SUPPLEMENTARY MATERIAL

Supplementary Table 1. Clinical outcomes and infusion parameters in published trials of gene therapy in Parkinson's disease

Vector	Therapeutic rationale	Trial phase, N	Dates of inclusion	Target	Anesthesia	Cannula design	Delivery parameters (per hemisphere)	Maximum vector dose	Volume per target	Infusion rate	Clinical outcome	References
AAV2-GAD	Correct pathological overactivity in STN by synthesis of GABA	Phase 1, N=12	August 2003–August 2005 (clinicaltrials.gov)	STN unilateral	Awake MAC (MER)	Rigid glass	Single tract, single point fusion, CED infusion	5×10^{10} vg	50 µL	0.5 µL/min	Improved UPDRS motor scores (on and off medication) at 12 months	17
		Phase 2, N=45 (n=22 active treatment)	August 2008–December 2010 (clinicaltrials.gov)	STN bilateral	Awake MAC (MER)	Flexible	Single tract, single point fusion, CED infusion	3.45×10^{10} vg per STN	34.5 µL per STN	0.23 µL/min	Improved UPDRS motor scores off medication vs sham surgery at 6 and 12 months	18,19
AAV2-neurturin	Promote survival of dopaminergic neurons through expression of neurotrophic factor neurturin	Phase 1, N=12	May 2005–March 2007	Putamen bilateral	Sedation	Guide tube with step to smaller cannula, rigid	4 tracts, 2 points per track, hand injection	2.7×10^{11} vg per putamen	40 µL per putamen	(no rate given; hand injection)	Improved UPDRS motor scores off medication vs baseline; no significant change on medication	27
		Phase 2, N=58 (n=38 active treatment)	December 2006–November 2008	Putamen bilateral	Deep sedation/ general anesthesia	Guide tube with step to smaller cannula, rigid	4 tracts, 2 points per track, hand injection	2.7×10^{11} vg per putamen	40 µL per putamen	2 µL/min	No significant change in UPDRS motor scores (on- and off-medication) vs sham surgery at 12 months	26

		Phase 1b, N=6	September 2009–March 2018 (estimated completion as per clinicaltrials.gov – same NCT# for both trials)	Putamen and substantia nigra bilateral	Deep sedation/ general anesthesia	Guide tube with step to smaller cannula, rigid	Putamen: 3 tracts, single point per tract; SNc: 1 tract, 2 points per tract; CED infusion	1×10^{12} vg per putamen; 2×10^{11} vg per substantia nigra	150 µL per putamen; 30 µL per substantia nigra	Putamen 3 µL/min; substantia nigra 2 µL/min	Trial focused on safety; small decreases in UPDRS motor scores off medication but minimal statistical analysis	30
		Phase 2b, N=51 (n=24 active treatment)		Putamen and substantia nigra bilateral	General anesthesia	Guide tube with step to smaller cannula, rigid	Putamen – 3 tracts, single point per tract; SNc: 1 tract, 2 points per tract; CED infusion	1×10^{12} vg per putamen; 2×10^{11} vg per substantia nigra	150 µL per putamen; 30 µL per substantia nigra	Putamen 3 µL/min; substantia nigra 2 µL/min	No significant difference vs sham surgery in UPDRS motor score (off medication) at minimum 15-month follow-up	31
Lentiviral TH, AADC, CH1	Expression of rate-limiting enzymes for local dopamine synthesis from tyrosine in putamen	Phase 1/2, N=15	January 2008–August 2011	Putamen, bilateral	General anesthesia	Rigid stainless steel	All putamen; cohort 1: 4 tracts, multiple points/tract; cohort 2a: 5 tracts, multiple points/tract; cohort 2b/3: 3 tracts, 1 point/tract	5×10^{7} transducing units per putamen	Not stated	1–3 µL/min	Significant improvement in UPDRS motor scores off medication at 6 and 12 months, but no dose-dependent effect between cohorts with different dosing levels	23,24
AAV2-hAADC	Expression of AADC in putamen to provide local dopamine synthesis from precursor levodopa	Phase 1, N=10	November 2004–March 2013	Putamen, bilateral	Sedation	Step design, rigid	2 tracts, single point/tract, CED infusion	1.5×10^{11} vg per putamen	100 µL per putamen	1 µL/min	Improved UPDRS motor scores off medication (but not on medication) at 6 months	20,21
		Phase 1, N=6	Unknown (not listed in article and	Putamen, bilateral	Unknown	Step design, rigid	2 tracts, single	1.5×10^{11} vg per putamen	100 µL per putamen	1 µL/min	Improved UPDRS motor scores off	22

			not listed in clinicaltrials.gov; Japanese trial)				point/tract, CED infusion				medication (but not on medication) at 6 months	
VY-AADC01		Phase 1 (PD-1101), N=15	October 2013–(ongoing)	Putamen, bilateral	General anesthesia	Step design, rigid (SmartFlow)	≥2 tracts, single or multiple points/tract, or progressive advancement with iMRI CED infusion	2.3×10^{12} vg per putamen	≤450 µL or ≤900 µL per putamen	≤30 µL/min	Dose-dependent improvements in UPDRS motor scores (on and off medication) up to 36 months	46
		Phase 1 (PD-1102), N=8	May 2017–(ongoing)	Putamen, bilateral	General anesthesia	Step design, rigid (SmartFlow)	Single tract, continuous iMRI CED infusion with progressive advancement	4.7×10^{12} vg per putamen	≤1800 µL per putamen	≤30 µL/min	Outcomes data not yet available	54
AAV2-GDNF	Promote survival of dopaminergic neurons through expression of neurotrophic factor GDNF	Phase 1, N=13 (early closure)	May, 2012–(ongoing; enrollment halted but follow-up continuing)	Putamen, bilateral	General anesthesia	Step design, rigid (SmartFlow)	2 trajectories, single point iMRI CED infusion	9×10^{11} vg per putamen	450 µL per putamen	1–5 µL/min	No changes in UPDRS motor scores	45

AADC, L-amino acid decarboxylase; AAV2, AAV serotype 2; CED, convection-enhanced delivery; CH1, cyclohydrolase 1; GABA, γ-aminobutyric acid; GAD, glutamic acid decarboxylase; GDNF, glial cell line-derived neurotrophic factor; hAADC, human AADC; iMRI, intraoperative magnetic resonance imaging; MAC, monitored anesthesia care; MER, microelectrode recording; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; TH, tyrosine hydroxylase; UPDRS, Unified Parkinson's Disease Rating Scale; vg, vector genome.