The Parkinson's Disease Educational Course for Industry Professionals
Honolulu, Hawaii, USA | October 4, 2025

International Parkinson and Movement Disorder Society

Cell Replacement and Trophic Factors and PD

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UNIVERSITY OF TORONTO
UHN Krembil Brain Institute
HUMANITAS NEURO CENTER

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Disclosures

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- Receipt of honoraria or consultation fees:
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- Participation in a company sponsored advisory board
  - Abbott, Abbvie, Boston Scientific, Ipsen, Medtronic, Sunovion

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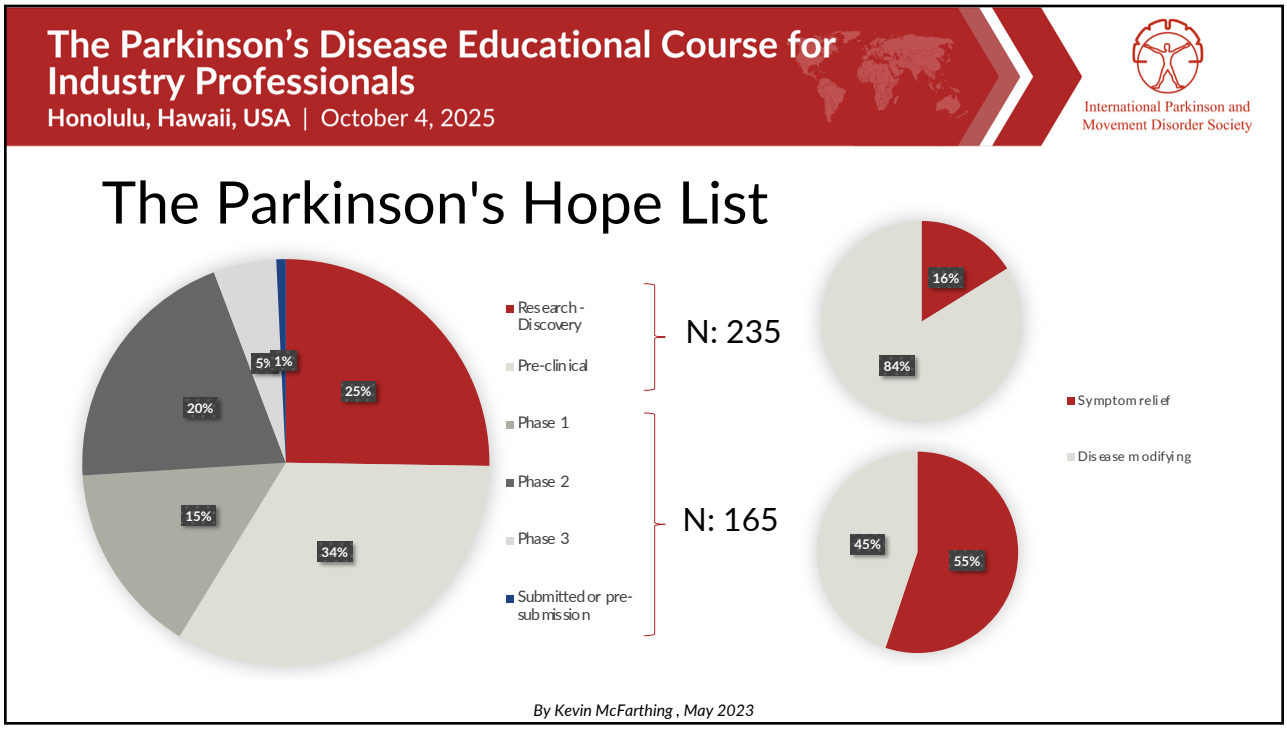
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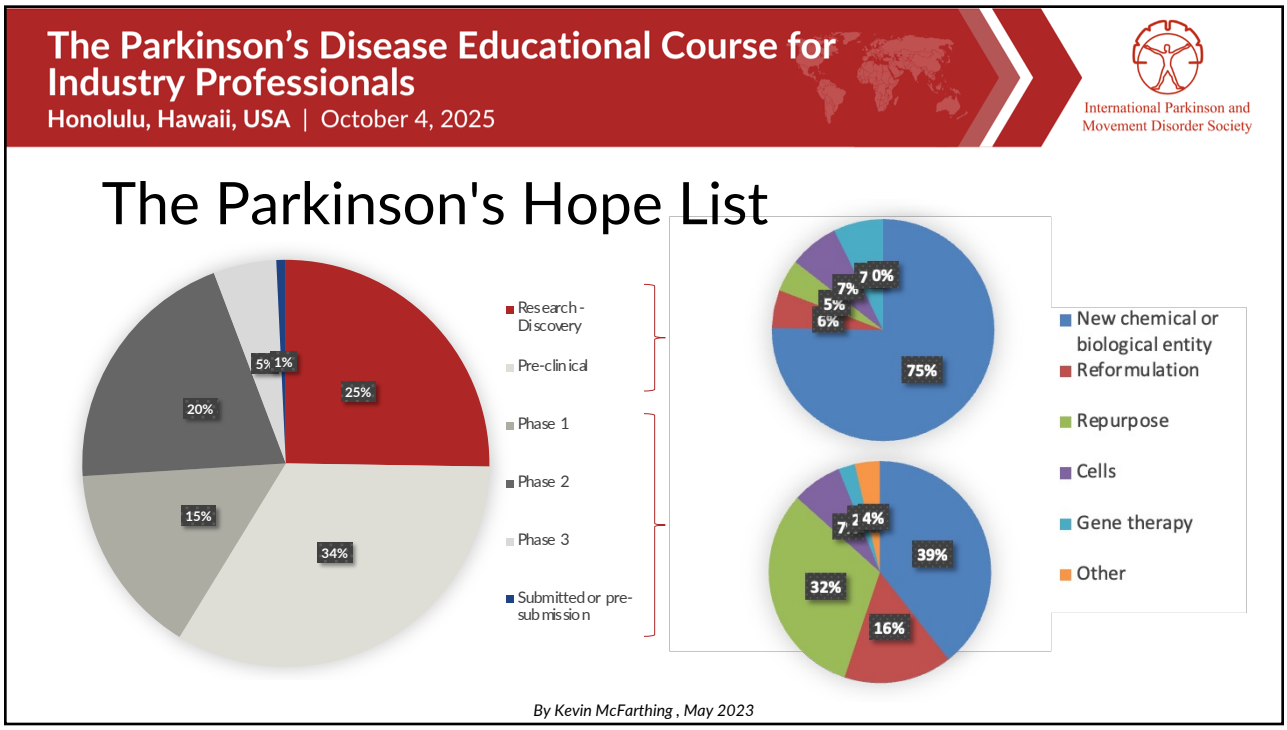
The Parkinson's Hope List
25%
34%
15%
20%
5%
1%
Research - Discovery
Pre-clinical
Phase 1
Phase 2
Phase 3
Submitted or pre-submission
N: 235
N: 165
16%
84%
45%
55%
Symptom relief
Disease modifying
By Kevin McFarthing , May 2023

3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Research - Discovery
Pre-clinical
Phase 1
Phase 2
Phase 3
Submitted or pre-submission
75%
6%
5%
7%
10%
39%
32%
16%
New chemical or biological entity
Reformulation
Repurpose
Cells
Gene therapy
Other
By Kevin McFarthing , May 2023

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Restorative cell/gene therapies for PD

Reconstitution of the nigrostriatal pathway/dopaminergic transmission

Rescuing & regrowing the nigrostriatal DA system	Replacement of the nigrostriatal DA system	Neuronal reprogramming	Restoring DA function by gene therapy
GDNF/Neurturin delivery to the striatum	Transplantation of DA neurons to the striatum	Turning host cells into functional DA neurons	Transfer of DA synthetic enzymes to the striatum
- Intrastriatal infusion of recombinant protein	- Neuroblasts derived from the ventral midbrain of human fetuses	- Transcription factor guided conversion of resident glia	- Transfer of the decarboxylating enzyme AADC to improve conversion of L-DOPA to DA
- Viral vector delivery of GDNF/Neurturin	- DA neuron progenitors derived from pluripotent stem cells	- Trans-differentiation of glia by depletion of the RNA-binding protein PTB	-Transfer of three enzymes, TH, AADC and GCH1 to restore DA synthesis in the striatum

Barker & Björklund, 2023

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Vol. 316 No. 14 AUTOTRANSPLANTATION AND PARKINSON'S DISEASE — MADRAZO ET AL. 831

OPEN MICROSURGICAL AUTOGRAFT OF ADRENAL MEDULLA TO THE RIGHT CAUDATE NUCLEUS IN TWO PATIENTS WITH INTRACTABLE PARKINSON'S DISEASE

Ignacio Madrazo, M.D., D.Sc., René Drucker-Colín, M.D., Ph.D., Víctor Díaz, M.D., Juan Martínez-Mata, M.D., César Torres, M.D., and Juan José Becerril, M.D.

Abstract Recent experimental studies and one clinical case have suggested that grafting tissue from the adrenal medulla into the brain may ameliorate the signs of Parkinson's disease. We describe the treatment of two young patients (35 and 39 years old) with intractable and incapacitating Parkinson's disease, in whom fragments of the adrenal medulla were autotransplanted to the right caudate nucleus. Clinical improvement was noted in both patients at 15 and 6 days (respectively) after implantation and has continued in both. Rigidity and akinesia had virtually disappeared in the first patient at 10 months after surgery, and his tremor was greatly reduced. A similar degree of improvement was present in the second patient at three months.

We conclude that autografting of the adrenal medulla to the right caudate nucleus was associated with a marked improvement in the signs of Parkinson's disease in two patients, but our results are preliminary and further work is necessary to see whether this procedure will be applicable over the long term in other types of patients with Parkinson's disease. (N Engl J Med 1987; 316: 831-4.)

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Cells	Advantages	Disadvantages
hESCs	• Wide differentiation potential (can differentiate into almost any type of cell) • Many cells for transplantation or research • Can replace damaged dopamine neurons	• Ethical issues (use of embryos) • Risk of rejection and need for immunosuppression • Precise differentiation and culture conditions are needed, control of cell purity is difficult
iPSCs	• Wide range of sources to avoid ethical issues • Can be obtained from the patient's own cells, reducing the risk of immune rejection • Can be used for individualized treatment strategies	• Low reprogramming efficiency and number of induced multifunctional stem cells generated • Further research is needed
MSCs	• Wide range of sources (e.g. adult adipose tissue) • Low risk of immune rejection for allogeneic transplantation • Anti-inflammatory properties and tissue repair capabilities	• Poor cell survival after transplantation • Challenges related to production and process standardization • Further research is still needed

hESCs: human embryonic stem cells; iPSCs: induced pluripotent stem cells; MSCs: mesenchymal stem cells
From: Wu et al., 2024

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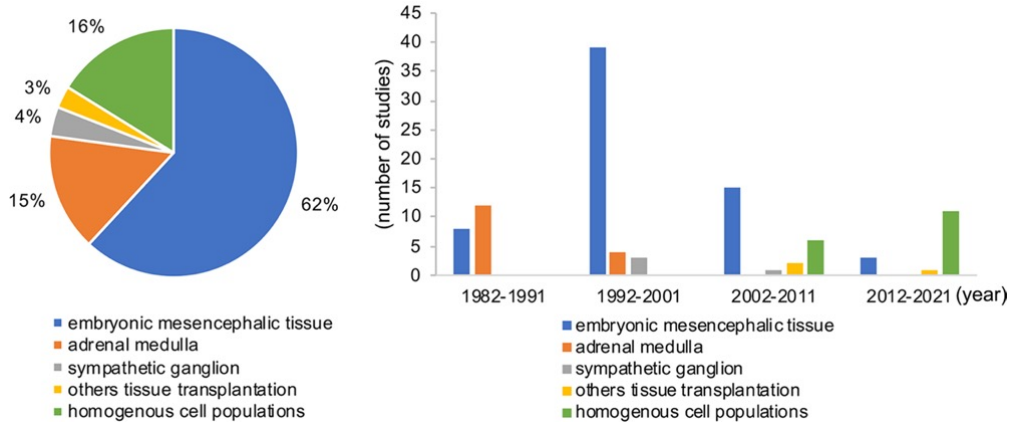
Rise and fall of different approaches



Wang et al, 2023

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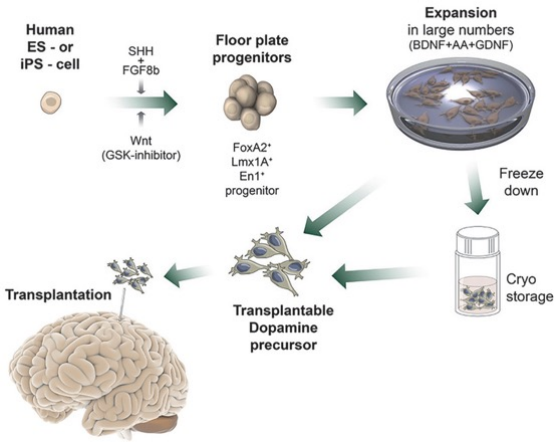
Floorplate protocols



Takahashi et al., 2007; Kriks et al., 2011; Kirkeby et al., 2012; Barker & Björklund, 2023

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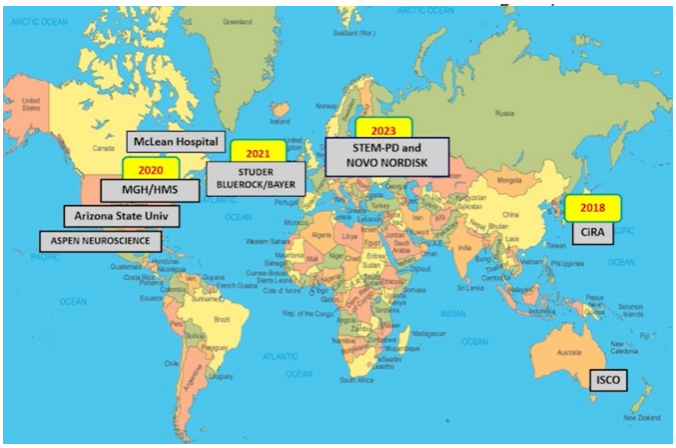

www.gforce-pd.com

Takahashi et al., 2007; Kriks et al., 2011; Kirkeby et al., 2012; Barker & Björklund, 2023

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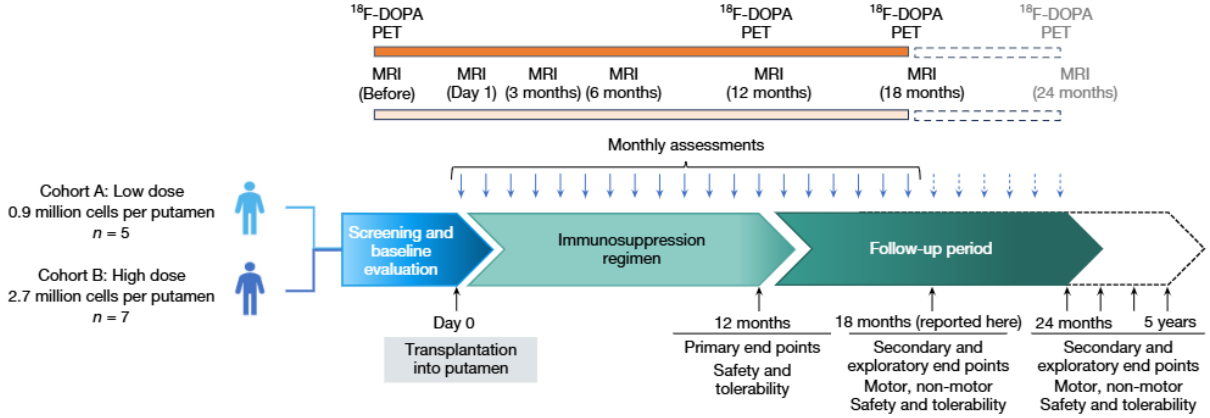
Bemdaneprocel (BRT-DA01), Phase 1



Tabar et al. 2025 (NCT04802733)

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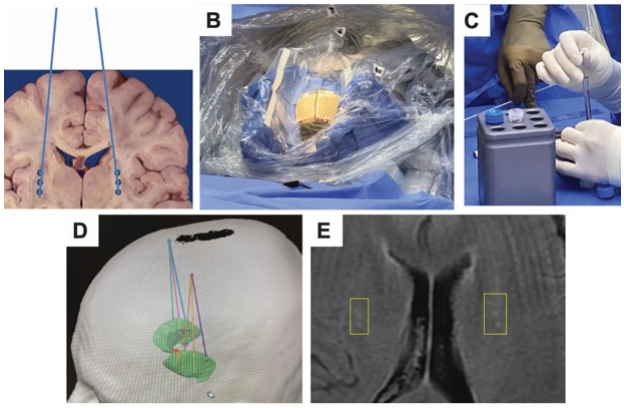
Procedures

- Cells administered in a single session of stereotactically guided injection
  - Single burr hole on each side
  - Intraoperative MRI guidance (n=9) or frame-based stereotaxis (n=3)
- Target: posterior putamen bilaterally.
- 3 passes of the cannula on each side
- 3 cell deposits per pass
  - total of 9 cell deposits per hemisphere.



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Immunosuppressive regimen

- Initiated intraoperatively and continued post-operatively for 1 year.
  - **Basiliximab** 20 mg iv intraoperatively and post-operative on Day 4
  - **Methylprednisolone** 500 mg iv prior to surgery, then tapered to oral prednisone and continued at 5 mg daily for 1 year
  - **Tacrolimus** orally started on the day after surgery (Day 1) and then adjusted to a target blood level of 4-7 ng/mL for 1 year

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Inclusion and Exclusion Criteria*

Inclusion

- Aged 50 to 78 y
- Diagnosed with PD 3 to 20 y ago
- Taking levodopa and experiencing complications of therapy

Exclusion

- Cognitive impairment (MoCA score < 26)[2]
- Dyskinesia (AIMS score > 2)[2]
- Diagnosis of primary mitochondrial disorder, epilepsy, stroke, multiple sclerosis, or other neurodegenerative diseases
- Prior DBS, lesion therapy, or gene therapy for PD
- Prior surgical or radiation therapy to the brain or spinal cord
- Any medical condition resulting in high risk for immunosuppressive drugs
- Inability to temporarily stop anticoagulant medications
- Previous or currently active cancer except for basal cell carcinoma or in situ uterine cervical carcinoma
- Severe obesity or any condition preventing the use of PET/MRI
- Contraindication to surgery or general anesthesia
- Pregnancy or breastfeeding

Tabar et al. 2025 (NCT04802733) *: slightly different between US and Canadian centers

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Safety

- No deaths
- No SAEs/AEs related to transplanted cells or immunosuppression
- No tumors, abnormal tissue overgrowth, or intracerebral hemorrhages
- No MRI evidence of changes in putaminal volume
- Over 18 mo, 1 SAE in the high-dose cohort
  - Single seizure within 24 h of surgery, treated with ASM, no recurrence once medication was discontinued
  - Seizure attributed to surgical procedure

Tabar et al. 2025 (NCT04802733)

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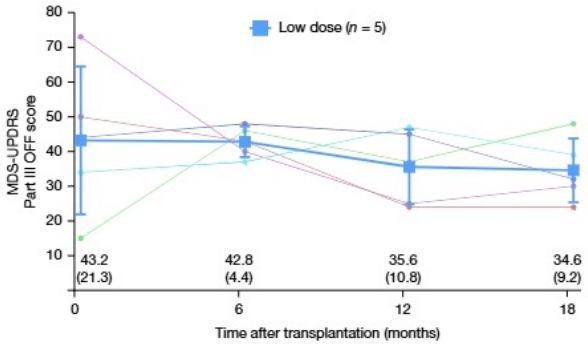
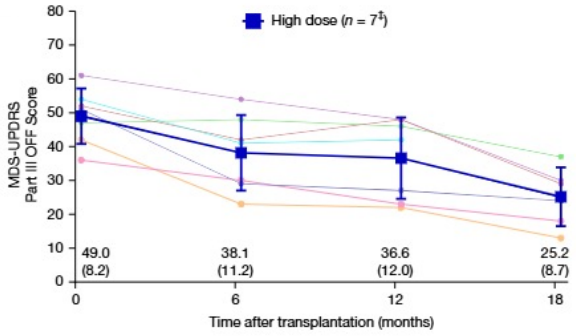
Change in MDS-UPDRS Part III OFF Scores



Mean Decrease of 8.6 Points From Baseline



Mean Decrease of 23 Points From Baseline

Tabar et al. 2025 (NCT04802733)

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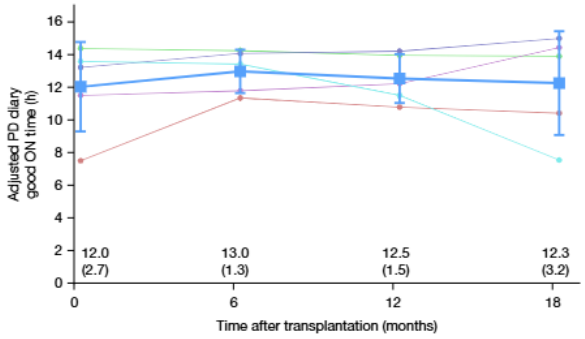
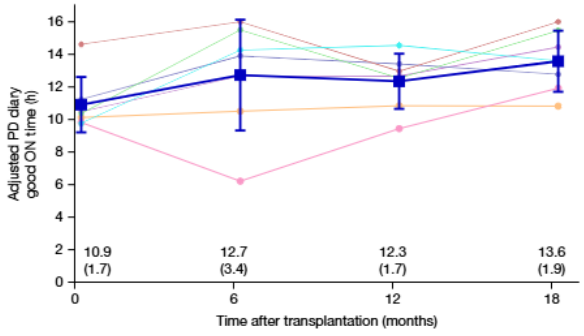
Change in Mean Good ON Times, Based on PD Diaries



Mean Increase of 0.2 h From Baseline



Mean Increase of 2.7 h From Baseline

Tabar et al. 2025 (NCT04802733)

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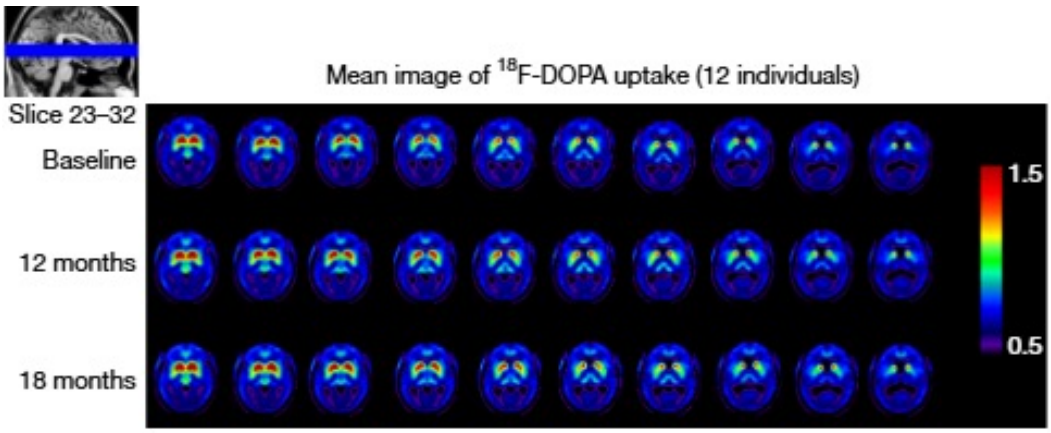
Graft Survival



Tabar et al. 2025 (NCT04802733)

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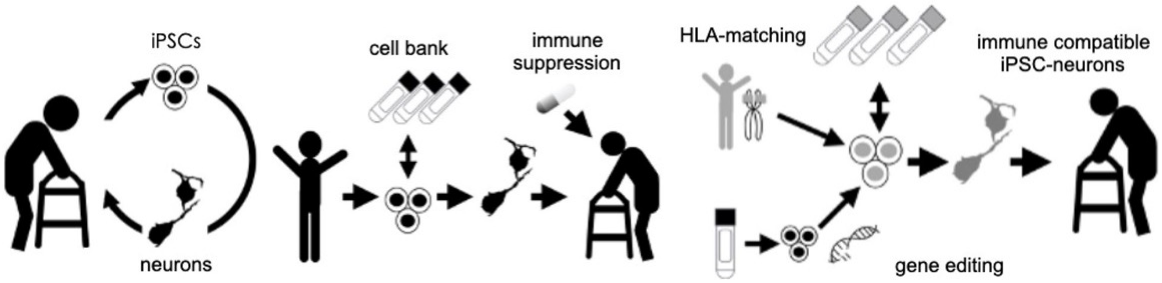
Induced Pluripotent Stem Cells (iPSCs)



Autologous transplantation with patient's own iPCS

Allogeneic transplantation with iPSCs from healthy donors or human embryonic stem cells without HLA-haplotype matching

Allogeneic transplantation with HLA-matching iPSCs
OR
with "universal cells" genetically edited to knock down HLA molecules

Morizane et al.2023

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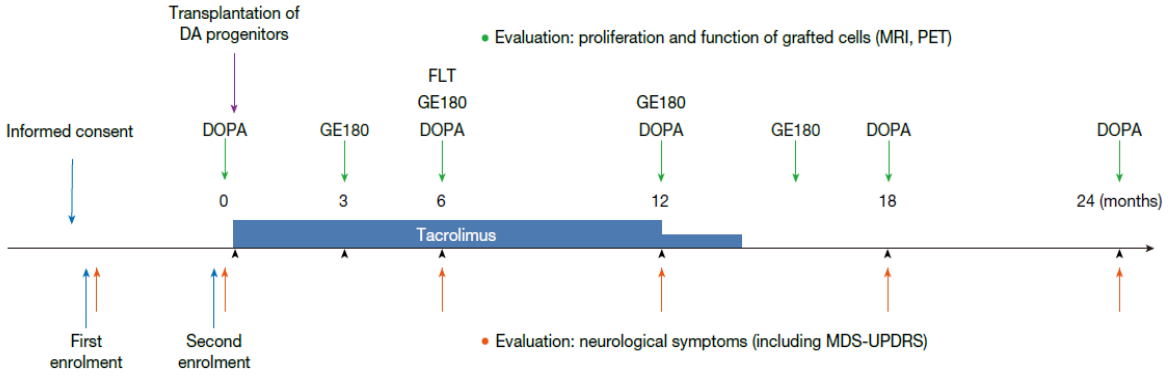
iPSC-Derived DA Progenitors—Phase 1/2 Clinical Trial (n: 7)



DOPA, ^{18}F-DOPA-PET; F-FLT, fluorine-18-fluorothymidine; GE180, fluorine-18-flutriciclamide.

Sawamoto et al. 2025

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Inclusion and Exclusion Criteria

- Inclusion
  - Aged 50 to 69 y
  - Disease duration > 5 y
  - Hoehn-Yahr stage 3 or worse during OFF and stage 3 or better during ON
  - At least 30% improvement with dopaminergic medication
  - Symptoms unresponsive to current medications
- Exclusion
  - Dementia or psychiatric issues
  - Etc.

Sawamoto et al. 2025

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Safety

- SAEs
  - No deaths
  - None requiring hospitalization
- AEs:
  - Most mild
  - One moderate case of dyskinesia
  - Most frequent: application site pruritus
  - One AE possibly related to transplantation: neck stiffness and painful dystonia during drug-ON state

Sawamoto et al. 2025

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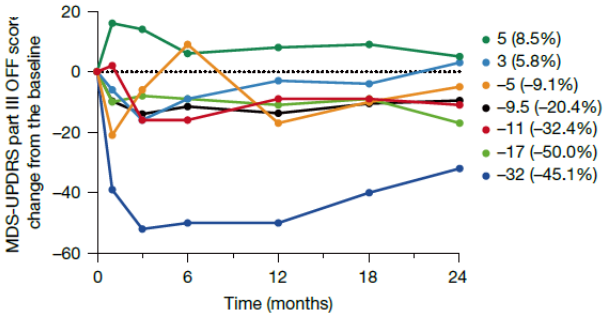
Change in MDS-UPDRS Part III Scores

Change in MDS-UPDRS Part III OFF Score



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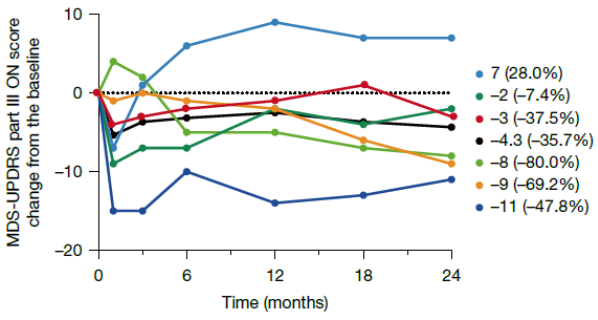

18F-DOPA results suggest increased dopamine synthesis in the putamen over 24 months

Sawamoto et al. 2025

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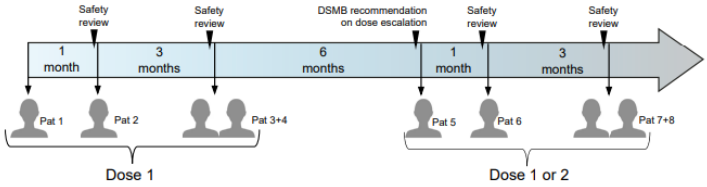
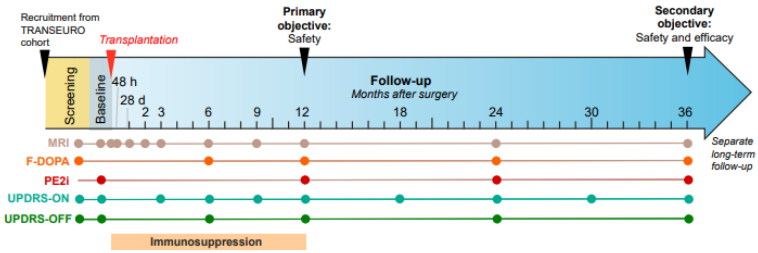
STEM-PD Phase 1/2a

Staggered dosing scheme



Overall trial design



Kirkeby et al., 2023, NCT05635409

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Inclusion and exclusion criteria

Inclusion criteria

- PD diagnosis based on Queens Square Brain Bank criteria
- Moderate disease (Hoehn and Yahr stage 2 to 3 in OFF state)
- Aged 50 to 75 y
- Significant response to dopamine therapies
- Symptoms not appropriately controlled by existing oral anti-PD medications
- **Followed in the TransEuro observational study for ≥ 12 mo**
- Able to travel for surgery

Exclusion criteria

- Tremor-dominant disease
- Significant drug-induced dyskinesias (score > 2 on AIMS scale)
- Major medical or psychiatric disorders that make participation unsuitable
- Unable to undergo MRI
- Extensive ventral striatal loss or normal findings on F-DOPA PET
- Significant cognitive impairment
- Concomitant treatment with neuroleptics and/or cholinesterase inhibitors
- Previous neurosurgery to the brain, previous cell or organ transplantation, or repeated blood transfusions
- Contraindication to immunosuppressive therapy or osteoporosis prophylaxis
- Severely reduced thiopurine methyltransferase activity
- Received an investigational drug or used an investigational device within 4 wk of screening

Kirkeby et al., 2023, NCT05635409

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Other clinical trials

Trial Identifier	Phase	Type of Stem Cells	Status
NCT05897957	Observational Continued evaluation of phase 1 trial of bemdaneprocel (BRT-DA01)	hESC-derived midbrain DA neurons	Enrolling by invitation
NCT06944522	3 (sham-controlled) Bemdaneprocel (exPDite-2)	hESC-derived midbrain DA neuron	Soon recruiting
NCT06344026	1/2a (ASPIRO)	ANPD001: DA-producing cells derived from iPSCs from patients' skin cells	Enrolling by invitation
NCT06482268	1/2 (CT1-DAP001)	CT1-DAP001: iPSC-derived DA progenitors	Recruiting

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Limitations of cell-based therapies for PD

- Efficacy
- Efficiency
- Immunological considerations
- Side effects
- Limited availability and scalability
- Ethical and regulatory considerations

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Limitations of cell-based therapies for PD

- Efficacy
- Efficiency
- Immunological co
- Side effects
- Limited availabilit
- Ethical and regulatory considerations

- The optimal drug type, dosage and timing of use still need to be determined
- Calculation based on the *assumption* that 15% are likely to survive and that approximately 100,000 surviving dopaminergic cells are needed to reinnervate each human putamen

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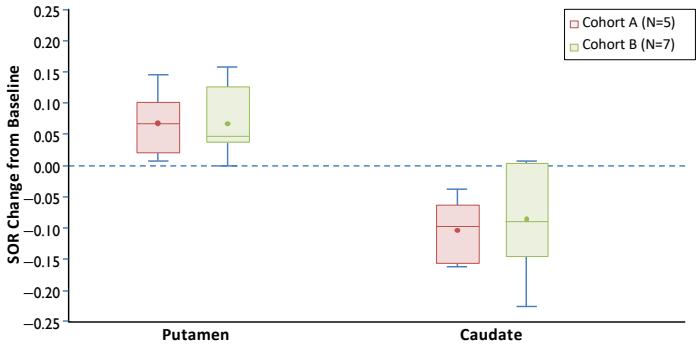
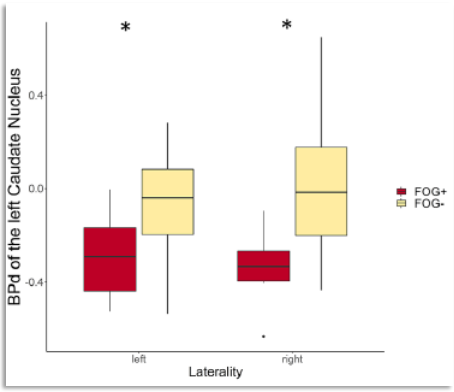
Pre vs Post-Commissural Putamen





SOR: striatal-to-occipital ratio
Data from Tabar et al. 2025; Steidel et al, 2021

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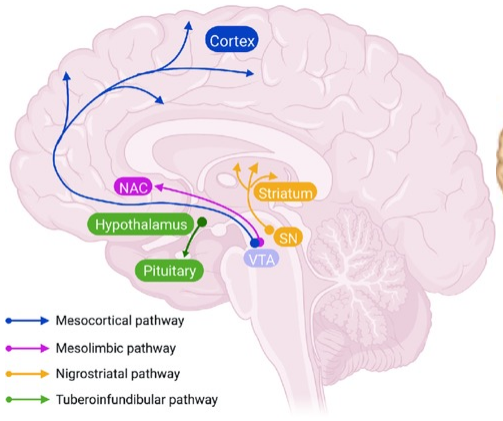
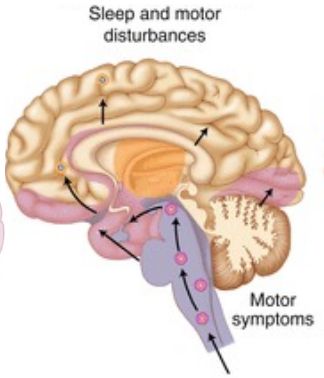
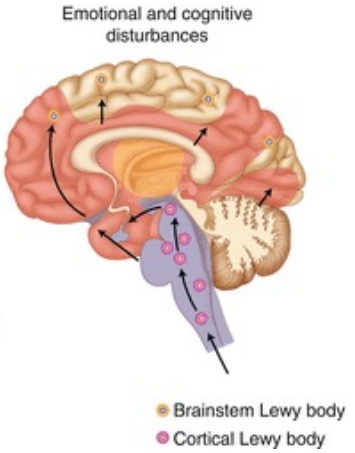
Not just Nigro-Striatal denervation







Jellinger et al., 2014; Xu & Yang, 2022

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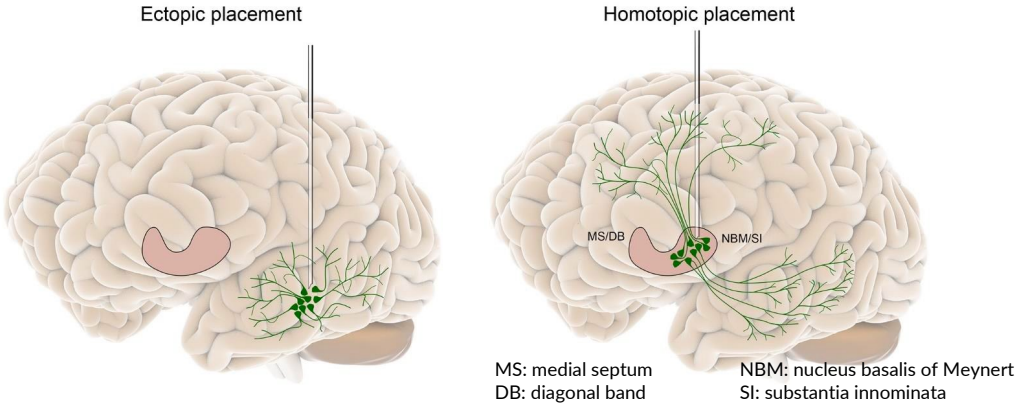
The basal forebrain cholinergic system as target for CRT in PD



MS: medial septum
DB: diagonal band
NBM: nucleus basalis of Meynert
SI: substantia innominata

Björklund & Barker, 2024

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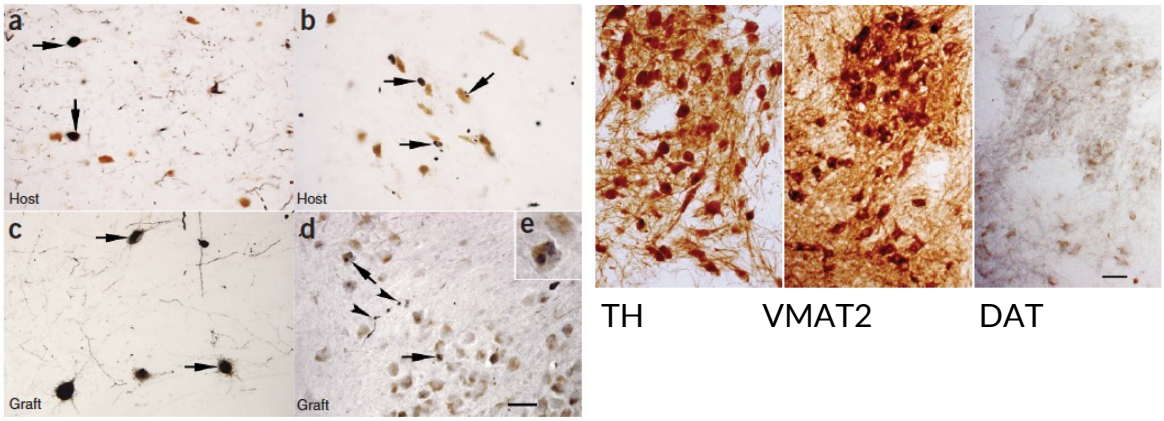
Lewy body-like pathology in long-term embryonic nigral transplants



Kordower et al., 2008

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Graft-induced dyskinesias

- 60-year-old patient in the Columbia-Colorado graft study
- Sham surgery in 1996
- Fetal mesencephalic grafts in 1998
- 30-40% reduction in her symptoms
- STN DBS in 2004

	Pretreatment With Buspirone		On Buspirone 30 mg/d	
UPDRS-IV	7		6	
UPDRS-IV dyskinesias subscore	12		11	
	UPDRS-III	AIMS	UPDRS-III	AIMS
Off stim/off med	66	19	65	20
On stim/off med	31	20	25	18
Off stim/on med	30	19	35	20
On stim/on med	25	24	31	21

Abbreviations: UPDRS-III, motor section of Unified Parkinson's Disease Rating Scale; AIMS, Abnormal Involuntary Movement Scale.

Med OFF/STN DBS ON + **buspirone 30 mg/day**

Freed et al., 2001; Beaulieu-Boire & Fasano, 2015

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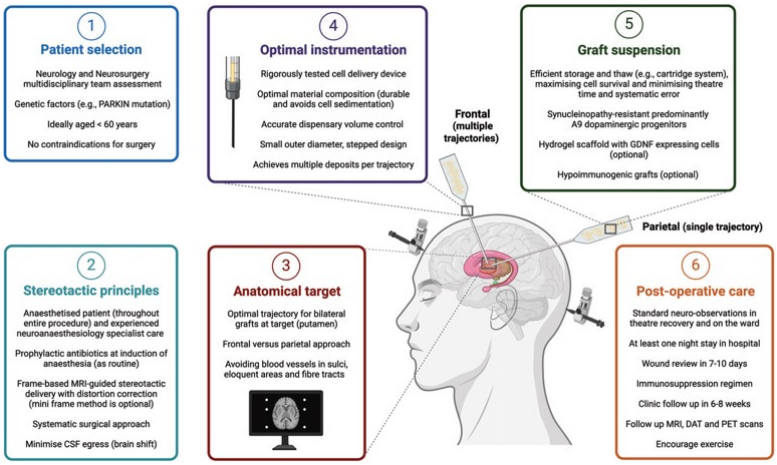
Not a single study like another



Maheshwari et al., 2024

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Forum

Sham surgery for the trialing of cell-based therapies to the CNS may not be necessary

Viviane Tabar[1,*] **and Roger A. Barker**[2]
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[2]Department of Clinical Neuroscience, John van Geest Centre for Brain Repair and Wellcome-MRC Stem Cell Institute, University of Cambridge, Cambridge, UK
*Correspondence: tabarv@mskcc.org
https://doi.org/10.1016/j.stem.2023.12.004

Sham surgery is often required for cell therapies adopting a randomized placebo-controlled double-blinded trial design. Using the case of dopamine neuron therapy for Parkinson's disease, we argue that alternative trial designs should be considered instead, for several reasons relating to ethics, patient burden, ease of unblinding, and cost.

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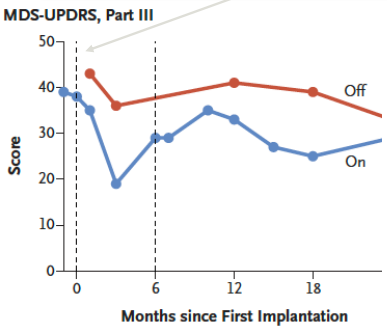
Personalized iPSC in a single PD patient

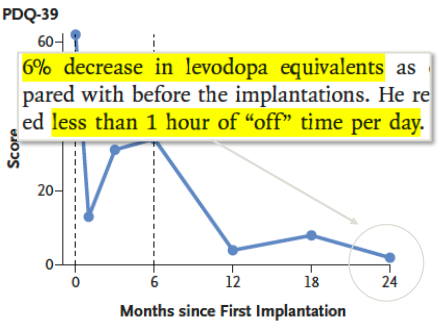
OVERSIGHT

Informed consent included a discussion of the risks associated with first-in-human use of this method in Parkinson's disease, with a review of currently available medical and surgical therapeutic options, including deep-brain stimulation.

The patient was a 69-year-old right-handed man with a 10-year history of progressive idiopathic Parkinson's disease. He was receiving extended-release carbidopa–levodopa (in capsules containing 23.75 mg and 95 mg, respectively, at a dose of three capsules four times daily), rotigotine (4 mg daily), and rasagiline (1 mg daily) (total daily dose, 904 mg of levodopa equivalents). He reported poor control of his symptoms, with 3 hours of "off" time per day, characterized by worsening tremor, posture, and fine motor control; increases in the levodopa dose beyond these doses caused orthostatic hypotension. The patient had not had dyskinesias.

ment therapy ("off") were not measured before the first implantation because the patient declined to cease medications owing to worsened symptoms. Scores in the off period were 43 at 4 weeks





6% decrease in levodopa equivalents as pared with before the implantations. He re ed less than 1 hour of "off" time per day.

Schweitzer et al., 2020

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Personalized iPSC in a single PD patient

OVERSIGHT

Informed consent included a discussion of the

ment therapy ("off") were not measured before the first implantation because the patient declined

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

Yes.

a. **Please describe those relationships.**
Concurrent with NIH and other reported funding sources disclosed by individual co-authors, the subject in this report has provided philanthropic support to Mclean Hospital and Massachusetts General Hospital, which is broadly designated for the development of cell therapy research for Parkinson's disease and administered by the two co-senior authors of this report: BSC and KSK. Past and ongoing use of this support includes the following: development of iPSC reprogramming technology; pre-clinical testing, cell product testing, and hospital costs in the current report; ongoing multi-patient variability study of iPSC reprogramming, and ongoing multi-patient Phase 1 clinical trial design and implementation.

What is the manuscript title?

Personalized iPSC-derived Dopaminergic Progenitor Therapy in a Patient with Idiopathic Parkinson's Disease

Months since First Implantation **Months since First Implantation**

Schweitzer et al., 2020

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Restorative cell/gene therapies for PD

Reconstitution of the nigrostriatal pathway/dopaminergic transmission

Rescuing & regrowing the nigrostriatal DA system	Replacement of the nigrostriatal DA system	Neuronal reprogramming	Restoring DA function by gene therapy
GDNF/Neurturin delivery to the striatum	Transplantation of DA neurons to the striatum	Turning host cells into functional DA neurons	Transfer of DA synthetic enzymes to the striatum
- Intrastriatal infusion of recombinant protein	- Neuroblasts derived from the ventral midbrain of human fetuses	- Transcription factor guided conversion of resident glia	- Transfer of the decarboxylating enzyme AADC to improve conversion of L-DOPA to DA
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Barker & Björklund, 2023

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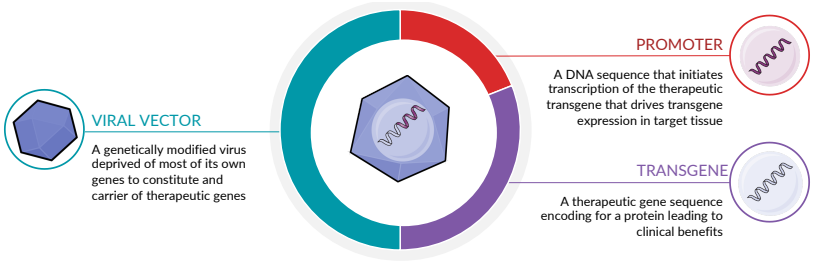
Gene Therapy Overview

- Introduction of functional genetic material into cells to correct defective genes or confer new functions
- Vectors used:
  - Adeno-associated virus (AAV): small, nonenveloped, single-stranded DNA viruses, long-term transcription of cargo sequences
  - Lentiviruses: enveloped RNA retroviruses, drive long-term expression via genomic integration



Buttery & Barker, 2020; Ebrahimi et al. 2024

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Completed enzyme-gene therapy trials in PD

Reference	N	Phase	Duration (y)	Agent/Target	Safety concerns	Outcome
Kaplitt et al., 2007	12	1	1	AAV-GAD (3 doses)/unilateral STN	No	Contralateral motor improvement
Christine et al., 2009; Mittermeyer et al., 2012	10	1	1 (extension up to 4)	AAV-hAADC/bilateral putamen	3 hemorrhages (2 symptomatic), headache Worsening of dyskinesias	Motor improvement, lost over time
Palfi et al., 2014	15	1/2	1	ProSavin* (3 doses)/bilateral putamen	Worsening of dyskinesias	Motor improvement
Christine et al., 2019; 2022	15	1	3	AAV-hAADC (3 doses)/bilateral putamen	Worsening of dyskinesias, headache	Motor improvement

*Lentivirus coding for, AADC, GTPCH

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New gene therapy trials in PD

Trial Identifier	Phase	Gene Therapy	Status
NCT04167540	1	AAV2-GDNF	Active, not recruiting
NCT07011771	1/2	CAP003: AAV-GBA1	Recruiting
NCT05894343	1/2	AAV-GAD	Active, not recruiting
NCT04127578	1/2	PR001: AAV-GBA1	Recruiting
NCT06285643	2	AB-1005: AAV2-GDNF	Recruiting
NCT05819359	2	BIA 28-6156: AAV-GBA1	Active, not recruiting

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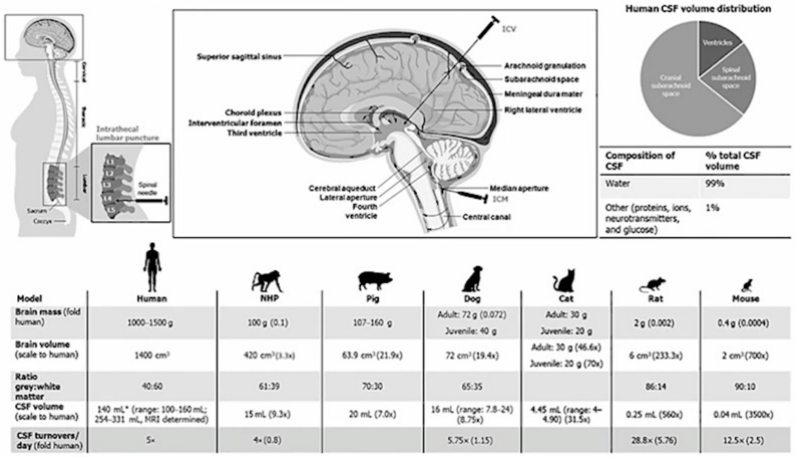
Issues with viral vectors



Composition of CSF	% total CSF volume
Water	99%
Other (proteins, ions, neurotransmitters, and glucose)	1%

Model	Human	NHP	Pig	Dog	Cat	Rat	Mouse
Brain mass (fold human)	1000-1500 g	100 g (0.1)	107-160 g	Adult: 72 g (0.072) Juvenile: 40 g	Adult: 30 g Juvenile: 20 g	2 g (0.002)	0.4 g (0.0004)
Brain volume (scale to human)	1400 cm³	420 cm³(3.3x)	63.9 cm³(21.9x)	72 cm³(19.4x)	Adult: 30 g (46.6x) Juvenile: 20 g (70x)	6 cm³(233.3x)	2 cm³(700x)
Ratio grey:white matter	40:60	61:39	70:30	65:35		86:14	90:10
CSF volume (scale to human)	140 mL* (range: 100-160 mL; 254-331 mL, MRI determined)	15 mL (9.3x)	20 mL (7.0x)	16 mL (range: 7.8-24) (8.75x)	4.45 mL (range: 4-4.90) (31.5x)	0.25 mL (560x)	0.04 mL (3500x)
CSF turnovers/ day (fold human)	5x	4x (0.8)		5.75× (1.15)		28.8× (5.76)	12.5× (2.5)

Chen et, 2019

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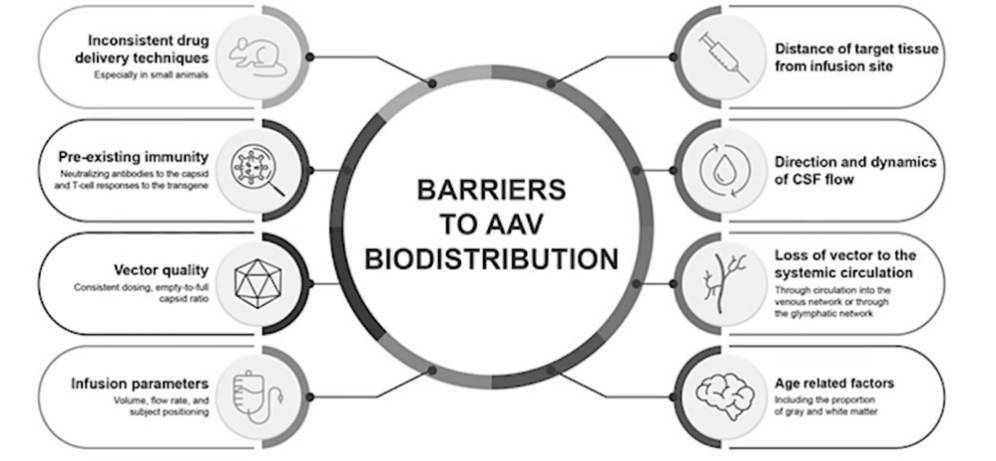
Issues with viral vectors



Chen et, 2019

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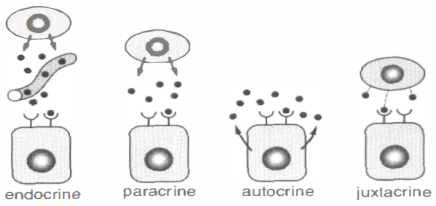
Neurotrophic Factors (NTFs)

- Proteins activating cell signaling pathways:
  - neuronal survival
  - differentiation and growth
  - regeneration
- Paracrine, autocrine or juxtacrine mechanisms
- NTFs for neurodegenerative disease feasible with advances in recombinant protein technologies (1980s)



d'Anglemont de Tassigny et al., 2015

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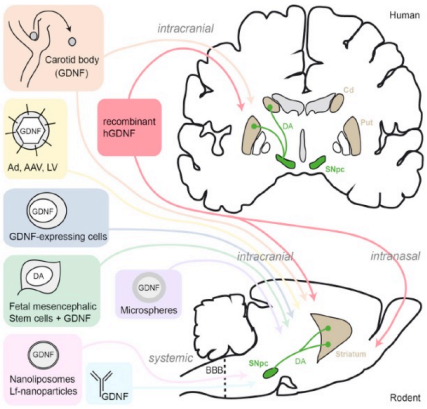

d'Anglemont de Tassigny et al., 2015

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Variable findings, generally disappointing

- Glial Cell Line-Derived Neurotrophic Factor (GDNF)
  - Most studied infused intracerebroventricularly or directly into the striatum
  - Double-blind Bristol trial 'positive' (Luz et al., 2020)
- Brain-Derived Neurotrophic Factor (BDNF) and Platelet-Derived Growth Factor (PDGF) in preclinical studies
  - BDNF has not been tested in patients
  - PDGF has been explored in a safety trial involving 12 PD patients
- Cerebral dopamine neurotrophic factor (CDNF)
  - open-label study in patients with PD in Scandinavia without major clinical benefits (press release)

Paul et al., 2015; Barker et al., 2020

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Barker & Björklund, 2023

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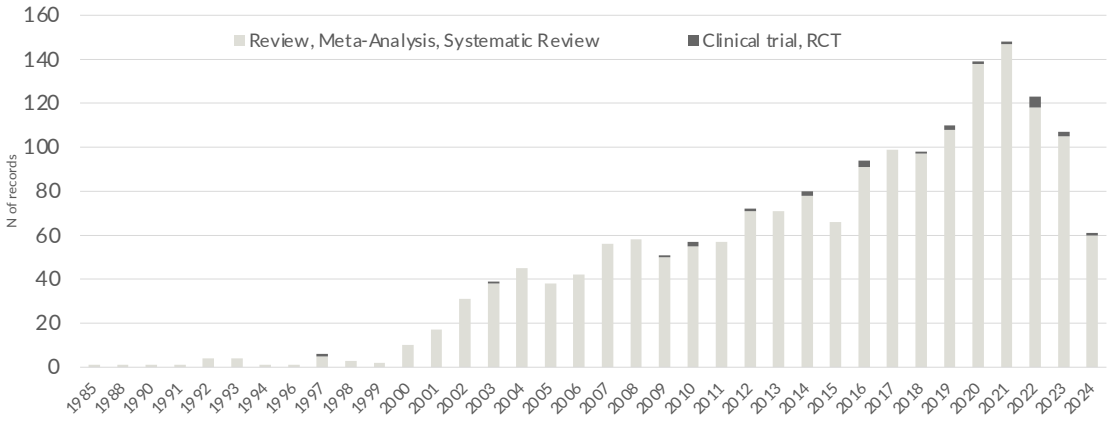
A topic for reviews only?



Pubmed search query: "stem cell Parkinson", June 2024

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Thank you
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