Small molecule	Kinase inhibitor	N/A	Phase I




Time for
Questions