Stem Cells Translational Medicine, 2023, **12**, 510–526
https://doi.org/10.1093/stcltm/szad041
Advance access publication 24 July 2023
Concise Review

Neural Cells for Neurodegenerative Diseases in Clinical Trials

Yiping Fan[1,2,3,*], Eyleen L.K. Goh[4], Jerry Kok Yen Chan[1,2,3]

[1]Department of Reproductive Medicine, KK Women's and Children's Hospital, Singapore, Singapore
[2]Experimental Fetal Medicine Group, Department of Obstetrics and Gynaecology, Yong Loo Lin School of Medicine, National University Health System, Singapore, Singapore
[3]Academic Clinical Program in Obstetrics and Gynaecology, Duke-NUS Medical School, Singapore, Singapore
[4]Neuroscience and Mental Health Faculty, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore

[*]Corresponding author: Yiping Fan, PhD, Department of Reproductive Medicine, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore. Email: fanyiping9@gmail.com

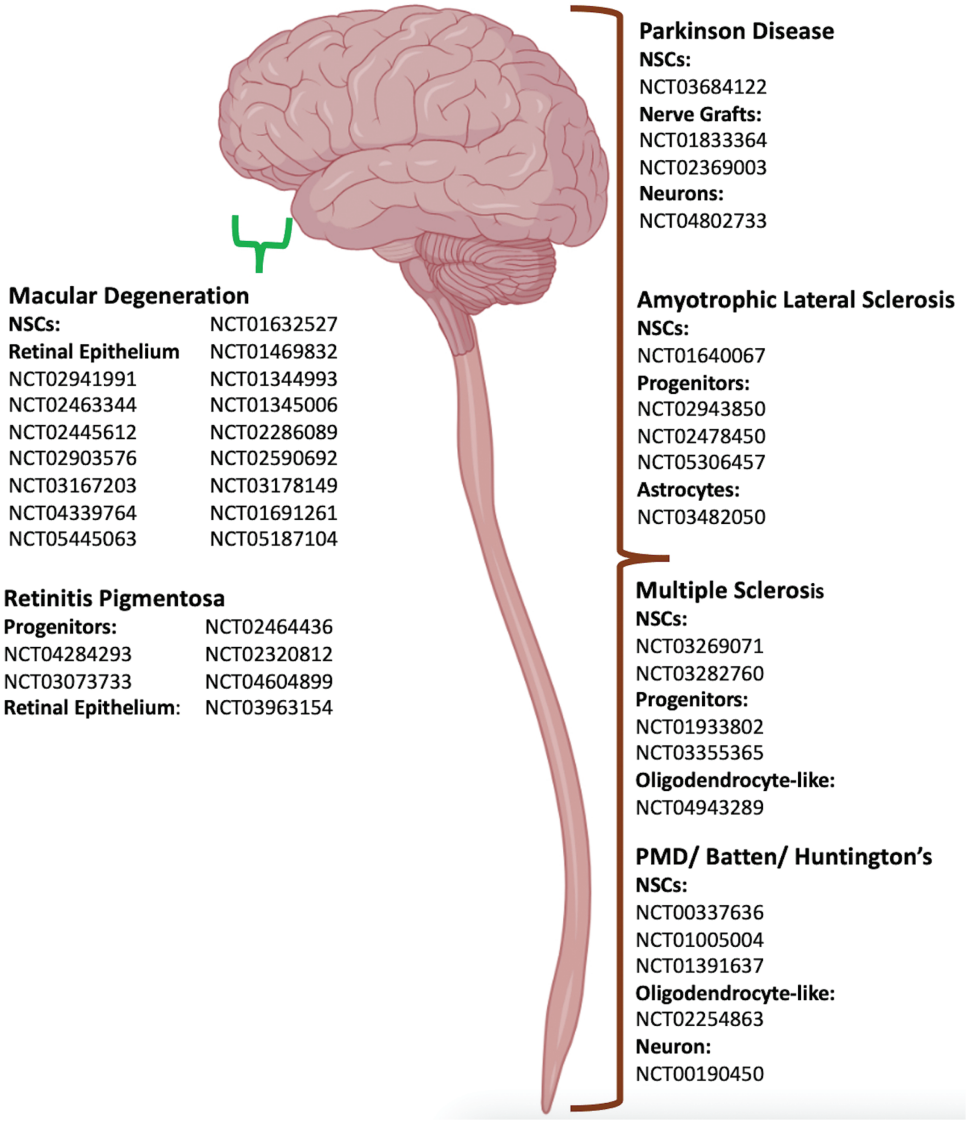
Abstract

Neurodegenerative diseases (ND) are an entire spectrum of clinical conditions that affect the central and peripheral nervous system. There is no cure currently, with treatment focusing mainly on slowing down progression or symptomatic relief. Cellular therapies with various cell types from different sources are being conducted as clinical trials for several ND diseases. They include neural, mesenchymal and hemopoietic stem cells, and neural cells derived from embryonic stem cells and induced pluripotent stem cells. In this review, we present the list of cellular therapies for ND comprising 33 trials that used neural stem progenitors, 8 that used differentiated neural cells ,and 109 trials that involved non-neural cells in the 7 ND. Encouraging results have been shown in a few early-phase clinical trials that require further investigations in a randomized setting. However, such definitive trials may not be possible given the relative cost of the trials, and in the setting of rare diseases.

Key words: neural stem cells; Parkinson's; cell therapy; clinical trials.

Received: 14 February 2023; Accepted: 11 June 2023.

Graphical Abstract



Introduction

Neural stem cells (NSCs) are multipotent cells found within the central nervous system (CNS) and can differentiate into neural lineages of neurons, glial, and oligodendrocytes.[1-5] Sources of NSCs for clinical transplantation range from fetal neural tissues, transdifferentiated cells from embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs). Neurodegenerative diseases (ND) are disorders characterized by progressive loss of neurons associated with deposition of proteins showing altered physicochemical properties in the brain and in peripheral organs.[6] Affecting hundreds of millions worldwide, they are debilitating and increasingly represent a major global health challenge worldwide today, with limited management options and mostly non-curative. A cellular therapy approach has been proposed to address the clinical gap to effect a cure for ND. The first clinical trials using stem cells in ND took place in mid-1980s with 3-400 participants treated with fetal cell transplantation for Parkinson's disease (PD), in the open-label format. Subsequently, patients with Huntington's have also experienced clinical benefits with implants of fetal neural grafts,[7-9] although temporal. Since then, many other neural and non-neural cell transplantation has been investigated for a range of neurological conditions.

Cell transplantation of neural lineages can exert clinical benefits through multiple mechanisms, such as (1) working synergistically with the endogenous microenvironment to upregulate intrinsic cell proliferation or neuroprotection enhancing the overall regenerative capacity of the transplanted tissue and (2) integrating into the endogenous host network, replacing the cells of interests/injured cells[10] as well as form functional synapses.[11] As such, the focus of this review is to detail the latest clinical trials using NSCs and cells of neural lineage for the treatment of ND. Clinical trials involving stem cells from other sources have also been listed but not elaborated upon.

Methods

For each disease, a search of the disease name (Parkinson's Disease, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Batten Disease, Pelizaeus-Merzbacher Disease, Huntington's

Disease, Macular Degeneration, Retinitis Pigmentosa, Alzheimer Disease, Niemann-Pick Diseases, Krabbe Disease, Gaucher Disease, Tay-Sachs Disease, Sandhoff Disease, Mucopolysaccharidoses, Spinocerebellar Ataxias, Dementia With Lewy Bodies, Frontotemporal Lobar Degeneration, Multiple System Atrophy), neural stem cells, neural cells, and cell therapy were performed on clinicaltrials.gov. Diseases with cell therapy using cells of neural lineage are discussed. They will also be listed in the tables, followed by the non-neural lineage cell clinical trials for each disease type. For this purpose, only interventional and not observational studies are included. Studies that were terminated, withdrawn, suspended, or unknown (past completion dates but status not verified for more than 2 years) were excluded. Similarly, studies not registered in clinicaltrials.gov were omitted from this study.

Parkinson's Disease

Parkinson's disease is a chronic ND characterized by the progressive loss of dopaminergic (DA) neurons in the substantia nigra. It is manifested by motor movement impairment such as bradykinesia, tremors, postural instability, and muscle rigidity. It can be effectively treated with medications such as levodopa, dopamine agonists, and monoamine oxidase inhibitors in the early stages but these medications are unable to stop the underlying neurodegeneration.[12,13] To date, no curative therapies are available to reverse the progression of the disease processes.[14] Since the late 80s, several groups have transplanted human fetal ventral mesencephalic (fVM) tissues into the caudate and putamen of PD patients, resulting in moderate amelioration of PD symptoms.[15-19] Further analysis of the human clinical trials with fVM transplantation demonstrated clinical improvements in various parameters[14] with the best outcomes for milder PD patients with a short disease duration. However, such grafts are associated with the development of dyskinesis,[20,21] postulated to be due to the presence of serotonergic cells in the donated grafts.[22] Han et al. have summarized in a book chapter the clinical outcomes of earlier trials of fetal brain-derived neural stem cell transplantation into PD patients. With the patients (*n* between 1 and 40) observed between 12 months and 24 years, symptom improvement was observed in 11 of the 13 trials, and dyskinesia was reported in 3 out of the 12 trials.[23] Moreover, graft survival is low, which necessitates multiple donors per patient. With the advancements made in the DA neurons differentiation protocols, DA neurons can be differentiated from various cell sources (ESCs, iPSCs, and MSCs) and these more defined and differentiated populations of cells, being more homogenous have led to new waves of initiatives for cell transplantation in PD patients.[14]

There have been 18 trials listed on clinicaltrials.gov with 4 being neural lineage and directly delivered into the brain (Table 1). There is 1 trial utilizing NSCs derived from Wharton's jelly (WJ) MSCs through in vitro differentiation (NCT03684122). The multipotency characteristic of MSCs enables them to differentiate into many cell types, including neurons and other neuronal cells.[24] WJ-MSCs differentiated into NSCs were found to have enhanced therapeutic potential compared to undifferentiated WJ-MSCs. These NSCs preserve their immunomodulatory properties while displaying neuroectodermal characteristics.[25] There are 2 other clinical trials using neural progenitor cells (NPCs)(NCT03309514 and NCT01329926) but both were withdrawn due to insufficient funding. Another 3 studies involved differentiated neural cells, specifically peripheral nerve grafts containing Schwann cells, and DA neurons differentiated from human embryonic stem cells. The 2 trials that implant autologous peripheral nerve graft directly into the substantia nigra showed that it is safe, feasible, and associated with clinical benefits.[26,27] The challenge with the use of peripheral nerve grafts is that they contain heterogenous populations of cell types. While it has been proven feasible and safe, more data awaits on its efficacy.[27]

Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a progressive motor neuron disease affecting motoneurons in the cortex, brain stems, and spinal cord with a worldwide incidence of 2-3 per 100 000.[28] Affected patients suffers from progressive muscle weakness, atrophy, spasticity, and paralysis, culminating in death within 3-5 years. The majority (90%) of the cases are sporadic with the remaining 10% being familial ALS.[29] As yet, there is neither a cure nor effective therapy to stop the progression of the disease. Stem cell transplantation has been proposed as a promising therapeutic option[11,30] as they are equipped with the complex cellular machinery to modify the local environment through secretions of neurotrophic factors[31,32] as well as possibly differentiate into astrocytes to increase the efficiency of glutamate re-uptake, a process disrupted in ALS.[33] In addition, transplanted stem cells that differentiate into neuronal cells may form synapses with the native motor neurons, providing trophic, and/ or contact-mediated support.[34] Several studies have demonstrated the safety and efficacy of stem cells from different sources such as fetal NSCs,[35-37] peripheral blood stem cells,[38,39] MSCs,[40-46] and olfactory ensheathing cells, a differentiated cell of neural lineage[47] in ALS patients.

Among the 32 cell transplantation clinical trials recorded, 5 are with cells that are neural-related and are delivered through direct injections (Table 2). Only one uses human fetal NSCs injected intraspinally, which showed the absence of progression of disease of all 6 enrolled participants for 18 months, with 2 experiencing improvements in ambulation scores.[48] This work, extended to another 12 participants showed neither severe adverse effects nor increased disease progression over 60 months, and improvement in ALS functional rating scale between 1st and 4th month after transplantation.[49] Next, Kadimastem et al. demonstrated that intrathecal injection of 100-250 million ESCs-derived astrocyte, AstroRx, significantly reduced the rate of disease progression by 6 months (NCT03482050).[50] There are another 2 trials, 1 using glial restricted progenitor cells (Q cell) that has yet to initiate recruitment and another using human NPCs genetically engineered to hyper-express glial-derived neurotrophic factor (GDNF) that showed a single administration of these cells was safe and are able to provide new support cells and deliver GDNF up to 42 months post-transplantation.[51]

MSCs are the most common cells used for the treatment of ALS (24 out of the 32 trials). Across the trials, 24 (73%) are phase I/II trials which are mainly safety trials with small patient samples, with 11 out of the 32 trials not specifying the cell dose. More studies are required to elucidate the most effective cells source and dose, method of administration, and frequency of transplantation,[29] along with the ability

Table 1. Clinical Trials listed on clinicaltrials.gov for Parkinson's disease.

No	Disease	Sponsor	Cell type	Route	Cell dose	Plannedparticipants	Year	Phase	Clinical trial #
1	Parkinson disease	Craig Van Horne	Autologous peripheral nerve graft	Implanted to substantia nigra	Not mentioned	8	2012	na	NCT01833364
2	Parkinson disease	Craig Van Horne	Autologous peripheral nerve graft	Implanted to substantia nigra	Not mentioned	70	2015	1	NCT02369003
3	Parkinson disease	University of Jordan	Allogenic WJSC and its derived NSC	MSC (IV, IT), NSCs (IT)	MSC for iv (120-180 M), MSC for IT (240-260 M), NSC (24-36 MM)	10	2018	1/2	NCT03684122
4	Advanced Parkinson disease	BlueRock Therapeutics	ESC-derived dopamine neurons (MSK-DA01)	Surgical transplanted into putamen	Not mentioned	12	2021	1	NCT04802733
5	Parkinson disease	The Foundation for Orthopaedics and Regenerative Medicine	Allogenic UC-MSC	IV	100M	20	2011	1	NCT05152394
6	Neurodegenerative disease	Elliot Lander	Autologous adipose-derived stromal vascular fraction	IV, intra-articular, and soft-tissue injections.	Not mentioned	3000	2013	na	NCT01953523
7	Stroke/TBI/Parkinson/ ALS/Alzheimer/Dementia	MD Stem Cells	Autologous BMSC	IV and intranasal	Not mentioned	500	2016	na	NCT02795052
8	TBI/Alzheimer's/Dementia/Parkinson-Dementia/ Late Encephalopathy	MD Stem Cells	Autologous BMSC	iv and intranasal	Not mentioned	100	2018	na	NCT03724136
9	Parkinson disease	The University of Texas Health Science Center	Allogenic BM MSC	IV	1,3,6, and 10 M/kg	20	2017	1	NCT02611167
10	Parkinson disease	The University of Texas Health Science Center	Allogenic BM MSC	IV	20 and 30 M/KG	45	2020	2a	NCT04506073
11	Parkinson disease	Belarusian Medical Academy of Post-Graduate Education	Autologous BM MSC	IV and intranasal	IV(0.5-2 M/kg), intranasal (5-12.6M) + IV (10-50 M)	50	2017	2,3	NCT04146519
12	Parkinson disease	Hebei Newtherapy Bio-Pharma Technology Co., Ltd	MSC	IV	10-20 M	20	2018	1	NCT03550183
13	Multiple system atrophy/ Parkinsonism	Indonesia University	Autologous adipose MSC, allogeneic UC MSC	IT	Adipose MSC (100M), uc MSC (100M)	15	2020	na	NCT04876326
14	Parkinson disease	Shanghai East Hospital	Human amniotic epithelial stem cells	Stereotactic implantation into lateral ventricle	50 M	3	2020	1	NCT04414813
15	Parkinson disease	Shanghai East Hospital	Human amniotic epithelial stem cells	Stereotactic implantation into lateral ventricle	50 M	12	2022	1	NCT05435755
16	Parkinson disease	Hope Biosciences Stem Cell Research Foundation	Allogenic adipose-derived MSC (HB-adMSCs)	IV	Not mentioned	60	2021	2	NCT04995081
17	Parkinson disease	Hope Biosciences Stem Cell Research Foundation	Autologous adipose-derived MSC (HB-adMSCs)	IV	Not mentioned	24	2021	2	NCT04928287
18	Idiopathic Parkinson disease	Taiwan Mitochondrion Applied Technology Co., Ltd	Autologous adipose-derived MSC (Mitocell)	Stereotactic intrastriatal implantation	60 M and 200M	9	2022	1	NCT05094011

Abbreviations: ALS, amyotrophic lateral sclerosis; BM-MSC, bone marrow mesenchymal stem cells; BMSC, bone marrow stem cells; IM, intramuscular; IT, intrathecal; IV, intravenous; M, million; na, not applicable TBI, traumatic brain injury; UC, umbilical cord.

Table 2 Clinical trials listed on clinicaltrials.gov for amyotrophic lateral sclerosis

No	Disease	Sponsor	Cell type	Route	Cell dose	Planned participants	Year	Phase	Clinical trial #
1	ALS	Azienda Ospedaliera Santa Maria, Terni, Italy	Human fetal NSC	Intraspinal	2.25 or 4.5 M	18	2011	1	NCT01640067
2	ALS	Cedars-Sinai Medical Center	Human neural progenitor cells expressing GDNF (CNS10-NPC-GDNF)	Unilateral lumbar spinal cord injections	0.2 M, 0.5 M	18	2017	1	NCT02943850
3	ALS	Kadimastem	ESC-derived astrocyte (AstroRx)	IT	100 M, 250 M	16	2018	1,2	NCT03482050
4	ALS	Q Therapeutics	Glial restricted progenitor cells (Q cell)	Transplantation into lumbar or cervical spinal cord	Lumbar (dose 1), cervical (dose 1,2,3,4,5)	30	2021	1,2	NCT02478450
5	ALS	Cedars-Sinai Medical Center	Human neural progenitor cells expressing GDNF (CNS10-NPC-GDNF)	Injection into motor cortex	5.25M, 10.5M	16	2022	1	NCT05306457
6	ALS	Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia	Autologous BMSC	Intraspinal	Not mentioned	11	2007	1/2	NCT00855400
7	ALS	Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia	Autologous BMSC	IT	Not mentioned	63	2010	1/2	NCT01254539
8	ALS	The First Affiliated Hospital of Dalian Medical University	Autologous peripheral blood MNC	Transplant into subarachnoid space	Not mentioned	14	2010	na	NCT03085706
9	ALS	Mayo Clinic	Autologous adipose MSC	Intraspinal	1 M	1	2010	1	NCT01142856
10	ALS	Mayo Clinic	Autologous adipose MSC	IT	10, 50, 100 M, 200 M	27	2012	1	NCT01609283
11	ALS	Mayo Clinic	Autologous adipose MSC	IT	60-150M	60	2017	2	NCT03268603
12	ALS	Corestem	Autologous BM MSC (HYNR-CS inj)	IT	2 M/kg	71	2011	1,2	NCT01363401
13	ALS	Corestem	Autologous BM MSC [Lenzumestrocel (Neuronata-R Inj.)]	IT	2 M/kg or 5 M/kg	115	2021	3	NCT04745299
14	ALS	Brainstorm-cell therapeutics	Autologous BM MSC secreting neurotrophic factors (MSC-NTF)	IT and IM	IT (24 M), I M (60 M)	12	2011	1,2	NCT01051882
15	ALS	Brainstorm-cell therapeutics	autologous BM MSC secreting neurotrophic factors (MSC-NTF)	IM	94 M, 141 M or 188 M	14	2012	2	NCT01777646
16	ALS/ND	Hanyang University Seoul Hospital	Autologous BM MSC (HYNR-CS inj)	IT	0.5,1 or 2 M/kg	6	2012	1	NCT01758510
17	ALS	Bioinova, s.r.o.	Autologous BM MSC	IT	15 ± 4.5 M cells	26	2012	1,2	NCT03828123
18	ALS	Hospital Universitario Dr. Jose E. Gonzalez	Autologous HSC	IT	Not mentioned	14	2012	2/3	NCT01933321
19	ALS	Royan Institute	Autologous BM MSC	IV	2 M/kg	6	2013	1	NCT01759797
20	ALS	Royan Institute	Autologous BM MSC	IT	2 M/kg	8	2013	1	NCT01771640
21	ALS	Royan Institute	Allogenic adipose MSC	IV	2 M/kg	19	2014	1	NCT02492516
22	ALS	Brainstorm-cell therapeutics	Autologous BM MSC (NurOwn)	IT and IM	Not mentioned	48	2014	2	NCT02017912

Table 2. Continued

No	Disease	Sponsor	Cell type	Route	Cell dose	Planned participants	Year	Phase	Clinical trial #
23	ALS	Brainstorm-cell therapeutics	Autologous BM MSC(NurOwn)	IT	Not mentioned	263	2017	3	NCT03280056
24	ALS	Andalusian initiative for advanced therapies - Fundación Pública Andaluza Progreso y Salud	Autologous adipose MSC	IV	1,2 or 4 M/kg	52	2014	1,2	NCT02290886
25	ALS	China Medical University Hospital	Autologous adipose MSC	IV and intracerebral	IV(200-800 M), IC (100-400 M)	1	2015	1	NCT02383654
26	ALS	Hospital e Maternidade Dr. Christóvão da Gama	Autologous MSC	IT	100 M	3	2015	1	NCT02987413
27	ALS	Mossakowski Medical Research Centre Polish Academy of Sciences	Autologous adipose regenerative cells	Intraspinal/ IT	44 M	30	2015	1	NCT03296501
28	ALS	Hadassah Medical Organization	Autologous BM MSC	IT	4 M/kg	20	2016	1,2	NCT04821479
29	Stroke/TBI/ Parkinson/ ALS/ Alzheimer/ Dementia	MD Stem Cells	Autologous BMSC	IV and intranasal	Not mentioned	500	2016	na	NCT02795052
30	ALS	Polski Bank Komorek Macierzystych JSC (PBKM)	WJ MSC	IT	Not mentioned	20	2020	1,2	NCT04651855
31	ALS	Rapa Therapeutics LLC	Autologous hybrid TREG/ Th2 Cell (RAPA-501)	IV	20 M or 80 M	21	2020	1/2	NCT04220190
32	ALS	Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia	Autologous BM MNC	IM	Not mentioned	100	2021	2	NCT04849065

Abbreviations: ALS, amyotrophic lateral aclerosis; BM, bone marrow; GDNF, glial-derived neurotrophic factors; HSC, hemopoietic stem cells; IM, intramuscular; IT, intrathecal; IV, intravenous; M, million; MNC, mononuclear cells; MSC, mesenchymal stem cells; na, not applicable NSC, neural stem cells; SC, stem cells; TBI, traumatic brain injury; UC, umbilical cord; WJ, Wharton Jelly.

to diagnose the disease earlier to improve outcomes of cell therapy before the onset of irreversible damage.[52]

Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the CNS resulting in CNS neurodegeneration and axonal loss. It is characterized by early acute lesions composed of discrete areas of inflammatory demyelination that either resolve by remyelination or evolve into chronic lesions with associated axonal loss, oligodendroglial cell loss, and glial scarring.[25] Current disease modifying therapies may prevent or delay disease progression through immunosuppression and immunomodulation[53-56] although beset with potentially serious adverse events.[57] Once progressive disability is established, there is currently no cure.[58]

A total of 48 studies involving cell therapy for MS was retrieved (Table 3), with 5 cell sources being of neural lineage (10.4%), 22 using MSCs as donor cells, and 10 studies utilizing dendritic and T cells as an immunotherapy approach. Among the clinical trials using cells of neural lineage, 2 used autologous sources while 3 were allogenic (2 fetal and 1 umbilical cord blood). Intrathecal/ intraventricular routes were the mode of administration for those cells. The first phase I trial commenced in 2014, with intrathecal autologous MSCs-derived NPCs given in 3 doses of 10 million cells 3 months apart.[25] MSCs-derived NPCs are a subpopulation of MSCs that exhibit neuroectodermal lineage characteristics with reduced capacity to undergo mesodermal differentiation,[59-63] minimizing risks of ectopic differentiation.[64] Similar to MSCs, these NPCs exhibit

Table 3. Clinical trials listed on clinicaltrials.gov for multiple sclerosis.

No	Disease	Sponsor	Cell type	Route	Cell dose	Planned participants	Year	Phase	Clinical trial #
1	MS	Tisch Multiple Sclerosis Research Center of New York	Autologous MSC-derived neural progenitors (MSC-NP)	IT	6-30M	20	2014	1	NCT01933802
2	MS	Tisch Multiple Sclerosis Research Center of New York	Autologous MSC-derived neural progenitors (MSC-NP)	IT	Not mentioned	50	2018	2	NCT03355365
3	Progressive Multiple Sclerosis	IRCCS San Raffaele	Fetal-derived NSC	IT	0.7 M, 1.4 M, 2.8 M, 5.7 M	4	2017	1	NCT03269071
4	Secondary progressive MS	Casa Sollievo della Sofferenza IRCCS	Fetal-derived NSC	Intraventricular	5, 10, 16, and 24 M	24	2017	1	NCT03282760
5	Primary progressive MS	Joanne Kurtzberg	UCB-derived oligodendrocyte-like cells (DUOC-01)	IT	10 M (3 pax), 10-25 M (3 pax), 25-50 M (16pax)	20	2021	1a	NCT04943289
6	MS	Baylor College of Medicine	Autologous CD34+ HSC	IV	3 M	10	1999	2	NCT00040482
7	MS	Ottawa Hospital Research Institute	Autologous CD34+ HSC	IV	Not mentioned	24	2001	2	NCT01099930
8	MS	Hadassah Medical Organization	Autologous T cell	SubC	10-30 M cells (×4 doses)	30	2002	1/2	NCT01448252
9	Relapse Remitting MS/ secondary Progressive MS	Opexa Therapeutics	Autologous myelin reactive T cell (Tovaxin)	SubC	6-9 M, 30-45 M, or 60-90 M	16	2002	1/2	NCT00587691
10	Relapse Remitting MS	Opexa Therapeutics	Autologous myelin reactive T cell (Tovaxin)	SubC	30-45 M	150	2006	2	NCT00245622
11	MS/secondary Progressive MS	Opexa Therapeutics	Autologous T cell (Tcelna/ Imilecleucel-T)	SubC	30-45M (×5 a yr) ×2 yrs	183	2012	2	NCT01684761
12	MS	Northwestern University	Autologous mobilized HSC	IV	Not mentioned	110	2005	2	NCT00273364
13	Relapse Remitting MS	National Institute of Allergy and Infectious Diseases (NIAID)	Autologous CD34+ HSC	IV	Not mentioned	25	2006	2	NCT00288626
14	Relapsing MS/relapsing remitting MS/secondary progressive MS	National Institute of Allergy and Infectious Diseases (NIAID)	Autologous HSC	IV	4-7.5M CD34+ cells/kg	156	2019	3	NCT04047628
15	MS	Hadassah Medical Organization	Autologous BM MSC	IT and IV	IT (1M/ kg) and IV (0.3-1M/ kg)	24	2006	1/2	NCT00781872
16	MS	Hadassah Medical Organization	Autologous BM MSC	IT and IV	IT (1M/ kg) and IV (1M/kg) up to 8 times	24	2013	1/2	NCT04823000
17	MS	Talaris Therapeutics	Allogenic HSC	IV	Not mentioned	3	2007	1/2	NCT00497952
18	MS	University of Cambridge	Autologous BM MSC	IV	up to 2 M/ kg	10	2008	1/2	NCT00395200
19	MS/autoimmune disease/cerebellar degeneration/	Fred Hutchinson Cancer Center	Autologous or syngeneic peripheral blood stem cell	IV	At least 4 M CD34+ cells/kg	80	2008	2	NCT00716066

Table 3. Continued

No	Disease	Sponsor	Cell type	Route	Cell dose	Planned participants	Year	Phase	Clinical trial #
20	Autoimmune disease/nervous system disease	Andalusian Initiative for Advanced Therapies - Fundación Pública Andaluza Progreso y Salud	Autologous adipose MSC	IV	4 M/kg	30	2010	1/2	NCT01056471
21	MS	Andalusian Initiative for Advanced Therapies - Fundación Pública Andaluza Progreso y Salud	Autologous BM MSC	IV	1-2 M/kg	26	2013	1/2	NCT01745783
22	MS	Royan Institute	Autologous BM MSC	IV	Not mentioned	22	2011	1/2	NCT01377870
23	Relapse remitting MS/secondary progressive MS/ progressive relapsing MS	The Cleveland Clinic	Autologous BM MSC	IV	1-2 M/kg	24	2011	1	NCT00813969
24	MS	University of Jordan	Autologous BM MSC	IT		13	2012	2	NCT01895439
25	MS	University of Jordan	Allogenic WJ MSC	IT and IV	IT(200 M) with 100 M (iv)	60	2017	1/2	NCT03326505
26	Progressive MS	North Bristol NHS Trust	Autologous BM cells	IV	Not mentioned	80	2012	2	NCT01815632
27	MS	North Bristol NHS Trust	Autologous BM cells	IV	Not mentioned	4	2014	na	NCT01932593
28	Relapse remitting MS	Germans Trias i Pujol Hospital	Autologous BM MSC	IV	1 M/kg	9	2012	1/2	NCT02035514
29	MS	Antonio Uccelli	Autologous BM MSC	IV	1-2m M/kg	20	2012	1/2	NCT01854957
30	MS	Imperial College London	Autologous BM MSC	IV	1-2 M/kg	21	2012	1/2	NCT01606215
31	MS	Karolinska Institutet	Autologous BM MSC	IV	1-2 M/kg	7	2012	1	NCT03778333
32	MS	Translational Biosciences	Allogenic WJ MSC	IV	140 M (over 7 days, 20 M/day)	20	2014	1/2	NCT02034188
33	MS	Sara Varea	Autologous tolerogenic dendritic cells	IV	Not mentioned	20	2015	1	NCT02283671
34	MS	Ottawa Hospital Research Institute	Autologous BM MSC	IV	1-2 M/kg	31	2015	2	NCT02239393
35	Relapse remitting MS/secondary progressive MS	Banc de Sang i Teixits	Autologous BM MSC (XCEL-MC-ALPHA)	IV	Not mentioned	8	2015	1/2	NCT02495766
36	MS	Dimitrios Karussis	Autologous BM MSC	IT or IV	1 M/kg	48	2015	2	NCT02166021
37	Relapse remitting MS/secondary progressive MS	Centro de Hematología y Medicina Interna	Autologous peripheral blood stem cells	IV	At least 1 M/kg CD34+ cells	1000	2015	na	NCT02674217
38	Relapse-remitting/chronic progressive MS	Fundació Institut Germans Trias i Pujol	Autologous VitD3 tolerogenic monocyte derived dendritic cells (tolDC-VitD3)	intranodal	5 M, 10 M, 15 M	16	2017	1	NCT02903537
39	MS	University Hospital, Antwerp	Autologous tolerogenic dendritic cells (tolDC)	intradermal	5 M, 10 M, 15 M	9	2017	1	NCT02618902
40	Primary and secondary progressive MS	Atara Biotherapeutics	Allogenic T Cell (ATA188)	IV	Not mentioned	265	2017	1/2	NCT03283826

Table 3. Continued

No	Disease	Sponsor	Cell type	Route	Cell dose	Planned participants	Year	Phase	Clinical trial #
41	Chronic progressive MS	Brainstorm-Cell Therapeutics	Autologous BM MSC (NurOwn)	IT	Not mentioned (3 doses)	20	2019	2	NCT03799718
42	Relapse-remitting MS	Judith Pich	Autologous peripheral blood differentiated adult tolerogenic dendritic cells	IV	Not mentioned	45	2020	2	NCT04530318
43	Relapse remitting MS	FibroBiologics	Tolerogenic fibroblasts	IV	100 M	5	2020	1	NCT05080270
44	MS	Nantes University Hospital	Autologous EBV-specific cytotoxic T-cell lymphocytes	IV	Not mentioned	7	2021	1	NCT02912897
45	Relapse remitting MS	Uppsala University	Autologous HSC	IV	Not mentioned	200	2021	na	NCT05029206
46	MS	Hope Biosciences Stem Cell Research Foundation	Adipose MSC (HB-adMSCs)	IV	Not mentioned	24	2021	2	NCT05116540
47	Progressive MS	Haukeland University Hospital	Autologous BM MSC	IT	Not mentioned	18	2021	1/2	NCT04749667
48	MS	ImStem Biotechnology	ESC MSC (IMS001)	IV	Low or high dose	30	2021	1	NCT04956744

Abbreviations: BM, bone marrow; BMSC, bone marrow stem cells; ESC; embryonic stem cells; HSC, hemopoietic stem cells; IT, intrathecal; IV, intravenous; M, million; MS. Multiple sclerosis; MSC, mesenchymal stem cells; na, not applicable NSC, neural stem cells; SubC, subcutaneous; UCB, umbilical cord blood; WJ, Wharton Jelly.

immunoregulatory and trophic properties both in vitro and in vivo along with upregulation of trophic factors including hepatocyte growth factor,[59,60,65] with encouraging results of improved muscle strength, and bladder function in half of the participants. Additionally, four-tenth of participants had a reduction in expanded disability status scale scores compared to baseline, with no serious adverse events reported.[25]

There had been some success reported with immunotherapy, such as the use of autologous T cells primed against myelin basic protein, myelin oligodendrocyte glycoprotein, and proteolipid protein (PLP) resulting in a reduced annualized relapse rate in a randomized controlled trial.[57] The large majority of trials using MSCs were of small number (n = 7-60), which showed similar outcomes with either intravenous or intrathecal approaches.[40,66-69]

Rare Neurodegenerative Diseases

A group of rare ND has been grouped into this section including Pelizaeus-Merzbacher disease (PMD), Batten disease, and a few enzymes deficiency disorders (Table 4). PMD is an X-linked hypomyelinating disorder that progressively degenerate the white matter of the brain causing problems in learning, coordination, and motor skills.[70-72] Gene duplications and point mutation of the PLP1 gene result in abnormal myelin production or abnormal trafficking in the endoplasmic reticulum of oligodendrocytes.[73,74] Neuronal Ceroid Lipofuscinosis (NCL), also known as Batten disease is a heterogenous class of lysosomal storage disease characterized by neurodegeneration that share common clinical features of progressive visual and cognitive decline.[75]

To date, there have been a few stem cell based clinical trials, with cell sources ranging from human fetal CNS-derived NSCs to hemopoietic stem cells (HSCs) from BM and perinatal tissues including placental, cord, and cord blood. Direct CNS delivery of allogeneic CNS-derived NSCs was used in 3 trials and umbilical cord blood-derived oligodendrocyte-like cells in one. The use of human CNS stem cells for treatment of NCL is a first-in-human clinical trial involving a purified population of human NSCs, for a ND (NCT00337636). Results concluded that neural cell transplantation in NCL is largely safe, with evidence of long-term engraftment determined at post-mortem, suggesting a therapeutic role for NSCs in ND. Nevertheless, it remains crucial to target earlier disease stages for a better runway to curtail disease progression and potential clinical improvement.[76]

In the case of PMD, a phase I trial with fetal NSCs in 4 PMD participants showed successful engraftment and donor-derived myelination in 2009.[71,72] However, there was evidence of disease progression in 2 subjects at long-term follow-up. There was evidence of donor-specific alloantibodies, which may necessitate immunosuppressive therapies for such allogeneic cell therapy. Kurtzberg et al. performed a clinical trial using cord blood-derived oligodendrocyte-like cells (DUOC-01) for inherited metabolic diseases (NCT02254863).[77] Preliminary results on participants (n = 7) with Batten disease demonstrated safety and feasibility parameters for transplantation of DUOC-01, and promising results in 4 out of the 5 survivors showing no evidence of the disease on magnetic resonance imaging.[78]

The rarity of such ND makes it challenging to recruit patients for any trials. As the use of autologous cells is precluded in genetic diseases, unless in the context of

Table 4. Clinical trials listed on clinicaltrials.gov for Batten and Pelizaeus-Merzbacher diseases.

No	Disease	Sponsor	Cell type	Route	Cell dose	Planned participants	Year	Phase	Clinical trial #
1	Batten disease	StemCells, Inc	CNS-SC	Stereotactic injection into subcortical sites and lateral ventricles	Low dose (700M), high dose (1400M)	6	2006	1	NCT00337636
2	PMD	StemCells, Inc.	CNS-SC	Intracerebral	300 M	4	2009	1	NCT01005004
3	PMD	StemCells, Inc.	CNS-SC	Intracerebral	300 M	4	2011	1	NCT01391637
4	Batten/MPS II/NP/ PMD/inborn metabolic brain disease/	Joanne Kurtzberg	UCB derived oligodendrocyte-like cells (DUOC-01)	IT	50.1-350.1 M/kg	12	2014	1	NCT02254863
5	Batten/NP/ Gaucher's/	Masonic Cancer Center	allogenic BM and UCB HSC	IV	Not mentioned	135	1995	2,3	NCT00176904
6	NP/PMD/Tay Sachs/Krabbe/ Batten/Sandhorf disease	Talaris Therapeutics Inc	allogenic HSC	IV	Not mentioned	30	2011	1,2	NCT01372228
7	Batten/MPS I and IV/NP/Gauchers/ Krabbe/Fucosidosis	New York Medical College	placental derived SC and cord blood	IV	Not mentioned	43	2013	1	NCT01586455

Abbreviations: BM, bone marrow; CNS SC, central nervous system neural stem cells; HSC, hemopoietic stem cells; IT, intrathecal; IV, intravenous; M, million; MPS, Mucopolysaccharidosis; NP, Niemann-Pick; PMD, Pelizaeus-Merzbacher disease; SC, stem cells; UCB, umbilical cord blood.

Table 5 Clinical Trials listed on clinicaltrials.gov for Huntington's disease

No	Disease	Sponsor	Cell type	Route	Cell dose	Planned participants	Year	Phase	Clinical trial #
1	Huntington's disease	Assistance Publique - Hôpitaux de Paris	Fetal neurons	Intracerebral	Not mentioned	54	2002	2	NCT00190450
2	Huntington's disease's	Azidus Brasil	Immature dental pulp MSC (NestaCell-HDTM)	IV	3 M/kg or 6 M/kg	6	2017	1	NCT02728115
3	Huntington's disease	Azidus Brasil	Immature dental pulp MSC (NestaCell-HDTM)	IV	9 M/kg or 18 M/kg	35	2018	2	NCT03252535
4	Huntington's disease	Azidus Brasil	Immature dental pulp MSC (NestaCell-HDTM)	IV	24 M/kg	35	2020	2,3	NCT04219241

Abbreviations: IV, intravenous; M, million; MSC, mesenchymal stem cells.

gene-edited approaches, the immediate focus should be the development of effective immunosuppressive protocols, and early administration of allogeneic stem cells.[75,79]

Huntington's Disease

Huntington's disease (HD) is an autosomal dominant ND where cognitive, motor, and psychiatric abilities progressively decline over 2-3 decades. HD mainly affects the medium spiny striatal neurons, making it an attractive target for cell therapy.[80] Of the 4 trials retrieved, only 1 used fetal neuronal tissue (Table 5). In that seminal French study, human fetal-derived graft demonstrated survival and significant improvements in both motor and cognitive function in 3 participants over a 6-year period[7,81] but faded off thereafter suggesting the lack of a permanent cure. The other 3 trials involved the use of MSCs, specifically Cellavita-HD, with the latest phase II/III trials initiated in 2020.

There are many other active clinical trials that aim to treat HD, as reviewed by Kim et al.,[82] with stem cell therapies accounting for around 10% (3/28). The advantage of stem cells is that the new neurons can replace degenerating cells in the affected brain regions and, consequently, ameliorate the disease profile. This efficacy might be further improved by engineering the cells to hyper-secrete BDNF, GDNF, or other neurotropic factors or combining stem cells with genetic modification therapy for HD.

Macular Degeneration

There are 2 main forms of macular degeneration (MD); Stargardt disease (STGD1) being the most common cause of MD in children and young adults,[83] and age-related macular degeneration affecting up to 8.7% of the world's population[84] and Stargardt disease results from ABCA4 gene mutations[85] and results in progressively severe impairment of sight. Atrophic age-related MD shares the key features of progressive atrophy of retinal pigment epithelium (RPE) and overlying photoreceptor cells as STGD1,[83] while age-related MD is due to exposure to immune-mediated and oxidative

Table 6. Clinical trials listed on clinicaltrials.gov for macular degeneration.

No	Disease	Sponsor	Cell type	Route	Cell dose	Planned participants	Year	Phase	Clinical trial #
1	Stargartd disease	Astellas Institute for Regenerative Medicine	ESC RPE (MA09-hRPE)	Subretinal	50 000, 100 000, 150 000 and 200 000	12	2011	1/2	NCT01469832
2	Stargartd disease	Astellas Institute for Regenerative Medicine	ESC RPE (MA09-hRPE)	Subretinal	50 000, 100 000, 150 000 and 200 000	12	2013	1/2	NCT02941991
3	AMD	Astellas Institute for Regenerative Medicine	ESC RPE (MA09-hRPE)	Subretinal	50 000, 100 000, 150 000 and 200 000	13	2011	1/2	NCT01344993
4	AMD	Astellas Institute for Regenerative Medicine	ESC RPE (MA09-hRPE)	Subretinal	50 000, 100 000, 150 000 and 200 000	11	2013	1/2	NCT02463344
5	Stargartd disease	Astellas Institute for Regenerative Medicine	ESC RPE (MA09-hRPE)	subretinal	50 000, 100 000, 150 000 and 200 000	13	2011	1/2	NCT01345006
6	Stargartd disease	Astellas Institute for Regenerative Medicine	ESC RPE (MA09-hRPE)	Subretinal	50 000, 100 000, 150 000 and 200 000	13	2012	1/2	NCT02445612
7	AMD	StemCells, Inc	CNS SC	Subretinal	200 000/ 1 M	15	2012	1/2	NCT01632527
8	AMD	Lineage Therapeutics/ Hoffmann-La Roche	ESC RPE (Opregen)	Subretinal	50 000-200 000	24	2015	1/2	NCT02286089
9	AMD/Stargartd	Federal University of São Paulo	ESC RPE	Subretinal	100 000	15	2015	1/2	NCT02903576
10	Dry MD/GA	Regenerative Patch Technologies, LLC	ESC RPE (CPCB-RPE1)	Subretinal	100 000	16	2016	1/2	NCT02590692
11	Macular degenerative disease	Astellas Institute for Regenerative Medicine	ESC RPE (ASP7316)	Subretinal	Not mentioned	36	2018	1/2	NCT03167203
12	AMD	Astellas Institute for Regenerative Medicine	ESC RPE (ASP7317)	Into the macular	Low, med, high cell dose	18	2018	1	NCT03178149
13	AMD	National Eye Institute	Autologous iPSC RPE	Subretinal	Not mentioned	20	2020	1/2a	NCT04339764
14	AMD	Moorfields Eye Hospital NHS Foundation Trust	ESC RPE (PF-05206388)	Intraocular	Not mentioned	10	2021	1	NCT01691261
15	Macular degeneration	Beijing Tongren Hospital	Autologous iPSC RPE	Subretinal	Not mentioned	10	2022	1	NCT05445063
16	AMD	Institute of Biophysics and Cell Engineering of National Academy of Sciences of Belarus	Autologous cultured retinal stem and progenitor cells	Subretinal	Not mentioned	20	2022	1/2	NCT05187104
17	AMD	Janssen Research & Development	Umbilical tissue cells (CNTO2476)	Subretinal	60 K, 120 K, 300 K, 560 K	39	2010	1/2	NCT01226628
18	GA MD	Janssen Research & Development	Umbilical tissue cells (CNTO2476)	Subretinal	0.3 M	21	2015	2	NCT02659098
19	AMD/Stargartd disease	University of San Paulo	Autologous BM SC	Intravitreal	10 M	20	2011	1/2	NCT01518127
20	Retinopathy/Age-related and hereditary macular degeneration	University of California	Autologous BM SC	Intravitreal	Not mentioned	15	2012	1	NCT01736059
21	Retinopathy/Age-related and hereditary macular degeneration	MD Stem Cells	Autologous BM SC	Retrobulbar, intravitreal, subretinal, intraoptic	240 M (retrobulbar), 4 M (intravitreal), 8 M (subretinal, intraoptic)	500	2016	na	NCT03011541

Table 6. Continued

No	Disease	Sponsor	Cell type	Route	Cell dose	Planned participants	Year	Phase	Clinical trial #
22	Macular degeneration/RP	Foundation of Orthopaedics and Regenerative Medicine	UC MSC	IV, subtenon	100 M	20	2022	1	NCT05147701

Abbreviations: AMD, age-related macular degeneration; BM SC, bone marrow stem cells; CNS SC, human central nervous system neural stem cells; ESC, embryonic stem cells; GA, geographic atrophy; iPSC, induced pluripotent stem cells; IV, intravenous; million; na, not applicable RP, retinitis pigmentosa; RPE, retinal pigment epithelium; UC MSC, umbilical cord mesenchymal stem cells.

stresses from genetic and environmental factors.[86] They are currently incurable although replenishment of degenerating RPE cells with healthy cells offers the possibility of benefit by supporting the function and survival of overlying photoreceptor cells.[86]

There are 22 trials listed of which 16 involved neural-related cells (Table 6). ESCs-derived RPE cells from the ESCs line MA09 were used in 6 of these trials. The first ESCs-derived RPE cells were initiated in 2011 with 12 participants (NCT01469832) where subretinal injections of 200 000 ESCs-RPE cells were found to be safe, although no benefit was established.[83] Another 2 trials (NCT01345006 for STGD1 and NCT01344993 for age-related MD) demonstrated similar reassuring safety outcomes using the same hESCs-RPE source for up to 37 months post-transplantation.[86,87] In these 2 trials where only 1 eye was treated, best-corrected visual acuity (BCVA) improved in the majority of treated eyes (10 out of 17) in addition to improvements in vision-related quality-of-life measures.[86] Since then, there have been at least 4 different ESCs derived RPE cell products (CPCB-RPE1, ASP7316, ASP7317, and PF-05206388) developed by 3 companies that are currently in phase I/II clinical trials for different forms of MD (Table 6). Among them, CPCB-RPE1 has been shown to be safe and well tolerated by participants with advanced dry age-related MD at 1-year post-transplantation with improvements of BCVA in 4 out of 15 participants.[88] Instances of focally reduced sensitivity and thinning in the hyperpigmented retina at higher doses of hESCs derived RPE has been observed which suggest the potential for harm and indicate that intervention at earlier stages of degeneration should be approached with caution.[83]

The first clinical trial using autologous human iPSCs derived RPE for MD was led by Dr Takahashi in 1 patient in 2013.[89] The patient suffered no severe adverse event or rejection aside from cystoid macular edema, with BCVA remaining stable at 1-year post-transplantation (JPRN-UMIN000011929).[89] There are currently 2 other autologous iPSCs-RPE trials for MD registered (NCT04339764 in 2020 and NCT05445063 in 2022).

The majority of the donor cells for treatment of MD are generally differentiated RPE cell types. Nonetheless, we found 6 trials using autologous bone marrow stem cells (BMSCs), human umbilical tissue-derived cells, and allogenic umbilical cord MSC for cell therapy through various routes (Table 6). There are currently no phase III trials using cell therapy for MD despite the first trial taking place back in 2011, alluding to the difficulties in developing effective cell therapies for MD.

Retinitis Pigmentosa

Retinitis pigmentosa (RP) is an inherited retinal dystrophy that is characterized by the onset of night blindness, loss of peripheral vision, and loss of central vision in the later stages through the death of photoreceptors.[90] There is no effective treatment for RP as once photoreceptors are lost, they do not regenerate, with most being legally blind by age 40.

Six of the 19 cell therapy trials are performed with cells of neural lineage (Table 7). Five of them used retinal progenitor cells (RPCs) that can be expanded and differentiated into retinal cells, and have been derived from either fetal ocular tissues (n = 4) or ESCs (n = 1). Transplanted RPCs have not been rejected immunologically, nor formed tumors in the absence of immunosuppressants.[91,92] Another trial transplanting 3-6 million fetal derived-RPCs intravitreally (n = 54) was shown to be safe at 12 months follow-up. Based on the results published on clinicaltrials.gov, there seems to have beneficial effects at the higher cell dose with significant improvement of BCVA and other measures between treated and non-treated eyes.[92] There is a single trial that utilizes human fetal NPCs directly instead of more differentiated and lineage-restricted retinal progenitor cells (NCT04284293), while others used BM-derived HSCs, or MSCs from different sources (Table 7). More research needs to be focused on (1) improving the efficacy of transplants with photoreceptor potential, (2) improve survival of cells implanted in the subretinal space in areas of geographic atrophy, and (3) factors impacting the immunological readiness of the subretinal space to facilitate longer survival of the transplanted cells.[93]

Discussion

We found 8 clinical trials involving NSCs, 10 involving neural progenitors, and 23 involving differentiated neural cells (Supplementary Table S1). However, only clinical trials listed on clinicaltrials.gov were covered and while it is the largest clinical trials registry, this would inevitably exclude those only listed on other trials' databases such as EU Clinical Trials Register and Japan Registry for Clinical Trials and others. NSCs have shown potential for the treatment of ND but have yet to be fully exploited. The mammalian brain has a limited ability for repair and regeneration through neurogenesis and gliogenesis. Of the available cell sources for therapy, NSCs have an advantage over the other cell sources as it can not only contribute to multipotent differentiation in replacing neural and non-neural cell types but also participate in modulating inflammatory damage through the secretion of trophic factors. Fetal tissue grafts on the other hand require multiple donors due to the small quantity of stem cells per donor and poor graft survival, with the need to coordinate collection, processing, and analysis before transplantation, and thus presents a significant logistical challenge. While tissue grafts serve to replace the required cells and produce cytokine/growth hormones etc., more

Table 7. Clinical trials listed on clinicaltrials.gov for retinitis pigmentosa.

No	Disease	Sponsor	Cell type	Route	Cell dose	Planned participants	Year	Phase	Clinical trial #
1	Retinitis Pigmentosa	ReNeuron Limited	fetal RPC	Subretinal	200K, 500K, 1M	29	2015	1/2	NCT02464436
2	Retinitis Pigmentosa	jCyte, Inc	Fetal RPC (jCell)	Intravitreal	0.5-3M	38	2015	1/2	NCT02320812
3	Retinitis Pigmentosa	jCyte, Inc	Fetal RPC (jCell)	Intravitreal	3 or 6M	84	2017	2	NCT03073733
4	Retinitis Pigmentosa	jCyte, Inc	Fetal RPC (jCell)	Intravitreal	6M	30	2020	2	NCT04604899
5	Retinitis Pigmentosa due to monogenic mutation	Centre d'Etude des Cellules Souches	ESCs retinal pigment epithelium	Subretinal	not mentioned	12	2019	1/2	NCT03963154
6	Retinitis Pigmentosa	Cedars-Sinai Medical Center	Fetal neural progenitor cells (CNS10-NPC)	Subretinal	300K and 1M	16	2021	1/2	NCT04284293
7	Retinitis Pigmentosa	University of Sao Paulo	Autologous BM SC	Intravitreal	10M	5	2009	1	NCT01068561
8	Retinitis Pigmentosa	University of Sao Paulo	Autologous BM SC	Intravitreal	10M	50	2011	2	NCT01560715
9	Retinitis Pigmentosa	University of California, Davis	Autologous BM CD34+ cells	Intravitreal	1-7 M	15	2012	1	NCT01736059
10	Retinitis Pigmentosa	University of California, Davis	Autologous BM CD34+ cells	Intravitreal	Not mentioned	4	2021	1	NCT04925687
11	Retinitis Pigmentosa	Mahidol University	Autologous BM MSC	Intravitreal	1 M	14	2012	1	NCT01531348
12	Retinitis Pigmentosa	Red de Terapia Celular	Autologous BM SC	Intravitreal	5-60 M	8	2014	1	NCT02280135
13	Retinitis Pigmentosa	MD Stem Cells	Autologous BM SC	Retrobulbar, Intravitreal, Subretinal, Intraoptic	240 M (retrobulbar), 4M(intravitreal), 8 M (subretinal, intraoptic)	500	2017	na	NCT03011541
14	Retinitis Pigmentosa	PT. Prodia Stem Cell Indonesia	UC MSC	Peribulbar	1 M	18	2018	1/2	NCT04315025
15	Retinitis Pigmentosa	Ankara Universitesi Teknokent	WJ MSC	Subtenon	2-6 M	32	2019	3	NCT04224207
16	Retinitis Pigmentosa	Jinnah Burn and Reconstructive Surgery Centre, Lahore	UC MSC	Subtenon, suprachoroidal	Not mentioned	50	2021	2	NCT04763369
17	Retinitis Pigmentosa	University of California, Davis	Autologous BM CD34+ cells	Intravitreal	Not mentioned	4	2021	1	NCT04925687
18	Retinitis Pigmentosa	TC Erciyes University	WJ MSC or exosomes	Subtenon	Not mentioned	135	2022	2,3	NCT05413148
19	Retinitis Pigmentosa	The Foundation for Orthopaedics and Regenerative Medicine	UC MSC	IV and subtenon	100 M	20	2022	1	NCT05147701

Abbreviations BM, bone marrow; ESC, embryonic stem cells; IV, intravenous; MSC, mesenchymal stem cells; na, not applicable RP, retinitis pigmentosa; RPC, retinal progenitor cells; SC, stem cells; UC, umbilical cord; WJ, Wharton Jelly.

such as repair of pathways, axonal outgrowth restorations are existing challenges that hamper the engraftment of tissue grafts, and their overall survival.[94] Bioengineered scaffolds that reproduce the conditions of the extracellular matrix, enhance exchange, and crosstalk between different cell types, engrafted and hosts' cells, and healthy and injured

tissues while providing cell support will be a step forward. The use of advanced cryopreservation techniques such as vitrification may help address some logistical issues with the scheduling of neurosurgical transplantation.[95] The use of hESCs-derived RPE has been extensively used for MD, which presents a theoretical risk of immune rejection. It is hoped that the advent of autologous-iPSCs-derived RPE/RPCs may circumvent the immune considerations although both hESCs and iPSCs-derived cells have tumorigenic potential albeit a small risk. To err on the side of caution, differentiated cells are preferred (Supplementary Table S1), where a very consistent and high purity cells of interest can be obtained for clinical use, doing away with the dangers of tumorigenicity and/or unintended differentiation or proliferation of stem cells. Further improvements in precise differentiation of the desired cells from different cell sources, with minimal risk of tumorigenicity remain a priority[80,96] with standardization in the characterization of these cells to define its multi-potency or lineage-restriction. For cell therapy via direct neurotransplantation, the need to develop minimally invasive but highly precise surgical techniques is also crucial and it is timely for now, with the higher resolution imaging currently available, to allow accurate graft placement, and post-surgery observation.[14] It is also important to design randomized placebo-controlled trials while standardizing the disease rating scales and long-term measurable outcomes to establish effectiveness of the treatment. Finally, we will need to push forward with earlier detection and intervention for the best potential of cellular therapy.

Acknowledgments

The graphical abstract was created with BioRender.com.

Funding

JKYC is supported by Singapore's Ministry of Health (MOH-001221-01, MOH-000932-00,) and National Medical Research Council (CIRG/1484/2018, NMRC CSA (SI)/008/2016, NMRC STaR22jul-0004).

Conflict of Interest

The authors indicated no potential conflicts of interest.

Author Contributions

YP: conceptualizing and design of the paper, data acquisition, analysis of data and drafting the manuscript, EG and JC: critical review of the manuscript. All authors: final approval of manuscript.

Data Availability

All data are incorporated into the article and its online supplementary material.

Supplementary Material

Supplementary material is available at *Stem Cells Translational Medicine* online.

References

1. Gage FH. Mammalian neural stem cells. *Science*. 2000;287(5457):1433-1438. https://doi.org/10.1126/science.287.5457.1433
2. Ray J, Peterson DA, Schinstine M, Gage FH. Proliferation, differentiation, and long-term culture of primary hippocampal neurons. *Proc Natl Acad Sci USA*. 1993;90(8):3602-3606. https://doi.org/10.1073/pnas.90.8.3602
3. Temple S. The development of neural stem cells. *Nature*. 2001;414(6859):112-117. https://doi.org/10.1038/35102174
4. Reynolds BA, Weiss S. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science*. 1992;255(5052):1707-1710. https://doi.org/10.1126/science.1553558
5. Fan Y, Marcy G, Lee ES, et al. Regionally-specified second trimester fetal neural stem cells reveals differential neurogenic programming. *PLoS One*. 2014;9(9):e105985. https://doi.org/10.1371/journal.pone.0105985
6. Kovacs GG. Concepts and classification of neurodegenerative diseases. *Handb Clin Neurol*. 2017;145:301-307. https://doi.org/10.1016/B978-0-12-802395-2.00021-3
7. Bachoud-Levi AC, Gaura V, Brugieres P, et al. Effect of fetal neural transplants in patients with Huntington's disease 6 years after surgery: a long-term follow-up study. *Lancet Neurol*. 2006;5(4):303-309. https://doi.org/10.1016/S1474-4422(06)70381-7
8. Cicchetti F, Saporta S, Hauser RA, et al. Neural transplants in patients with Huntington's disease undergo disease-like neuronal degeneration. *Proc Natl Acad Sci USA*. 2009;106(30):12483-12488. https://doi.org/10.1073/pnas.0904239106
9. Keene CD, Chang RC, Leverenz JB, et al. A patient with Huntington's disease and long-surviving fetal neural transplants that developed mass lesions. *Acta Neuropathol*. 2009;117(3):329-338. https://doi.org/10.1007/s00401-008-0465-0
10. Fink KD, Deng P, Torrest A, et al. Developing stem cell therapies for juvenile and adult-onset Huntington's disease. *Regen Med*. 2015;10(5):623-646. https://doi.org/10.2217/rme.15.25
11. Chen KS, Sakowski SA, Feldman EL. Intraspinal stem cell transplantation for amyotrophic lateral sclerosis. *Ann Neurol*. 2016;79(3):342-353. https://doi.org/10.1002/ana.24584
12. Finberg JP, Rabey JM. Inhibitors of MAO-A and MAO-B in Psychiatry and Neurology. *Front Pharmacol*. 2016;7:340. https://doi.org/10.3389/fphar.2016.00340
13. Guo X, Tang L, Tang X. Current developments in cell replacement therapy for Parkinson's disease. *Neuroscience*. 2021;463:370-382. https://doi.org/10.1016/j.neuroscience.2021.03.022
14. Jang SE, Qiu L, Chan LL, Tan E-K, Zeng Li. Current status of stem cell-derived therapies for Parkinson's disease: from cell assessment and imaging modalities to clinical trials. *Front Neurosci*. 2020;14:558532. https://doi.org/10.3389/fnins.2020.558532
15. Lindvall O, Rehncrona S, Gustavii B, et al. Fetal dopamine-rich mesencephalic grafts in Parkinson's disease. *Lancet*. 1988;2(8626-8627):1483-1484. https://doi.org/10.1016/s0140-6736(88)90950-6
16. Madrazo I, Leon V, Torres C, et al. Transplantation of fetal substantia nigra and adrenal medulla to the caudate nucleus in two patients with Parkinson's disease. *N Engl J Med*. 1988;318(1):51. https://doi.org/10.1056/NEJM198801073180115
17. Freed CR, Breeze RE, Rosenberg NL, et al. Transplantation of human fetal dopamine cells for Parkinson's disease. Results at 1 year. *Arch Neurol*. 1990;47(5):505-512. https://doi.org/10.1001/archneur.1990.00530050021007
18. Freed CR, Greene PE, Breeze RE, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med*. 2001;344(10):710-719. https://doi.org/10.1056/NEJM200103083441002
19. Olanow CW, Goetz CG, Kordower JH, et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. *Ann Neurol*. 2003;54(3):403-414. https://doi.org/10.1002/ana.10720

20. Olanow CW, Gracies JM, Goetz CG, et al. Clinical pattern and risk factors for dyskinesias following fetal nigral transplantation in Parkinson's disease: a double blind video-based analysis. *Mov Disord*. 2009;24(3):336-343. https://doi.org/10.1002/mds.22208
21. Carlsson T, Winkler C, Lundblad M, et al. Graft placement and uneven pattern of reinnervation in the striatum is important for development of graft-induced dyskinesia. *Neurobiol Dis*. 2006;21(3):657-668. https://doi.org/10.1016/j.nbd.2005.09.008
22. Politis M, Wu K, Loane C, et al. Serotonergic neurons mediate dyskinesia side effects in Parkinson's patients with neural transplants. *Sci Transl Med*. 2010;2(38):38ra46. https://doi.org/10.1126/scitranslmed.3000976
23. Han F, Hu B. Stem cell therapy for Parkinson's disease. *Adv Exp Med Biol*. 2020;1266:21-38. https://doi.org/10.1007/978-981-15-4370-8_3
24. Urrutia DN, Caviedes P, Mardones R, et al. Comparative study of the neural differentiation capacity of mesenchymal stromal cells from different tissue sources: An approach for their use in neural regeneration therapies. *PLoS One*. 2019;14(3):e0213032. https://doi.org/10.1371/journal.pone.0213032
25. Harris VK, Stark J, Vyshkina T, et al. Phase I trial of intrathecal mesenchymal stem cell-derived neural progenitors in progressive multiple sclerosis. *EBioMedicine*. 2018;29:23-30. https://doi.org/10.1016/j.ebiom.2018.02.002
26. van Horne CG, Quintero JE, Slevin JT, et al. Peripheral nerve grafts implanted into the substantia nigra in patients with Parkinson's disease during deep brain stimulation surgery: 1-year follow-up study of safety, feasibility, and clinical outcome. *J Neurosurg*. 2018;129(6):1550-1561. https://doi.org/10.3171/2017.8.JNS163222
27. Quintero JE, Slevin JT, Gurwell JA, et al. Direct delivery of an investigational cell therapy in patients with Parkinson's disease: an interim analysis of feasibility and safety of an open-label study using DBS-Plus clinical trial design. *BMJ Neurol Open*. 2022;4(2):e000301. https://doi.org/10.1136/bmjno-2022-000301
28. Mao Z, Zhang S, Chen H. Stem cell therapy for amyotrophic lateral sclerosis. *Cell Regen*. 2015;4:11. https://doi.org/10.1186/s13619-015-0026-7
29. Sykova E, Rychmach P, Drahoradova I, et al. Transplantation of mesenchymal stromal cells in patients with amyotrophic lateral sclerosis: results of phase I/IIa clinical trial. *Cell Transplant*. 2017;26(4):647-658. https://doi.org/10.3727/096368916X693716
30. Pandya RS, Mao LL, Zhou EW, et al. Neuroprotection for amyotrophic lateral sclerosis: role of stem cells, growth factors, and gene therapy. *Cent Nerv Syst Agents Med Chem*. 2012;12(1):15-27. https://doi.org/10.2174/187152412800229152
31. Lunn JS, Sakowski SA, Kim B, Rosenberg AA, Feldman Eva L. Vascular endothelial growth factor prevents G93A-SOD1-induced motor neuron degeneration. *Dev Neurobiol*. 2009;69(13):871-884. https://doi.org/10.1002/dneu.20747
32. Xu L, Yan J, Chen D, et al. Human neural stem cell grafts ameliorate motor neuron disease in SOD-1 transgenic rats. *Transplantation*. 2006;82(7):865-875. https://doi.org/10.1097/01.tp.0000235532.00920.7a
33. Lepore AC, Rauck B, Dejea C, et al. Focal transplantation-based astrocyte replacement is neuroprotective in a model of motor neuron disease. *Nat Neurosci*. 2008;11(11):1294-1301. https://doi.org/10.1038/nn.2210
34. Hefferan MP, Galik J, Kakinohana O, et al. Human neural stem cell replacement therapy for amyotrophic lateral sclerosis by spinal transplantation. *PLoS One*. 2012;7(8):e42614. https://doi.org/10.1371/journal.pone.0042614
35. Glass JD, Boulis NM, Johe K, et al. Lumbar intraspinal injection of neural stem cells in patients with amyotrophic lateral sclerosis: results of a phase I trial in 12 patients. *Stem Cells*. 2012;30(6):1144-1151. https://doi.org/10.1002/stem.1079
36. Riley J, Glass J, Feldman EL, et al. Intraspinal stem cell transplantation in amyotrophic lateral sclerosis: a phase I trial, cervical microinjection, and final surgical safety outcomes. *Neurosurgery*. 2014;74(1):77-87. https://doi.org/10.1227/NEU.0000000000000156
37. Feldman EL, Boulis NM, Hur J, et al. Intraspinal neural stem cell transplantation in amyotrophic lateral sclerosis: phase 1 trial outcomes. *Ann Neurol*. 2014;75(3):363-373. https://doi.org/10.1002/ana.24113
38. Appel SH, Engelhardt JI, Henkel JS, et al. Hematopoietic stem cell transplantation in patients with sporadic amyotrophic lateral sclerosis. *Neurology*. 2008;71(17):1326-1334. https://doi.org/10.1212/01.wnl.0000327668.43541.22
39. Cashman N, Tan LY, Krieger C, et al. Pilot study of granulocyte colony stimulating factor (G-CSF)-mobilized peripheral blood stem cells in amyotrophic lateral sclerosis (ALS). *Muscle Nerve*. 2008;37(5):620-625. https://doi.org/10.1002/mus.20951
40. Karussis D, Karageorgiou C, Vaknin-Dembinsky A, et al. Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. *Arch Neurol*. 2010;67(10):1187-1194. https://doi.org/10.1001/archneurol.2010.248
41. Prabhakar S, Marwaha N, Lal V, et al. Autologous bone marrow-derived stem cells in amyotrophic lateral sclerosis: a pilot study. *Neurol India*. 2012;60(5):465-469. https://doi.org/10.4103/0028-3886.103185
42. Baek W, Kim Ys Fau - Koh SH, Koh Sh Fau - Lim SW et al. Stem cell transplantation into the intraventricular space via an Ommaya reservoir in a patient with amyotrophic lateral sclerosis. (0390-5616 (Print)).
43. Mazzini L, Mareschi K, Ferrero I, et al. Autologous mesenchymal stem cells: clinical applications in amyotrophic lateral sclerosis. *Neurol Res*. 2006;28(5):523-526. https://doi.org/10.1179/016164106X116791
44. Mazzini L, Mareschi K, Ferrero I, et al. Stem cell treatment in amyotrophic lateral sclerosis. *J Neurol Sci*. 2008;265(1-2):78-83. https://doi.org/10.1016/j.jns.2007.05.016
45. Mazzini L, Mareschi K, Ferrero I, et al. Mesenchymal stromal cell transplantation in amyotrophic lateral sclerosis: a long-term safety study. *Cytotherapy*. 2012;14(1):56-60. https://doi.org/10.3109/14653249.2011.613929
46. Mazzini L, Ferrero I, Luparello V, et al. Mesenchymal stem cell transplantation in amyotrophic lateral sclerosis: a phase I clinical trial. *Exp Neurol*. 2010;223(1):229-237. https://doi.org/10.1016/j.expneurol.2009.08.007
47. Chen L, Chen D, Xi H, et al. Olfactory ensheathing cell neurorestorotherapy for amyotrophic lateral sclerosis patients: benefits from multiple transplantations. *Cell Transplant*. 2012;21(Suppl 1):S65-S77. https://doi.org/10.3727/096368912X633789
48. Mazzini L, Gelati M, Profico DC, et al. Human neural stem cell transplantation in ALS: initial results from a phase I trial. *J Transl Med*. 2015;13:17. https://doi.org/10.1186/s12967-014-0371-2
49. Mazzini L, Gelati M, Profico DC, et al; ALS-NSCs Trial Study Group. Results from phase I clinical trial with intraspinal injection of neural stem cells in amyotrophic lateral sclerosis: a long-term outcome. *Stem Cells Transl Med*. 2019;8(9):887-897. https://doi.org/10.1002/sctm.18-0154
50. Balfour H. AstroRx® shows promise in early phase amyotrophic lateral sclerosis trial. Available at https://doi.org/https://www.europeanpharmaceuticalreview.com/news/137141/astrorx-shows-promise-in-early-phase-amyotrophic-lateral-sclerosis-trial/. Published 2020. Accessed 27 September, 2022.
51. Baloh RH, Johnson JP, Avalos P, et al. Transplantation of human neural progenitor cells secreting GDNF into the spinal cord of patients with ALS: a phase 1/2a trial. *Nat Med*. 2022;28(9):1813-1822. https://doi.org/10.1038/s41591-022-01956-3
52. Sykova E, Cizkova D, Kubinova S. Mesenchymal stem cells in treatment of spinal cord injury and amyotrophic lateral sclerosis. *Front Cell Dev Biol*. 2021;9:695900. https://doi.org/10.3389/fcell.2021.695900

53. Comi G, Radaelli M, Soelberg Sorensen P. Evolving concepts in the treatment of relapsing multiple sclerosis. *Lancet*. 2017;389(10076):1347-1356. https://doi.org/10.1016/S0140-6736(16)32388-1
54. Kieseier BC, Hartung HP. Current disease-modifying therapies in multiple sclerosis. *Semin Neurol*. 2003;23(2):133-146. https://doi.org/10.1055/s-2003-41138
55. Johnson KP. Natalizumab (Tysabri) treatment for relapsing multiple sclerosis. *Neurologist*. 2007;13(4):182-187. https://doi.org/10.1097/01.nrl.0000263760.53418.5b
56. Jeffery DR, Markowitz CE, Reder AT, Weinstock-Guttman B, Tobias K. Fingolimod for the treatment of relapsing multiple sclerosis. *Expert Rev Neurother*. 2011;11(2):165-183. https://doi.org/10.1586/ern.10.193
57. Fox E, Wynn D, Cohan S, et al. A randomized clinical trial of autologous T-cell therapy in multiple sclerosis: subset analysis and implications for trial design. *Mult Scler*. 2012;18(6):843-852. https://doi.org/10.1177/1352458511428462
58. Ontaneda D, Thompson AJ, Fox RJ, Cohen JA. Progressive multiple sclerosis: prospects for disease therapy, repair, and restoration of function. *Lancet*. 2017;389(10076):1357-1366. https://doi.org/10.1016/S0140-6736(16)31320-4
59. Harris VK, Faroqui R, Vyshkina T, Sadiq SA. Characterization of autologous mesenchymal stem cell-derived neural progenitors as a feasible source of stem cells for central nervous system applications in multiple sclerosis. *Stem Cells Transl Med*. 2012;1(7):536-547. https://doi.org/10.5966/sctm.2012-0015
60. Harris VK, Yan QJ, Vyshkina T, et al. Clinical and pathological effects of intrathecal injection of mesenchymal stem cell-derived neural progenitors in an experimental model of multiple sclerosis. *J Neurol Sci*. 2012;313(1-2):167-177. https://doi.org/10.1016/j.jns.2011.08.036
61. Fu L, Zhu L, Huang Y, et al. Derivation of neural stem cells from mesenchymal stemcells: evidence for a bipotential stem cell population. *Stem Cells Dev*. 2008;17(6):1109-1121. https://doi.org/10.1089/scd.2008.0068
62. Hermann A, Gastl R, Liebau S, et al. Efficient generation of neural stem cell-like cells from adult human bone marrow stromal cells. *J Cell Sci*. 2004;117(Pt 19):4411-4422. https://doi.org/10.1242/jcs.01307
63. Mareschi K, Novara M, Rustichelli D, et al. Neural differentiation of human mesenchymal stem cells: evidence for expression of neural markers and eag K+ channel types. *Exp Hematol*. 2006;34(11):1563-1572. https://doi.org/10.1016/j.exphem.2006.06.020
64. Grigoriadis N, Lourbopoulos A, Lagoudaki R, et al. Variable behavior and complications of autologous bone marrow mesenchymal stem cells transplanted in experimental autoimmune encephalomyelitis. *Exp Neurol*. 2011;230(1):78-89. https://doi.org/10.1016/j.expneurol.2011.02.021
65. Cristofanilli M, Harris VK, Zigelbaum A, et al. Mesenchymal stem cells enhance the engraftment and myelinating ability of allogeneic oligodendrocyte progenitors in dysmyelinated mice. *Stem Cells Dev*. 2011;20(12):2065-2076. https://doi.org/10.1089/scd.2010.0547
66. Mohyeddin Bonab M, Yazdanbakhsh S Fau - Lotfi J, Lotfi J Fau - Alimoghaddom K, et al. Does mesenchymal stem cell therapy help multiple sclerosis patients? Report of a pilot study. *Iran J Immunol*. 2007;4(1735-1383 (Print):50-57.
67. Yamout B, Hourani R, Salti H, et al. Bone marrow mesenchymal stem cell transplantation in patients with multiple sclerosis: a pilot study. *J Neuroimmunol*. 2010;227(1-2):185-189. https://doi.org/10.1016/j.jneuroim.2010.07.013
68. Connick P, Kolappan M, Patani R, et al. The mesenchymal stem cells in multiple sclerosis (MSCIMS) trial protocol and baseline cohort characteristics: an open-label pre-test: post-test study with blinded outcome assessments. *Trials*. 2011;12:62. https://doi.org/10.1186/1745-6215-12-62
69. Bonab MM, Sahraian MA, Aghsaie A, et al. Autologous mesenchymal stem cell therapy in progressive multiple sclerosis: an open label study. *Curr Stem Cell Res Ther*. 2012;7(6):407-414. https://doi.org/10.2174/157488812804484648
70. Helman G, Van Haren K, Bonkowsky JL, et al; GLIA Consortium. Disease specific therapies in leukodystrophies and leukoencephalopathies. *Mol Genet Metab*. 2015;114(4):527-536. https://doi.org/10.1016/j.ymgme.2015.01.014
71. Gupta N, Henry RG, Kang SM, et al. Long-term safety, immunologic response, and imaging outcomes following neural stem cell transplantation for Pelizaeus-Merzbacher disease. *Stem Cell Rep*. 2019;13(2):254-261. https://doi.org/10.1016/j.stemcr.2019.07.002
72. Gupta N, Henry RG, Strober J, et al. Neural stem cell engraftment and myelination in the human brain. *Sci Transl Med*. 2012;4(155):155ra137. https://doi.org/10.1126/scitranslmed.3004373
73. Pouwels PJ, Vanderver A, Bernard G, et al. Hypomyelinating leukodystrophies: translational research progress and prospects. *Ann Neurol*. 2014;76(1):5-19. https://doi.org/10.1002/ana.24194
74. Schneider A, Montague P, Griffiths I, et al. Uncoupling of hypomyelination and glial cell death by a mutation in the proteolipid protein gene. *Nature*. 1992;358(6389):758-761. https://doi.org/10.1038/358758a0
75. Kruer MC, Pearce DA, Orchard PJ, Steiner RD. Prospects for stem cell therapy in neuronal ceroid lipofuscinosis. *Regen Med*. 2013;8(5):527-529. https://doi.org/10.2217/rme.13.46
76. Selden NR, Al-Uzri A, Huhn SL, et al. Central nervous system stem cell transplantation for children with neuronal ceroid lipofuscinosis. *J Neurosurg Pediatr*. 2013;11(6):643-652. https://doi.org/10.3171/2013.3.PEDS12397
77. Kurtzberg J, Buntz S, Gentry T, et al. Preclinical characterization of DUOC-01, a cell therapy product derived from banked umbilical cord blood for use as an adjuvant to umbilical cord blood transplantation for treatment of inherited metabolic diseases. *Cytotherapy*. 2015;17(6):803-815. https://doi.org/10.1016/j.jcyt.2015.02.006
78. Brondon J, Page K, Polishchuk V, et al. Outcomes of umbilical cord blood transplantation in children with batten disease. *Stem Cells Transl Med*. 2019;8:S12. https://doi.org/10.1002/sctm.12557
79. Miller WP, Rothman SM, Nascene D, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. *Blood*. 2011;118(7):1971-1978. https://doi.org/10.1182/blood-2011-01-329235
80. Precious SV, Zietlow R, Dunnett SB, Kelly CM, Rosser AE. Is there a place for human fetal-derived stem cells for cell replacement therapy in Huntington's disease? *Neurochem Int*. 2017;106:114-121. https://doi.org/10.1016/j.neuint.2017.01.016
81. Bachoud-Levi AC, Remy P, Nguyen JP, et al. Motor and cognitive improvements in patients with Huntington's disease after neural transplantation. *Lancet*. 2000;356(9246):1975-1979. https://doi.org/10.1016/s0140-6736(00)03310-9
82. Kim A, Lalonde K, Truesdell A, et al. New avenues for the treatment of Huntington's disease. *Int J Mol Sci*. 2021;22(16):8363.
83. Mehat MS, Sundaram V, Ripamonti C, et al. Transplantation of human embryonic stem cell-derived retinal pigment epithelial cells in macular degeneration. *Ophthalmology*. 2018;125(11):1765-1775. https://doi.org/10.1016/j.ophtha.2018.04.037
84. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2(2):e106-e116. https://doi.org/10.1016/S2214-109X(13)70145-1
85. Allikmets R, Singh N, Sun H, et al. A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. *Nat Genet*. 1997;15(3):236-246. https://doi.org/10.1038/ng0397-236
86. Schwartz SD, Regillo CD, Lam BL, et al. Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. *Lancet*.

2015;385(9967):509-516. https://doi.org/10.1016/S0140-6736(14)61376-3
87. Schwartz SD, Hubschman JP, Heilwell G, et al. Embryonic stem cell trials for macular degeneration: a preliminary report. *Lancet*. 2012;379(9817):713-720. https://doi.org/10.1016/S0140-6736(12)60028-2
88. Kashani AH, Lebkowski JS, Rahhal FM, et al. One-year follow-up in a phase 1/2a clinical trial of an allogeneic rpe cell bioengineered implant for advanced dry age-related macular degeneration. *Transl Vis Sci Technol*. 2021;10(10):13.
89. Mandai M, Kurimoto Y, Takahashi M. Autologous induced stem-cell-derived retinal cells for macular degeneration. *N Engl J Med*. 2017;377(8):792-793. https://doi.org/10.1056/NEJMc1706274
90. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. *Lancet*. 2006;368(9549):1795-1809. https://doi.org/10.1016/S0140-6736(06)69740-7
91. Liu Y, Chen SJ, Li SY, et al. Long-term safety of human retinal progenitor cell transplantation in retinitis pigmentosa patients. *Stem Cell Res Ther*. 2017;8(1):209. https://doi.org/10.1186/s13287-017-0661-8
92. Beathard R. *Safety and Efficacy of Intravitreal Injection of Human Retinal Progenitor Cells in Adults With Retinitis Pigmentosa*. Available at https://doi.org/https://clinicaltrials.gov/ct2/show/results/NCT03073733. Published 2022. Accessed 12 October, 2022.
93. Cotrim CC, Jorge R, Oliveira MC, et al. Clinical studies using stem cells for treatment of retinal diseases: state of the art. *Arquivos Brasileiros de Oftalmologia*. 2020;83(2):160-167.
94. Martinez B, Peplow PV. Biomaterial and tissue-engineering strategies for the treatment of brain neurodegeneration. *Neural Regen Res*. 2022;17(10):2108-2116. https://doi.org/10.4103/1673-5374.336132
95. Chong YK, Toh TB, Zaiden N, et al. Cryopreservation of neurospheres derived from human glioblastoma multiforme. *Stem Cells*. 2009;27(1):29-39. https://doi.org/10.1634/stemcells.2008-0009
96. Fan Y, Tong ZP, Goh EL, et al. Regionally-derived second-trimester primary hfNSCs have different neurogenic capacity for neuronal differentiation. *J Stem Cell Res Ther*. 2019;9(5):1000451.