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Cell therapy for neurological disorders

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Cell therapies for neurological disorders are entering the clinic and present unique challenges and opportunities compared with conventional medicines. They have the potential to replace damaged nervous tissue and integrate into the brain or spinal cord to produce functional effects for the lifetime of the patient, which could revolutionize the way clinicians treat debilitating neurological disorders. The major challenge has been cell sourcing, which historically relied mainly on fetal brain tissue. This has largely been overcome with the advent of pluripotent stem cell technology and the ability to make almost any cell of the nervous system at scale. Furthermore, advances in gene editing now allow the generation of genetically modified cells that could perform better and evade the immune system. With all the remarkable new approaches to treat neurological disorders, we take a critical look at the state of current clinical trials and how challenges may be overcome with the evolving technology and innovation occurring in the stem cell field.

Cell therapy has the potential to change medicine in a way not seen since small-molecule therapies were developed. Historically, the hematopoietic system has led the way following the discovery that replacing blood stem cells in the bone marrow can reconstitute the entire hematopoietic system[1]. This led to bone marrow transplantation clinical programs for certain types of blood cancer and other diseases that have an autoimmune component. Furthermore, CART technology, in which a patient's T cells are engineered to target their cancer, is now a US Food and Drug Administration (FDA)-approved treatment, and one of the most rapidly advancing cell therapy areas[2]. However, most cellular therapy approaches outside the blood system remain in the clinical trial arena as they push toward approval with the FDA and other regulatory authorities worldwide.

Broadly speaking, these cell therapies fall into two categories. The first involves infusion of cells into patients that can activate repair mechanisms through either release of factors and exosomes, or modulation of the host immune system, without long-term survival or tissue integration. A prime example is delivery of mesenchymal stem cells extracted from the bone marrow or adipose tissue and expanded in culture. Many clinical trials exist with mesenchymal stem cells for neurological conditions[3–6], yet most have not met primary efficacy endpoints and none have gained FDA approval in the USA[7]. The second approach is cell-replacement therapy (CRT) to provide cells that can replace or protect diseased or dying cells. This is an ambitious concept that often requires surgical delivery of the cells followed by maturation and, in some cases, integration of the transplanted cells into functional units. In theory, this treatment could lead to long-term recovery of the patient, for instance, with stem cell-derived islet cells to treat diabetes[8,9] and cardiomyocytes to treat heart disease[10]. CRT also holds great potential for retinal disease as elegantly covered in recent reviews[11,12]. Here, this Review focuses on cell-based therapy using a variety of cell sources as a promising approach for several disorders of the nervous system (Fig. 1).

Replacement of diseased cells by activating resident stem cells has been assessed for neurological disorders, although this has not been translated to humans (Box 1). Instead, the use of exogenous cells as a source of functional brain cells has shown to be a more fruitful approach to CRT (Fig. 2). Fetal-derived primary tissue has been extensively used, as for Parkinson's disease (PD) and Huntington's disease (HD) (Box 2); however, sufficient and precise tissue collection and storage have proved difficult[13]. Alternatively, fetal-derived multipotent progenitor cells can be isolated and expanded with specific mitogens into glial and neuronal cells and cryopreserved[14–16]. However, cultured cells have reduced differentiation and expansion potential over time[17,18].

The discovery of human pluripotent embryonic stem (ES) cells provided a source that would not senesce following expansion yet still generates all neuronal and glial cell subtypes[19]. However, these cells have created moral and ethical concerns in some countries due to the use of embryos and the requirement for immunosuppression in recipients. The revolutionizing technology of human induced pluripotent

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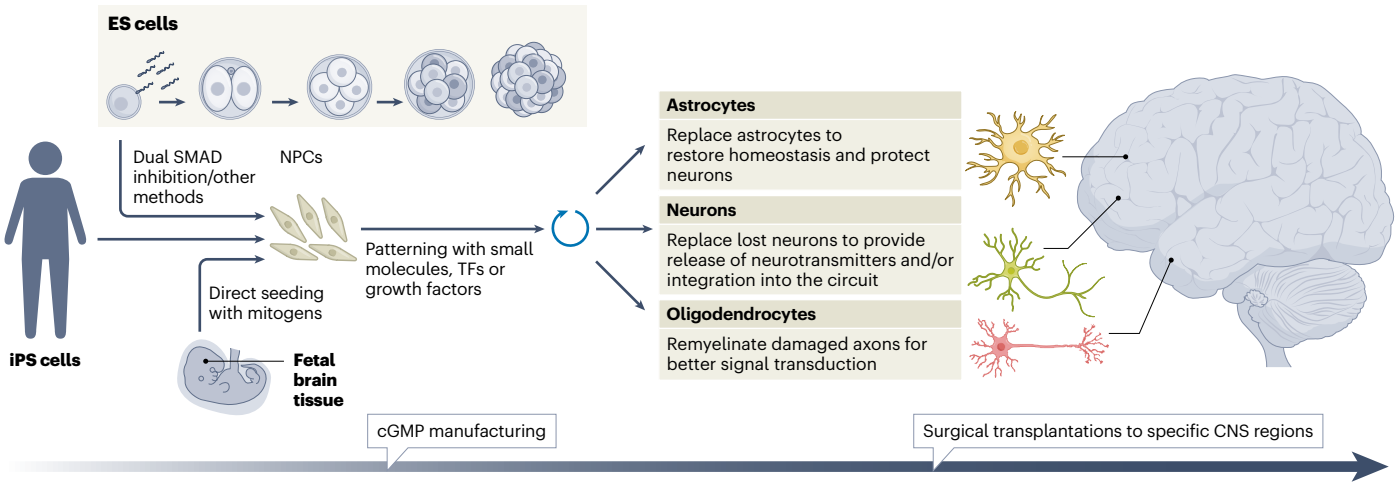

Fig. 1 | Cell therapy approaches currently in the clinic for neurological disorders. Several cell sources have been used in trials. One source is fetal brain or spinal cord tissue that is derived from either elective abortions or miscarriages. From this source, primary fetal tissue can be isolated from discrete regions and at specific developmental time points for direct delivery to the patient, which does not require cell expansion manufacturing. Alternatively, fetal tissue can provide multipotent progenitor cells that are expanded with defined patterning cues and that differentiate into neuronal and glial cells after transplantation. An alternate source comes from human embryos, often from the excess of in vitro fertilization clinics. Pluripotent ES cells can be isolated and expanded from the inner cell mass of the developing blastocyst. A final source comes from adult cells, for instance, fibroblasts or blood cells, that are reprogrammed back to a pluripotent state, and are called iPS cells. Human ES cells, iPS cells or their neural derivatives can be expanded under cGMP and then differentiated into the required cell type. Differentiation into specific neurons, astrocytes and oligodendrocytes can be achieved through developmentally appropriate mitogens or specific transcription factors (TFs). Often an early progenitor state for the desired cell type is delivered, with the cell fully maturing after transplantation into specific brain or spinal cord regions where repair or replacement can take place. The specific neurological disorder dictates the cell type to be generated and the region of the CNS for delivery.

BOX 1

Resident adult brain cells for neurological repair in humans

Resident stem cells exist in the mouse brain, within the subventricular zone (involved in olfaction) and hippocampus (involved in memory) that can generate neurons throughout the animal's lifespan[187]. However, while these 'neurogenic' regions exist in the adult human brain[188], more recent studies suggest they may not be as abundant as in rodents, calling into question this approach for CRT[189]. The mouse brain also contains NG2 progenitor cells that can generate glia in response to damage[190]; however, while these cells also exist in the human brain[191], their potential for repair remains unknown. Microglia residing in the mouse brain can repopulate areas of damage, although this has not been shown for the human brain[192]. Studies have also shown that transcription factor-based conversion of astrocytes into neurons may facilitate repair after damage in the mouse brain[193–195]. However, this approach has been called into question by subsequent studies[196–198] and because astrocytes are an essential part of CNS repair[199].

stem (iPS) cells demonstrated that adult cells could be reprogrammed to a pluripotent state, providing cells with very similar characteristics to ES cells[20,21]. This permits autologous transplantation or gene editing to potentially avoid the need for immunosuppression. However, although embryos are not destroyed, ethical concerns can still exist with iPS cell technology—including possible breaches to personal identities for the cell donors, as well as diverse donor recruitment[22].

Various cell sources have been used throughout the years and, with emerging cellular technologies, the field continues to evolve for modern CRT approaches[23]. In this Review, we focus on promising stem and progenitor cell-based CRT approaches for neurological disorders that are nearing or have already entered the clinic (Table 1). We discuss lessons from these pioneering clinical studies, the challenges facing the field and the future of CRT for neurological disorders.

Into the clinic for neurological diseases

Parkinson's disease

PD is a complex disorder but one of the cardinal features is loss of dopamine neurons in the substantia nigra that project to the striatum, leading to various motor symptoms[24]. Pioneering studies showed that the substantia nigra from the fetal brain could be dissociated to a cell suspension and transplanted into the striatum of rodent models of PD in which, remarkably, the cells survived and generated dopamine neurons that could reverse many symptoms of the modeled disease[25,26]. This work led to some of the earliest hallmark CRT trials for a neurodegenerative disorder (Box 2). However, long-term, placebo-controlled trials failed to demonstrate efficacy and the use of fetal-derived tissue as a cell source was problematic, necessitating novel ways to provide dopamine neurons as a sustainable therapy.

The CRT field for PD has now switched the focus to human ES cells and iPS cells, facilitated by the development of current good manufacturing practice (cGMP) to generate high numbers of relatively pure dopamine neurons[27–30]. These cells survive in rodents and primates, and provide similar effects to fetal-derived cells[31,32]. On the basis of strong preclinical studies and the generation of clinically applicable human ES cell-derived dopaminergic neurons[33–35], BlueRock Therapeutics have performed a phase 1 study (NCT04802733) that reached the endpoint of safety, along with evidence of cell survival based on positron emission tomography (PET) imaging, according to their press release[36]. Further studies using human ES cell-derived dopamine neurons are currently ongoing worldwide, including a study in Sweden and the UK called Stem-PD (NCT05635409)[28,37], as well as studies in Korea[29] (NCT05887466), China (NCT03119636)[38] and Australia (NCT02452723)[39].

On the basis of preclinical data showing the effectiveness of iPS cell-derived dopaminergic neurons in treating PD[40,41], there is an

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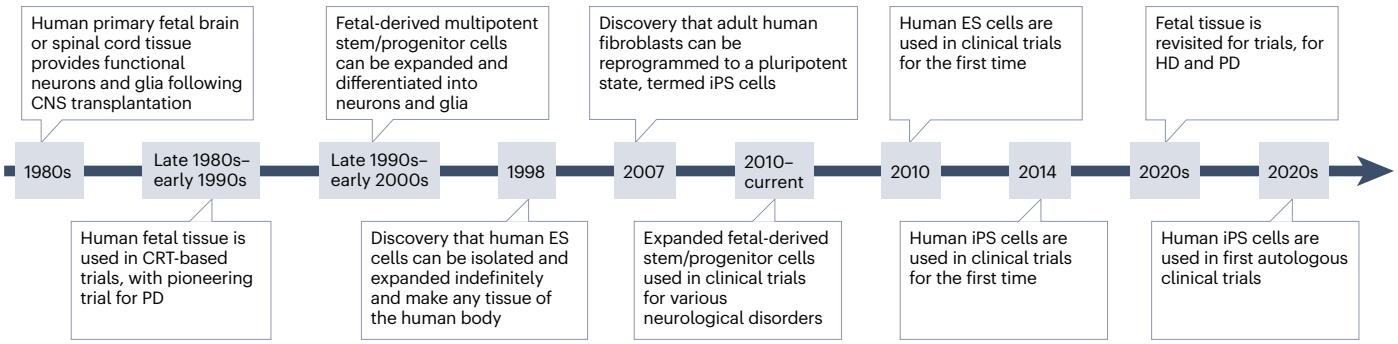

Fig. 2 | Notable events in CRT for neurological disorders. Primary fetal tissue has been used extensively for PD and HD, with the hallmark trial starting in Sweden. Trials declined due to concerns about reliable and sufficient tissue collection, as well as inconsistent long-term efficacy. After nearly a decade, larger controlled trials have been renewed in order to optimize conditions, although these too have been stalled due to tissue collection difficulties. Fetal-derived multipotent progenitor cells have been used for various neurological disorders, but these cells undergo senescence over time and cannot provide all required cell types. A breakthrough in the field came from the finding that human pluripotent ES cells could be isolated and cultured indefinitely. A decade later came the hallmark discovery that adult fibroblasts, and subsequently other cell types, could be used to generate iPS cells. Pluripotent stem cells have revolutionized the CRT field and are currently being used in clinical trials for various neurological conditions. Thus far, ES cells have been utilized more than iPS cells in the clinic, but current trials are moving toward iPS cells.

BOX 2

Setting the stage for stem cell-based CRT

Human fetal tissue has been used for many of the hallmark CRT clinical trials for neurodegenerative disorders. For PD, tissue from the substantia nigra of five to seven human embryos was used to prepare cell suspensions that were directly injected into the putamen of patients, with the hallmark trials led by Sweden and followed by centers worldwide[200–203]. The trials demonstrated general safety with encouraging improvements in secondary outcome measures and the transplanted fetal neurons could survive and produce dopamine for extended time periods[204]. However, subsequent placebo-controlled efficacy trials did not meet endpoints of long-term improvement[137,177,205,206]. Similarly, human fetal-derived striatal tissue has been used in a small number of trials for HD, with some data demonstrating feasibility and safety, as well as cell survival[207–209], yet positive effects of the transplant are not sustained[210–212]. As poor long-term results for both diseases may be related to inconsistent tissue collection and low numbers of surviving cells within the transplant, larger follow-up trials to optimize fetal grafting are being pursued. For Parkinson's disease, the TRANSEURO team initiated a recent study that planned to transplant a much larger group of patients (NCT01898390)[213], and a phase 1 clinical trial, TRIDENT, was initiated in 2017 for HD using a higher cell dose-escalation paradigm (ISRCTN52651778)[214]. However, enrollment remains incomplete in both trials, due mainly to challenges gathering reliable and sufficient fetal tissue. This ultimately suggests the need for a cell source that allows better control of the quantity and homogeneity of the cell product.

ongoing trial in Kyoto (UMIN000033564). In this trial, patients have been transplanted with dopaminergic neurons from one iPS cell line derived from a patient with a common haplotype in Japan that may reduce immune reactions to the allogeneic product, although participants were not matched to this haplotype[42]. The patients are currently being monitored and the FDA has granted approval for this group to do a similar trial in the USA, once institutional review board approval is obtained (J. Takahashi, personal communication).

A clear attraction of autologous iPS cell transplants is the potential reduction in immune rejection issues, as demonstrated in primate studies[43,44]. Recently, autologous iPS cell-derived dopaminergic neurons have advanced to a compassionate use case study, with a single patient with PD treated in the USA and some evidence of safety and cell survival—although a single case does not constitute a formal safety study[45]. Additionally, the company XellSmart Biomedical in China has recently initiated a phase 1 trial to use autologous iPS cells, although no details have been published thus far (NCT06145711). Finally, the company Aspen Neuroscience has initiated a phase 1/2a trial (NCT06344026) using an autologous iPS cell approach from individual patients, which are differentiated into dopamine neuronal precursor cells, with their first patient just dosed in April 2024, according to their press release[46].

Huntington's disease

HD is caused by an expansion of CAG repeats in the huntingtin gene[47], ultimately leading to a loss of gamma-aminobutyric acid (GABA)-ergic medium spiny neurons (primarily in the striatum) along with cortical degeneration. HD is a debilitating motor, cognitive and psychiatric disorder with no current treatments. While an understanding of the genetics allows disease modification through genetic correction or antisense oligonucleotides (ASOs), these avenues have not been effective thus far, with several recent clinical trials being stopped due to no effects or adverse effects[48]. There is a strong rationale for CRT in HD, in which the aim would be to provide new cells directly in the region of neuron loss—differing from the PD context, which involves ectopic delivery. Extensive animal studies support that human fetal-derived medium spiny neurons can provide functional effects[49]. However, clinical trials do not show long-term effects (Box 2) and, as with PD trials, suggest the need for an alternative strategy. A cGMP-compliant human ES cell line differentiated into neural stem cells was shown to rescue functional deficits in the HD mouse[50,51], leading to the recent and first investigational new drug authorization by the FDA for an ES cell-derived product for HD, with plans for a clinical trial underway. Additionally, transplanting human iPS cell-derived striatal progenitors into the mouse striatum provided some functional recovery[52,53], and could be pursued as an autologous approach in future clinical studies.

Alzheimer's disease

Alzheimer's disease (AD) involves progressive neuronal death in various brain regions, leading to impairment in memory and cognition[54]. While diffuse neuronal loss in AD provides the potential for CRT, it

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Table 1 | Stem and progenitor cell-based clinical trials for neurological disorders

Trial number and product details	Trial name and design	Sponsor, enrollment and status	Trial findings	Related publications
PD				
NCT04802733 Origin: human ES cell line (W9) Product[a]: BRT- or MSK-DA01	Phase 1 safety and tolerability study of MSK-DA01 cell therapy for advanced PD Open label; bilateral striatal delivery	BlueRock Therapeutics Enrollment: 12 Active, not recruiting	Endpoint of safety was reached with secondary endpoints showing evidence of cell survival and engraftment based on PET imaging for dopamine uptake.	33–36
NCT05635409 Origin: human ES cell line (RC17) Product[b]: STEM-PD	A trial to determine the safety and tolerability of transplanted stem cell-derived dopamine neurons to the brains of individuals with PD (STEM-PD) Phase 1; open label; dose escalation; bilateral striatal delivery	Region Skåne Enrollment: 8 Active, recruiting	No clinical trial findings reported to date.	28,37
NCT05887466 Origin: human ES cells Product[b]: A9-DPC	Study to evaluate the safety and efficacy of ES cell-derived dopamine progenitor cell therapy in patients with PD Phase 1/2a; open label; dose escalation of two doses (n=6 per dose)	S.Biomedics, Korea Enrollment: 12 Active, not recruiting	No clinical trial findings reported to date.	29
NCT03119636 Origin: Human ES parthenogenetic cells Product[c]: Q-CTS-hESC-2	Safety and efficacy study of human ES cell-derived neural precursor cells in the treatment of PD Phase 1/2a; open label; single dose; delivery to striatum	Chinese Academy of Sciences Enrollment: 50 Unknown recruitment status	No clinical trial findings reported to date.	38
NCT02452723 Origin: Human parthenogenetic stem cells Product[c]: ISC-hpNSC	A study to evaluate the safety of neural stem cells in patients with PD Phase 1; open label; dose escalation; three doses (n=4 per dose); bilateral delivery to striatum and substantia nigra	Cyto Therapeutics Pty, Australia Enrollment: 12 Unknown recruitment status	No clinical trial findings reported to date.	39
UMIN000033564 Origin: Human iPS cells Product[b]: no name	Kyoto trial to evaluate the safety and efficacy of iPS cell-derived dopaminergic progenitors in the treatment of PD Phase 1/2a; two doses (n=3 and n=4 per dose); Bilateral striatal delivery	Kyoto University Hospital Enrollment: 7	No clinical trial findings reported to date.	41,42
NCT06145711 Origin: Human iPS cells Autologous Product[b]: hiPS cell-DAP	A clinical trial of PD treatment by human iPS cells derived dopaminergic neural precursor cells (hiPS cell-DAP) Interventional; unilateral globus pallidus internal delivery	Shanghai East Hospital Enrollment: 3 Not yet recruiting	No clinical trial findings reported to date.	
NCT06344026 Origin: Human iPS cells Autologous Product[d]: ANPD001	Phase 1/2a study of ANPD001 in PD (ASPIRO) Dose escalation; bilateral delivery to putamen	Aspen Neuroscience Enrollment: 9 Treated: 1 Currently enrolling	No clinical trial findings reported to date.	46
ALS				
NCT01348451 Origin: Human spinal stem cells Product[e]: NSI-566	Human spinal cord-derived neural stem cell transplantation for the treatment of ALS Phase 1; delivery to spinal cord	NeuralStem Enrollment: 18 Completed	First-in-human trial to demonstrate safety of stem cell delivery to the lumbar spinal cord and subsequently the cervical spinal cord of patients with ALS.	67
NCT01730716 Origin: Human spinal stem cells Product[e]: NSI-566	Dose escalation and safety study of human spinal cord-derived neural stem cell transplantation for the treatment of ALS Phase 2; open label; multi-site; Delivery to spinal cord	NeuralStem Enrollment: 18 Completed	Demonstrated safety; however, there was no significant functional improvement across patients, due to variation in disease progression rates, and the trial was underpowered to establish efficacy.	68,69
NCT01640067 Origin: Human fetal-derived tissue Product[c]: no name	Human neural stem cell transplantation in ALS (hNSCALS) Phase 1; open label; unilateral or bilateral delivery to spinal cord	Azienda Ospedaliera Santa Maria, Terni, Italy Enrollment: 18 Completed	No increase of disease progression due to the treatment for up to 18 months after surgery. Two patients showed improvement of the subscore ambulation on the ALS-FRS-R scale, but this was transitory.	
NCT02943850 Origin: Human fetal cortical tissue Product[f]: CNS10-NPC-GDNF	CNS10-NPC-GDNF for the treatment of ALS Phase 1/2a; open label; unilateral delivery to lumbar spinal cord	Cedars-Sinai Medical Center Enrollment: 18 Treated: 18 Completed	Demonstrated safety and cell survival with GDNF production up to 42 months after treatment.	75,77
NCT05306457 Origin: Human fetal cortical tissue Product[f]: CNS10-NPC-GDNF	CNS10-NPC-GDNF delivered to the motor cortex for ALS Phase 1/2a; open label; unilateral delivery to motor cortex	Cedars-Sinai Medical Center Enrollment: 16 Treated: 5 Recruiting	No clinical trial findings reported to date.	78

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Table 1 (continued) | Stem and progenitor cell-based clinical trials for neurological disorders

Trial number and product details	Trial name and design	Sponsor, enrollment and status	Trial findings	Related publications
Stroke				
NCT01151124 Origin: Human fetal cortex Product[c]: CTX0E03	Pilot Investigation of Stem Cells in Stroke (PISCES) Phase 1; open label; dose escalation (four doses; *n*=3 per dose); delivery to ipsilateral putamen	ReNeuron Limited Enrollment: 11 Complete	The first-in human study using neural stem cells for stroke. Cell delivery induced no adverse events and was associated with improved neurological function.	88–90
NCT02117635 Origin: Human fetal cortex Product[c]: CTX0E03	Pilot Investigation of Stem Cells in Stroke Phase II Efficacy (PISCES-II) Open label; one dose; intrastriatal delivery ipsilateral to the stroke location	ReNeuron Limited Enrollment: 23 Treated: 23 Complete	No cell-related adverse events occurred during up to 12 months of follow-up. Improvement was shown in one participant at 3 months and in three participants at 6 months and 12 months, but only in those with residual upper-limb movement at baseline.	91
NCT03296618 Origin: Human fetal spinal cord Product[e]: NSI-566	Intracerebral transplantation of neural stem cells for the treatment of ischemic stroke Phase 1; open label; intracranial delivery; dose escalation (three doses/three patients)	NeuralStem Enrollment: 18 Treated: 9 Complete	This trial performed in China showed all cell doses were well tolerated. Mean changes remained stable for six participants who were followed up for 24 months. Longitudinal MRI indicated cavity filling by new neural tissue formation in all treated patients.	92
NCT04631406 Origin: Human ES cells Product[c]: NR1	A safety and tolerability study of neural stem cells (NR1) in participants with chronic ischemic subcortical stroke Phase 1/2a; open label; intracerebral delivery; dose escalation; up to four cohorts/dose	Stanford University Enrollment: 18 Treated: 18	NR1 transplantation appears safe and early results suggest improved motor function.	96
Epilepsy				
NCT05135091 Origin: Human ES cells Product[g]: NRTX-1001	First-in-human study of NRTX-1001 neural cell therapy in drug-resistant unilateral mesial temporal lobe epilepsy Two-stage: stage 1 open label, dose escalation (*n*=10); stage 2 parallel, randomized, two-arm controlled (*n*=20 treated, *n*=10 placebo).	Neurona Therapeutics Enrollment: 40 Recruiting	In stage 1, the five patients treated so far received the study's lower dose. Findings presented in April 2024 show early safety results and a reduction in seizure activity.	103–106
Demyelinating				
NCT03282760 Origin: Human fetal brain Product[c]: no name	Safety study of human neural stem cells injections for secondary progressive multiple sclerosis patients (NSC-SPMS) Phase 1; intracerebroventricular delivery; dose escalation	Casa Sollievo della Sofferenza IRCCS Enrollment: 24 Completed	No treatment-related serious adverse events observed. Participants displayed stability of functional and structural outcomes.	114
NCT03269071 Origin: Human fetal brain Product[c]: no name	Neural stem cell transplantation in multiple sclerosis patients (STEMS) Phase 1; intrathecally transplanted; Dose escalation	IRCCS San Raffaele Enrollment: 4 Completed	Primary outcome of safety was reached at 2-year follow-up. Exploratory secondary analyses showed lower rate of brain atrophy in patients receiving the highest cell dose and increased levels of anti-inflammatory and neuroprotective molecules.	113
NCT01005004 Origin: Human CNS Product[h]: HuCNS-SC	Study of human CNS stem cell transplantation in patients with Pelizaeus–Merzbacher disease Phase 1; intracerebral delivery	StemCells Enrollment: 4 Completed	One-year trial showed some increased signal changes and favorable safety data. MRI results suggest cell engraftment and donor-derived myelin in the transplanted white matter. A LTFU study (NCT01391637) demonstrated that transplants were well tolerated. At year 2, all patients exhibited diffusion MRI changes at implantation sites and in more distant brain regions. Three patients had increased signal changes up to year 5. Two patients developed donor-specific HLA alloantibodies.	116,117
SCI				
NCT01772810 Origin: Human spinal cord Product[e]: NSI-566	Safety study of human spinal cord-derived neural stem cell transplantation for the treatment of chronic SCI Phase 1; open label; single site	NeuralStem Enrollment: 8 Status unknown	Results support the safety of NSI-566 delivery into the SCI site and early signs of potential efficacy in three patients. The trial lacked the statistical power and control group needed to evaluate functional changes after grafting.	122
NCT02163876 Product[h]: HuCNS-SC	Study of human CNS stem cell transplantation in cervical SCI Phase 2; single blind; randomized	StemCells Enrollment: 31 Trial terminated	Interim analysis demonstrated a trend toward improved motor function in the treated participants, but at a magnitude below the required clinical efficacy threshold set by the sponsor to support further development, resulting in early study termination.	123

Table 1 (continued) | Stem and progenitor cell-based clinical trials for neurological disorders

Trial number and product details	Trial name and design	Sponsor, enrollment and status	Trial findings	Related publications
KCT0000879 Origin: Human fetal telencephalon Product[c]: no name	Phase 1/2a; open label	Yonsei University College of Medicine in Korea Treated: 19	Procedure was well tolerated and provided modest neurological benefit up to 1 year.	126
NCT01217008 Origin: Human ES cells (H1 line) Product[i]: GRNOPC1 (AST-OPC1)	Safety study of GRNOPC1 in SCI Phase 1; single dose; one injection of 2 million AST-OPC1 cells	Geron (Lineage Cell Therapeutics) Enrollment: 5 Treated: 5 Completed	Showed that this first-in-human ES cell-derived therapy was well tolerated by patients with SCI, with MRI showing that 80% of patients had favorable T2 signal changes. An active LTFU study (NCT05919563) is assessing patients for 15 years after cell delivery.	129
NCT02302157 Origin: Human ES cells (H1 line) Product[i]: AST-OPC1	Dose-escalation study of AST-OPC1 in SCI Phase 1/2a; dose escalation; cohorts receive one injection of 2 million or 10 million cells, or two injections of 10 million cells LTFU study of participants with cervical SCI who received AST-OPC1	Lineage Cell Therapeutics Enrollment: 25 Treated: 25 Completed	Initial trial showed a favorable safety profile and promising improvement in neurological function at the 1-year follow-up; 21/22 (96%) of the treated group recovered one or more levels of neurological function on at least one side of their body, and 7/22 (32%) recovered two or more levels of neurological function on at least one side. An active LTFU study (NCT05975424) is assessing patients for 15 years after cell delivery.	130
UMIN000035074 Origin: Human iPS cells Product[c]: no name	Regenerative medicine for SCI at subacute stage using human iPS cell-derived neural stem/progenitor cells Open label; dose of 2×10^6 cells	Keio University in Japan Treated: 4	No clinical trial findings reported to date.	131–134

Mechanism of action: [a]Provide brain cells that make dopamine [b]Provide dopamine neuron progenitor cells [c]Provide neural stem/progenitor cells [d]Provide cells that mature into dopamine-producing neurons [e]Provide cells that differentiate into neurons and secrete protective factors [f]Provide neural progenitors that generate astrocytes and release GDNF [g]Provide GABA-secreting interneurons [h]Provide neurons, astrocytes and oligodendrocytes [i]Provide oligodendrocytes

also makes it challenging compared with more localized cell death. A landmark phase 1 trial attempted to protect cholinergic neurons by delivering fibroblasts genetically engineered with nerve growth factor to the forebrain of patients with mild AD. While no long-term adverse effects occurred and there was suggested improvement in the rate of cognitive decline and activation of neuronal activity[55], trials using these cells have not been pursued.

Several neural stem/progenitor cell products used in clinical trials for other neurological conditions described below have been tested in preclinical AD models. The company NeuralStem (now named Seneca) has generated a human fetal spinal cord-derived neural stem cell product (NSI-566) that was engineered to produce insulin-like growth factor 1 for AD[56]; however, this strategy is unlikely to be translated to the clinic given the company shift out of this field. StemCells has developed a cell product (huCNS-SC), in which human neural stem cells are isolated from multiple fetal brains, sorted and expanded in mitogens to yield cells that can differentiate into neurons, astrocytes or oligodendrocytes following transplantation[57]. While research-grade huCNS-SC delivered to mouse models of AD provided improved cognition[58], the clinical-grade huCNS-SC showed no cognitive benefits[59], highlighting the importance of the manufacturing process to product performance. A fetal cortical-derived human neural progenitor cell (NPC) line (CNS10-NPC), which is currently being used in a trial for retinitis pigmentosa (NCT04284293), reduces behavioral deficits and neuropathology in a mouse model of dementia[60]. Finally, human ES cells and iPS cells can provide cognitive benefits in mouse models[61,62], suggesting the potential of CRT for AD in future trials.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a devastating disease caused by progressive loss of motor neurons in both the cortex and spinal cord, ultimately leading to paralysis and death typically only 3–5 years from diagnosis[63]. ALS can be genetic, for which there have been exciting gene modification approaches using ASOs[64]. Nevertheless, over 85% of ALS cases either involve complex genetics that are not targetable by a single ASO or may be caused by nongenetic, environmental factors. In these cases, CRT represents a promising therapeutic approach. Using CRT to directly replace lost motor neurons would require cell delivery to the motor cortex and/ or spinal cord; subsequently, the axons would need to extend long distances to their targets, which is not currently possible in adult humans. However, providing supportive glial cells or interneurons to maintain existing motor neurons is a very active area undergoing clinical evaluation.

The largest set of cell therapy trials for ALS thus far were performed by the company NeuralStem (Seneca), using their NSI-566 product, which was shown in animals to differentiate mostly into interneurons (and less frequently into astrocytes) and release numerous growth factors, including glial cell line-derived neurotrophic factor (GDNF)[65,66]. The phase 1 first-in-human trial showed safe delivery of cells to the lumbar spinal cord and subsequently the cervical spinal cord of patients with ALS (NCT01348451)[67]. The phase 2 study (NCT01730716), with dose escalation and delivery to the lumbar and/or cervical spinal cord[68,69] again met the primary endpoint of safety; however, there was no significant functional improvement across patients, likely due to variation in disease progression rates, and the trial was underpowered to establish efficacy. A recently completed trial in Europe using expanded human fetal-derived neural stem cells (NCT01640067) has reported no detrimental effects of treatment for up to 60 months after surgery[70], and decreased progression of the ALS Functional Rating Scale, but this was transitory.

Motor neurons can be protected by healthy astrocytes as well as by growth factors, namely, GDNF[71,72]. We have, therefore, pursued a synergistic cell and gene therapy for ALS in which human fetal cortical-derived NPCs, which can differentiate into astrocytes following transplantation, were genetically engineered to stably produce GDNF[73,74]. This clinical-grade product, CNS10-NPC-GDNF[75], was recently delivered to

the unilateral spinal cord of patients with ALS in a phase 1/2a clinical trial (NCT02943850). As left-versus-right leg muscle function deteriorates at a similar rate in ALS[76], this trial's unilateral design could increase the power to determine outcome measures by having the untreated leg serve as the control for the same patient, rather than untreated patients with ALS, as in previous cell trials. This study met the endpoint of safety, showed modest but nonsignificant improvements in leg strength on the treated side, and spinal cords from patients that came to postmortem showed the presence of transplanted cells secreting GDNF up to 42 months after treatment[77]. Ultimately for ALS, CRT needs to target both upper and lower motor neurons. On the basis of the finding that CNS10-NPC-GDNF delivered to the motor cortex could survive, release GDNF, slow disease progression and extend lifespan in a rat model of ALS[78], this product is currently being delivered unilaterally to the hand knob region of the motor cortex in patients with ALS in an ongoing phase 1/2a clinical trial (NCT05306457). The ultimate goal would be to transplant CNS10-NPC-GDNF into the spinal cord and motor cortex to protect both motor neuron pools[79]. A recent paper showed that iPS cell-derived neural cells releasing GDNF could provide beneficial effects in a rodent model of ALS[80], yet currently, ES cells or iPS cells are used mainly for disease modeling and drug screening applications[81–83].

Stroke

Blockage of blood flow to the brain can cause an ischemic stroke, leading to the extensive death of brain cells and an inflammatory response, with lasting brain damage and substantial disability. Cell therapy for stroke has largely focused on human fetal brain-derived neural stem cells that can differentiate into neurons and astrocytes to provide neuronal replacement and release factors to increase the plasticity of the remaining damaged neurons, respectively, in animal models[84–87].

In particular, a conditionally immortalized clonal human neural stem cell line, CTX0E03, showed promising effects through a proposed paracrine trophic mechanism that was able to restore neurogenesis[88,89]. This led to a first-in-human phase 1 trial (by the company Reneuron) named PISCES (NCT01151124), which used human neural stem cells for chronic ischemic stroke[90]. Cell delivery induced no adverse events and was associated with improved neurological function, providing the foundation for the phase 2 PISCES-II study (NCT02117635) that showed no cell-related adverse events and modest improvement in a small subset of participants at 3, 6 and 12 months, although it should be noted that effects occurred only in participants with residual upper-limb movement at baseline and, therefore, natural recovery could also play a part[91]. The FDA approved the commencement of a randomized, placebo-controlled, phase 2b PISCES III trial, which was designed to enroll approximately 130 patients living with chronic stroke disability across multiple centers in the USA; however, following a strategic decision, the trial was terminated once the already treated patients were followed up in line with the clinical trial protocol and no more information is currently available. The company NeuralStem (Seneca) also led a trial for intracerebral transplantation for the treatment of ischemic stroke, delivering escalating doses of their NSI-566 cells (NCT03296618). While treatment was well tolerated and longitudinal magnetic resonance imaging (MRI) studies indicated cavity filling by new neural tissue formation[92], there are currently no additional trials with these cells for ischemic stroke.

Preclinical studies have now shown that transplanted human ES cell-derived neural precursor cells can promote functional recovery[93–95]. Based on this, an ongoing phase 1/2a trial for chronic ischemic stroke is transplanting ES-derived neural stem cells (named NR1) into the patient brain near the stroke site (NCT04631406). The proposed mechanism of action involves these cells secreting factors that enhance the recovery of damaged neurons and blood vessels, rather than replacing neurons in the lesion site. Early results presented at meetings indicate that NR1 transplantation is safe and improves motor function starting at 1 month after treatment[96].

Epilepsy

Epilepsy often involves a disturbance of the excitation/inhibition balance that can lead to disinhibition and subsequent uncontrolled circuit firing and seizures. With the development of spontaneous chronic seizures, there can be a reduction in specific GABAergic inhibitory interneurons, although changes in other neuronal subtypes are also critical[97,98]. Pharmacology is the current standard of care for seizures, although severe or nonresponsive seizures may require implanting brain stimulation devices or lesioning epileptic foci[99]. While many patients can remain seizure free for long periods after temporal lobectomy[100], this surgery can only address unilateral seizures and poses cognitive risks. An alternative therapeutic approach involves the delivery of inhibitory neurons, which dampens seizures in animal studies[101,102] and has now moved to clinical testing. Neurona Therapeutics manufactured human ES cell-derived functional inhibitory GABA interneurons under cGMP conditions (NRTX-1001)[103–105], which are being delivered into the nondominant hemisphere around the seizure focus of patients with mesial temporal lobe sclerosis in a recently initiated phase 1/2a trial (NCT05135091). Recently presented findings describe early safety results for the five patients treated with the lower dose, and a seizure reduction of >95% for two patients at 16 months and 21 months after treatment[106]. The remaining three patients have been followed for 6 months after treatment, with seizure reductions of 33%, 74% and 75%. The first two patients in the higher-dose cohort have not reported any serious adverse events thus far. The phase 2 trial plans to treat 20 patients with NRTX-1001 and 10 patients with a placebo. While NRTX-1001 appears promising as a CRT approach, it will be critical to assess findings when the trial moves to a sham-controlled design and treats the dominant side. Thus far, the effects on seizures were very rapid, which may suggest a release of GABA, rather than synaptic connections that would take longer to establish. However, this ongoing study has a strong safety profile and encouraging clinical effects on a measurable outcome of seizure activity. Importantly, this approach allows bilateral transplants if required; and, if the transplant is ineffective, patients can still get a resection of the focal area for seizures. Human iPS cell-derived GABAergic interneurons also show promise in preclinical animal models, but these cells have yet to reach human trials[107,108].

Demyelinating disorders

Multiple sclerosis is a complex autoimmune inflammatory disorder in which the primary pathology is demyelination in multiple axonal tracks of the central nervous system (CNS)[109]. In initial stages, the demyelination and associated loss of function is often relapsing and remitting, but ultimately progresses to chronic lesions and functional deficits. An obvious target for CRT has been to provide myelinating cells through the transplantation of stem cell-derived oligodendrocytes[110,111]. Many studies in demyelinating animal models have been able to replace lost oligodendrocytes through direct transplantation of either fetal or pluripotent stem cell-derived progenitors[109]; however, direct cell injections have not progressed to clinical trials. Challenges include the selection of an optimal area to target and concerns that the host immune response could compromise the transplanted cells. However, it would seem that a small focused trial in humans could address both of these issues by selecting an area that, if repaired, would generate clear changes in outcome measures, for example, visual system effects in multiple sclerosis[112].

Two recent phase 1 trials have taken a different approach and simply injected neural stem cells derived and expanded from fetal brain tissue into patients with multiple sclerosis either intrathecally (NCT03269071) or intraventricularly (NCT03282760)[113,114]. The mechanism of action was clearly not replacement of oligodendrocytes in the CNS, but rather generation of neural cells within the cerebral spinal fluid that could perhaps interact with the periphery of the brain and modulate inflammation through uptake and release of various factors.

Both trials reached the endpoint of safety, although they were not powered to determine an effect on the disease and did not show any significant positive effect in secondary clinical outcomes in this small group of patients.

Childhood leukodystrophies comprise a group of hereditary disorders characterized by the absence, malformation or destruction of myelin. Glial cell replacement using pluripotent stem cell-derived neural or glial progenitor cells may provide a promising strategy for structural remyelination and metabolic rescue[115]. In patients with the childhood demyelinating disorder, Pelizaeus–Merzbacher disease, delivery of huCNS-SC (from StemCells) to the brain showed some increased MRI signal changes (consistent with myelination) and favorable safety data in a 1-year phase 1 trial (NCT01005004)[116]. However, in the long-term follow-up (LTFU) study (NCT01391637), two of four patients developed donor-specific human leukocyte antigen (HLA) alloantibodies, demonstrating that neural stem cells can elicit an immune response when injected into the CNS, and highlighting the importance of monitoring immunologic parameters in future studies[117].

Spinal cord injury

Spinal cord injury (SCI) affects a large number of people worldwide and results in long-term disability. Patients are often relatively young, perhaps allowing better cell integration, and there is a clear time of injury from which point CRT can be initiated. Furthermore, CRT can provide multiple possible mechanisms of action, including simply filling the cystic cavitation (syringomyelia) that often occurs following SCI, remyelinating damaged axons[118] and, in some cases, forming synaptic connections across injury sites to provide functional benefit[119,120]. The challenges are mainly the diversity in SCI outcomes, which make any functional improvements related to CRT products hard to demonstrate, and the dissociation between acute injury and chronic injury—for which it is likely that putting cells in early will be beneficial, although the majority of current SCI cases are chronic in nature[121].

Early CRT studies for SCI were pioneered using fetal-derived spinal cord preparations with direct transplantation into the damaged region, with the idea that the cells would fill the cavity and perhaps provide some relay messages to connect the upper and lower segments of the cord. There are two published, completed US trials using fetal-derived human neural stem cell products for chronic SCI. The first was a phase 1 study performed by NeuralStem (Seneca) using their NSI-566 product for patients with chronic thoracic SCI (NCT01772810). While results supported safety and some effects on outcomes, increased statistical power and a control group will be needed to robustly evaluate functional changes[122]. A phase 2 trial (NCT02163876) led by StemCells using their huCNS-SC product, may have shown trends toward improved motor function in patients with SCI, but this could not be confirmed with follow-up because of premature termination of the trial based on an underpowered a priori futility analysis[123]. There was also concern about manufacturing of the clinical-grade cells, as preclinical studies comparing the performance of clinical-grade and research-grade huCNS-SC in mouse models of SCI and AD both found that research-grade lines showed a treatment benefit, while the clinical-grade cells did not[59,124,125]. This may be partly a consequence of cell line generation from numerous fetal samples, creating large variability between lines. A phase 1/2a trial performed in Korea (KCT0000879) has shown that delivery of human neural stem cells to patients with SCI is well tolerated and provided modest neurological benefit up to 1 year[126]. However, none of these studies reached the point of FDA approval and again the field has moved to ES cell and iPS cell options.

The most advanced and established program for subacute SCI uses human ES cell-derived oligodendrocyte progenitors, with the idea that, in addition to filling the cavity, many of the demyelinated axons within the damaged area would be remyelinated—leading to increased function[127]. One such cell product was initially named GRNOPC1, then AST-OPC1, and subsequently LCTOPC1—reflecting turnover of the Sponsor company from Geron, to Asterias and then Lineage Cell Therapeutics[128]. The phase 1 trial (NCT01217008) and LTFU study (NCT05919563) showed that this ES cell-derived therapy was well tolerated by patients with SCI for up to 10 years, with 80% of patients demonstrating favorable signal changes at the T2 vertebra (injury site)[129]. A phase 1/2a cervical dose-escalation trial with LCTOPC1 (NCT02302157) showed a favorable safety profile and improvement in neurological function at the 1-year follow-up[130], supporting an observational LTFU study to monitor safety for 15 years (NCT05975424). This is probably the most mature CRT program using human ES cell technology and it is very encouraging for the field to see that this approach is safe and potentially efficacious, providing hope to patients with SCI and investors in the CRT space. Finally, on the basis of successful preclinical studies[131–133], a phase 1 study using iPS cells for complete subacute SCI has been initiated at Keio University in Japan (UMIN000035074), with the transplantation of iPS cell-derived NPCs into four patients who are now under continued observation[134].

Unique challenges and opportunities for CRT

As cell sources for CRT have evolved over the years, so have various technologies to help the field advance. But beyond the manufacturing of high-quality and effective cell products, additional challenges arise from the mode of delivery, potential immune interactions and other clinical issues—not to mention costs.

To suppress or not suppress—that is the question

Although the blood–brain barrier provides the brain with some immune privilege[135], insertion of a cannula for cell delivery penetrates this barrier, which could allow the immune system to detect allogenic cells before closure. There is also growing evidence that some level of continual immune surveillance occurs in the brain, especially after inflammatory events, such as an infusion of cells[136]. Interestingly, non-matched allogeneic fetal transplants can have robust long-term survival without host immunosuppression[137]. However, it remains possible that suppression would further improve cell survival and function, and indeed, most trials of allogenic CRT products use some level of immunosuppression[138]. Testing for donor-specific antibodies is possible when the haplotype of the product is known, and positivity should be considered as an exclusion criterion in CRT trials[139]. However, with short-term immunosuppression for 6–12 months, fetal cell-derived dopaminergic graft survival has been shown up to 24 years following transplantation to the brain[140]. The side effects of immunosuppression make CRT trials more complicated, although most patients understand the need and are willing to participate. But there is a consensus that optimizing suppression will be critical for future CRT trials for neurological diseases.

This has led to the development of several approaches unique to stem cell products that could substantially reduce immunological challenges for CRT. The first is to use the patient's own iPS cells to generate the required neural tissues. However, this autologous approach increases the complexity of the cGMP manufacturing process, because each cell product is produced and cultured from a single patient[141]—rather than having a large batch of allogenic product that can be extensively tested in preclinical studies and potentially used in multiple clinical trials. In addition, some questions remain about the effects of in vitro growth, expansion and differentiation on cell immunogenicity, as demonstrated by rejection of isogenic iPS cell-derived mouse cell transplants[142].

The second opportunity is to generate a 'bank' of iPS cells collected from donors with a wide variety of HLA haplotypes that would at least cover a major percentage of the target population. This has recently been done for 20% and 40% of the Spanish and Japanese populations, respectively, in which iPS cells were generated from cord blood collections in which HLA haplotyping had been done[143,144]. MHC matching offers the possibility to augment survival of allogenic transplants and

reduce the need for immunosuppression, as shown in non-human primates; however, rejection occurred in HD lesioned non-human primates, hence this area needs further examination[145,146].

The third opportunity is based on technological breakthroughs in CRISPR editing and new iPS cell models of human disease. It is now possible to engineer human cells with gene editing to both eliminate major HLA systems that might activate a T cell response and at the same time use viral systems to express protection signals—such as CD47 from the AAVS1 safe harbor locus that would prevent the innate immune system from detecting foreign cells[147–150]. This has been used to generate hypoimmune iPS cell-derived islet cells that can survive long term in fully immunocompetent, allogeneic rhesus macaques[151]. These remarkable technologies are poised to revolutionize the cell transplant field and could simplify and strengthen trial designs that would no longer have to include immunosuppression. One major challenge for this approach is that, should the cells become cancerous, they could evade the immune system; however, this could be avoided by engineering in 'killer switches' to allow the elimination of abnormal cells[150]. This safety is particularly important for long-surviving cell transplants into the nervous system.

Location, location, location

In many instances, CRT provides new cells within the region in which host cells are lost. However, CRT-based trials for PD use ectopic placement of dopaminergic neurons to the striatum, as dopaminergic neurons transplanted in the adult human substantia nigra likely could not project axons to their target striatum. Therefore, although there is local dopamine release, the normal neural circuits that control movement are not replaced. Ectopic placement, along with the presence of co-grafted serotonergic neurons, may in some cases lead to graft-induced dyskinesias[137,152–154]. Furthermore, it is clear that simply providing dopamine neurons does not address cell loss in other locations[155]. While these issues continue to be actively addressed by the field, a cell product to restore functional dopaminergic neurons would be a remarkable treatment for patients and, hence, high investment continues in this space.

A major challenge for CRT trials is the surgical delivery of the cells to precise regions of the brain or spinal cord. In some cases when the target area can be activated, functional brain mapping can be used to localize the area—for example, using hand tasks to surgically target specific regions of the motor cortex[156]. Another challenge is how to deliver cells while minimizing damage, blood–brain barrier penetration and vascular leakage. Traditional solid, wider-bore cannulas can create major damage on entry to the brain and also cause reflux issues. Convection-enhanced delivery, used for gene therapy products, is not appropriate for cellular delivery because this technique is too harsh on cells and does not disperse them through interstitial tissue. Exciting new approaches include a system that inserts a wider cannula into the target location and then uses radial branched deployment of cells through a smaller flexible cannula that is inserted into the tissue[157]. This can provide better cell distribution than single-cannula insertion, although an increased risk of bleeding is a concern with such adaptations. Other approaches to enhance cell migration and survival include altering CXR receptors, providing chemokines or co-grafting regulatory T cells[120,158–160]. To facilitate cell entry into focal regions, MRI-guided ultrasound can be used to transiently open the blood–brain barrier[161]; however, possible side effects of transfusing neural cells into the peripheral blood system will have to be carefully examined before using this approach in patients.

Finally, the field would benefit from being able to monitor the survival and migration of the transplanted cells. There are several techniques to achieve this, including using paramagnetic iron beads to label the cells before grafting, for subsequent MRI detection[162,163]. This technology allows the location of the transplant to be visualized, but the most critical aspect is whether the cells survived. Unfortunately, various host cells can phagocytose both dead cells and the iron beads, making it impossible to distinguish graft from host[164]. This, along with potential effects on cell function or health[165], remains a challenge to establish cell survival in patients.

Can disease be spread?

An interesting hurdle for certain CRT-based therapies arises from the demonstration that various disease pathologies of PD and HD can spread from the host brain to the transplanted cells[140,166–168]. However, while a theoretical risk, the number of transplanted cells that show these changes is relatively small, leaving the majority of the graft to function normally and perhaps survive for the patients' lifetime. Issues of disease spread could also pertain to patient-derived iPS cells that develop disease phenotypes in vitro[169] and can continue to manifest the disease, show deficits compared with control lines, and even spread the pathology to healthy host cells after transplantation into rodent models[170,171]. This risk from diseased iPS cells could be mitigated by gene correction for genetic-based disorders, but adds another layer of complexity for iPS cell-based CRT[172].

Unique aspects of clinical trial design for CRT

Invasive therapy approaches in which cells are infused directly into the brain or spinal cord require careful thought about clinical trial design and eventual regulatory approval. Reaching phase 1 or 2a clinical studies, with the primary outcome of safety, normally involves between 5 and 15 patients, and often a dose-escalation phase, to determine the final dose and to assess side effects[173]. Subsequently, a phase 2 trial can enroll enough patients to establish safety, as well as explore preliminary efficacy (through secondary outcomes), and some regulatory authorities encourage placebo controls even at this early stage.

Decisions around placebo-controlled surgical trials are a balance between ethical considerations of performing sham surgery versus the need to test efficacy of the cell product, as well as challenges around how to maintain blinding when immunosuppression is used[174,175]. This can be particularly critical in open-label trials for PD when a patient knows they are receiving a cell treatment, given that the role of dopamine in reward processing[176] could lead to an increased dopamine signal in PET studies and hence a placebo effect[174,177,178]. Sham trials should be sufficiently powered and include LTFU to determine cell product efficacy. Assessing effects of cannula damage to both the CNS and treatment outcomes would require that sham surgeries include cannula insertion and vehicle delivery. This, however, needs to be carefully considered in the light of potential serious risks from needle trauma, disrupting the blood–brain barrier, and inducing inflammatory responses[160].

Many drug trials stop when the drug is no longer delivered at the end of the protocol, yet cells delivered to the brain and spinal cord have the potential for long-term survival beyond the trial duration. As with gene therapy products[179], regulatory agencies could require a LTFU protocol to ensure patient safety related to immunological status[139], and to monitor for potential aberrant proliferation of transplanted cells over time. However, many small companies pioneering this technology are not well financed and close shortly after the protocol ends—or even sooner if company focus changes. Examples include StemCells' closure after performing CRT on several patients, as well as Geron's termination of their SCI trial before treating all enrolled patients[128]. This leaves patients who received transplants vulnerable without continual monitoring, and deprives the field of valuable lessons from these important early studies. Better federal guidelines, regulations and oversight are required to ensure the safety of CRT trials, and phase 4 studies should be considered to monitor effects of the product after approval[180]. Furthermore, postmortem analysis of the brain or spinal cord of patients who received CRT is also critical to learn as much as possible from CRT studies, as has been so elegantly shown for PD and HD. This is particularly critical to assess long-term cell survival and to

understand potential disease spread. Ideally, the CRT field needs to establish guidelines for transplant studies of neurological diseases that incorporate these issues, as has been previously done for stroke[181].

Is the price right?

The amount of investment in time and cost for surgical cell delivery to the CNS of a single patient is high compared with typical orally administered or infused drugs. However, unlike most other therapies, the transplanted cells should replace diseased cell function and should not need frequent readministration. This shifts the cost recovery structure of the therapy for companies, requiring a large upfront payment for the procedure to replace continual revenue from pills or infusions. This has been well established for gene therapy trials, exemplified by the approved product Zolgensma (onasemnogene abeparvovec) for spinal muscular atrophy, which has an upfront cost of over US $2 million.

The cost may be similar for the first stem cell-based CRT products that receive approval for neurological diseases, and will stimulate discussion about how any healthcare system can sustain these types of cost—in particular for more common neurological diseases. However, the treatment cost has to be weighed against cost to the healthcare system to maintain these patients for their lifespan. Furthermore, as for all novel therapies, the cost will inevitably decrease following innovations in stem cell manufacturing, scaling of cellular products and increased efficiencies in delivery to the CNS, combined with market pressure as more companies enter this new field. Of great interest is the flagship CRT approach of transplanting dopaminergic neurons to treat PD, with a large number of new companies now entering this field—suggesting promise and potential commercialization of this approach.

From a regulatory standpoint, the FDA is encouraging CRT, understands the complexities and has put forward novel pathways such as regenerative medicine advanced therapy designation, fast track, and accelerated development to expedite approval of cellular products. However, to achieve the promise of this growing field, more investment is needed, as well as transparency of findings by companies in this space[182].

Future outlook

While complex and challenging, the idea of using CRT for neurological disease remains a vital area of investigation for medicine. Over the past decade, many drug companies have pulled back from neuroscience due to the cost of drug development and the lack of promising targets[183], which has created a desperate need in this arena. The idea of replacing sick or dying neurons and glia remains strong and early evidence supports clinical efficacy in some areas. New studies continue to excite the field, including the demonstration that young glial progenitors transplanted into the mouse brain may not only survive, but also out-compete and replace old or diseased cells while restoring function, as well as emerging evidence that microglial replacement may be able to modulate inflammation and increase neuronal survival[184,185].

Novel technologies are allowing faster production of specific neural cell types using direct reprogramming methods that express unique transcription factors to drive differentiation[186]. The technology continues to evolve for novel automated manufacturing protocols at scale, as well as genetically engineering cells to evade the immune system, release therapeutic molecules or activate 'killer switches' for safety reasons. Finally, the emergence of AI could assist in many aspects of these complex approaches, from cell production and qualification to interpretation of clinical trial outcomes.

All these advances, along with adaptive clinical protocols, industry engagement and a growing acceptance of the concept of CRT for neurological disorders, will drive the field to new heights over the next decade. Hopefully, this will lead to an era of new approved CRT products for the growing number of neurological diseases that will be an increasing future challenge for our aging population.

References

1. Weissman, I. L. & Shizuru, J. A. The origins of the identification and isolation of hematopoietic stem cells, and their capability to induce donor-specific transplantation tolerance and treat autoimmune diseases. *Blood* **112**, 3543–3553 (2008).
2. Finck, A. V., Blanchard, T., Roselle, C. P., Golinelli, G. & June, C. H. Engineered cellular immunotherapies in cancer and beyond. *Nat. Med.* **28**, 678–689 (2022).
3. Kim, H. J. et al. Stereotactic brain injection of human umbilical cord blood mesenchymal stem cells in patients with Alzheimer's disease dementia: a phase 1 clinical trial. *Alzheimers Dement.* **1**, 95–102 (2015).
4. Liu, X. & Jia, X. Neuroprotection of stem cells against ischemic brain injury: from bench to clinic. *Transl. Stroke Res.* https://doi.org/10.1007/s12975-023-01163-3 (2023).
5. Kawabori, M. et al. Cell therapy for chronic TBI: interim analysis of the randomized controlled STEMTRA trial. *Neurology* **96**, e1202–e1214 (2021).
6. Wu, H., Fan, Y. & Zhang, M. Advanced progress in the role of adipose-derived mesenchymal stromal/stem cells in the application of central nervous system disorders. *Pharmaceutics* **15**, 2637 (2023).
7. Levy, O. et al. Shattering barriers toward clinically meaningful MSC therapies. *Sci. Adv.* **6**, eaba6884 (2020).
8. Feng, X. et al. From stem cells to pancreatic β-cells: strategies, applications, and potential treatments for diabetes. *Mol. Cell. Biochem.* https://doi.org/10.1007/s11010-024-04999-x (2024).
9. Keymeulen, B. et al. Encapsulated stem cell-derived β cells exert glucose control in patients with type 1 diabetes. *Nat. Biotechnol.* https://doi.org/10.1038/s41587-023-02055-5 (2023).
10. Ashur, C. & Frishman, W. H. Cardiosphere-derived cells and ischemic heart failure. *Cardiol. Rev.* **26**, 8–21 (2018).
11. Van Gelder, R. N. et al. Regenerative and restorative medicine for eye disease. *Nat. Med.* **28**, 1149–1156 (2022).
12. Klymenko, V., González Martínez, O. G. & Zarbin, M. Recent progress in retinal pigment epithelium cell-based therapy for retinal disease. *Stem Cells Transl. Med.* **13**, 317–331 (2024).
13. Dunnett, S. B., Kendall, A. L., Watts, C. & Torres, E. M. Neuronal cell transplantation for Parkinson's and Huntington's diseases. *Br. Med. Bull.* **53**, 757–776 (1997).
14. Carpenter, M. K. et al. In vitro expansion of a multipotent population of human neural progenitor cells. *Exp. Neurol.* **158**, 265–278 (1999).
15. Villa, A., Snyder, E. Y., Vescovi, A. & Martínez-Serrano, A. Establishment and properties of a growth factor-dependent, perpetual neural stem cell line from the human CNS. *Exp. Neurol.* **161**, 67–84 (2000).
16. Svendsen, C. N. et al. A new method for the rapid and long term growth of human neural precursor cells. *J. Neurosci. Methods* **85**, 141–152 (1998).
17. Wright, L. S., Prowse, K. R., Wallace, K., Linskens, M. H. K. & Svendsen, C. N. Human progenitor cells isolated from the developing cortex undergo decreased neurogenesis and eventual senescence following expansion in vitro. *Exp. Cell. Res.* **312**, 2107–2120 (2006).
18. Zietlow, R. et al. The survival of neural precursor cell grafts is influenced by in vitro expansion. *J. Anat.* **207**, 227–240 (2005).
19. Thomson, J. A. et al. Embryonic stem cell lines derived from human blastocysts. *Science* **282**, 1145–1147 (1998).
20. Yu, J. et al. Induced pluripotent stem cell lines derived from human somatic cells. *Science* **318**, 1917–1920 (2007).
21. Takahashi, K. et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* **131**, 861–872 (2007).

22. Fung, R. K. F. & Kerridge, I. H. Uncertain translation, uncertain benefit and uncertain risk: ethical challenges facing first-in-human trials of induced pluripotent stem cells. *Bioethics* **27**, 89–96 (2013).
23. Temple, S. Advancing cell therapy for neurodegenerative diseases. *Cell Stem Cell* **30**, 512–529 (2023).
24. Mulroy, E., Erro, R., Bhatia, K. P. & Hallett, M. Refining the clinical diagnosis of Parkinson's disease. *Parkinsonism Relat. Disord.* **122**, 106041 (2024).
25. Brundin, P. et al. Behavioural effects of human fetal dopamine neurons grafted in a rat model of Parkinson's disease. *Exp. Brain Res.* **65**, 235–240 (1986).
26. Björklund, A., Stenevi, U., Dunnett, S. B. & Gage, F. H. Cross-species neural grafting in a rat model of Parkinson's disease. *Nature* **298**, 652–654 (1982).
27. Barker, R. A., Parmar, M., Studer, L. & Takahashi, J. Human trials of stem cell-derived dopamine neurons for Parkinson's disease: dawn of a new era. *Cell Stem Cell* **21**, 569–573 (2017).
28. Kirkeby, A. et al. Preclinical quality, safety, and efficacy of a human embryonic stem cell-derived product for the treatment of Parkinson's disease, STEM-PD. *Cell Stem Cell* **30**, 1299–1314 (2023).
29. Park, S. et al. Preclinical and dose-ranging assessment of hESC-derived dopaminergic progenitors for a clinical trial on Parkinson's disease. *Cell Stem Cell* **31**, 25–38 (2024).
30. Foltynie, T. Scaling up GMP-grade dopaminergic cells for Parkinson's disease. *Cell Stem Cell* **31**, 5–6 (2024).
31. Grealish, S. et al. Human ESC-derived dopamine neurons show similar preclinical efficacy and potency to fetal neurons when grafted in a rat model of Parkinson's disease. *Cell Stem Cell* **15**, 653–665 (2014).
32. Emborg, M. E. et al. Intracerebral transplantation of differentiated human embryonic stem cells to hemiparkinsonian monkeys. *Cell Transplant.* **22**, 831–838 (2013).
33. Kim, T. W. et al. Biphasic activation of WNT signaling facilitates the derivation of midbrain dopamine neurons from hESCs for translational use. *Cell Stem Cell* **28**, 343–355 (2021).
34. Piao, J. et al. Preclinical efficacy and safety of a human embryonic stem cell-derived midbrain dopamine progenitor product, MSK-DA01. *Cell Stem Cell* **28**, 217–229 (2021).
35. Takahashi, J. Clinical trial for parkinson's disease gets a green light in the US. *Cell Stem Cell* **28**, 182–183 (2021).
36. BlueRock. BlueRock's phase I study with bemdaneprocel in patients with Parkinson's disease meets primary endpoint. https://www.bluerocktx.com/bluerocks-phase-i-study-with-bemdaneprocel-in-patients-with-parkinsons-disease-meets-primary-endpoint/ (2023).
37. Kirkeby, A., Parmar, M. & Barker, R. A. Strategies for bringing stem cell-derived dopamine neurons to the clinic: a European approach (STEM-PD). *Prog. Brain Res.* **230**, 165–190 (2017).
38. Wang, Y. -K. et al. Human clinical-grade parthenogenetic ESC-derived dopaminergic neurons recover locomotive defects of nonhuman primate models of Parkinson's disease. *Stem Cell Rep.* **11**, 171–182 (2018).
39. Garitaonandia, I. et al. Neural stem cell tumorigenicity and biodistribution assessment for phase I clinical trial in parkinson's disease. *Sci. Rep.* **6**, 34478 (2016).
40. Nakamura, R. et al. A defined method for differentiating human iPSCs into midbrain dopaminergic progenitors that safely restore motor deficits in Parkinson's disease. *Front. Neurosci.* **17**, 1202027 (2023).
41. Doi, D. et al. Pre-clinical study of induced pluripotent stem cell-derived dopaminergic progenitor cells for Parkinson's disease. *Nat. Commun.* **11**, 3369 (2020).
42. Takahashi, J. iPS cell-based therapy for Parkinson's disease: a Kyoto trial. *Regen. Ther.* **13**, 18–22 (2020).
43. Hallett, P. J. et al. Successful function of autologous iPSC-derived dopamine neurons following transplantation in a non-human primate model of Parkinson's disease. *Cell Stem Cell* **16**, 269–274 (2015).
44. Tao, Y. et al. Autologous transplant therapy alleviates motor and depressive behaviors in parkinsonian monkeys. *Nat. Med.* **27**, 632–639 (2021).
45. Schweitzer, J. S. et al. Personalized iPSC-derived dopamine progenitor cells for Parkinson's disease. *N. Engl. J. Med.* **382**, 1926–1932 (2020).
46. Aspen Neuroscience. Aspen Neuroscience announces first patient dosed in first-in-human phase 1/2a clinical trial of autologous neuronal cell replacement therapy for Parkinson's disease. https://aspenneuroscience.com/aspen-neuroscience-announces-first-patient-dosed-in-first-in-human-phase-1-2a-clinical-trial-of-autologous-neuronal-cell-replacement-therapy-for-parkinsons-disease/ (2024).
47. Gusella, J. F., Lee, J. -M. & MacDonald, M. E. Huntington's disease: nearly four decades of human molecular genetics. *Hum. Mol. Genet.* **30**, R254–R263 (2021).
48. Tabrizi, S. J. et al. Potential disease-modifying therapies for Huntington's disease: lessons learned and future opportunities. *Lancet Neurol.* **21**, 645–658 (2022).
49. Nakao, N. & Itakura, T. Fetal tissue transplants in animal models of Huntington's disease: the effects on damaged neuronal circuitry and behavioral deficits. *Prog. Neurobiol.* **61**, 313–338 (2000).
50. Reidling, J. C. et al. Human neural stem cell transplantation rescues functional deficits in R6/2 and Q140 huntington's disease mice. *Stem Cell Rep.* **10**, 58–72 (2018).
51. Holley, S. M. et al. Transplanted human neural stem cells rescue phenotypes in zQ175 Huntington's disease mice and innervate the striatum. *Mol. Ther.* **31**, 3545–3563 (2023).
52. Mu, S. et al. Transplantation of induced pluripotent stem cells improves functional recovery in Huntington's disease rat model. *PLoS ONE* **9**, e101185 (2014).
53. Park, H. J. et al. Human iPSC-derived neural precursor cells differentiate into multiple cell types to delay disease progression following transplantation into YAC128 Huntington's disease mouse model. *Cell Prolif.* **54**, e13082 (2021).
54. Goel, P. et al. Neuronal cell death mechanisms in Alzheimer's disease: an insight. *Front. Mol. Neurosci.* **15**, 937133 (2022).
55. Tuszynski, M. H. et al. Nerve growth factor gene therapy: activation of neuronal responses in alzheimer disease. *JAMA Neurol.* **72**, 1139–1147 (2015).
56. McGinley, L. M. et al. Human neural stem cell transplantation improves cognition in a murine model of Alzheimer's disease. *Sci. Rep.* **8**, 14776 (2018).
57. Tsukamoto, A., Uchida, N., Capela, A., Gorba, T. & Huhn, S. Clinical translation of human neural stem cells. *Stem Cell Res. Ther.* **4**, 102 (2013).
58. Ager, R. R. et al. Human neural stem cells improve cognition and promote synaptic growth in two complementary transgenic models of Alzheimer's disease and neuronal loss. *Hippocampus* **25**, 813–826 (2015).
59. Marsh, S. E. et al. HuCNS-SC human NSCs fail to differentiate, form ectopic clusters, and provide no cognitive benefits in a transgenic model of Alzheimer's disease. *Stem Cell Rep.* **8**, 235–248 (2017).
60. Goldberg, N. R. S. et al. Human neural progenitor transplantation rescues behavior and reduces α-synuclein in a transgenic model of dementia with Lewy bodies. *Stem Cells Transl. Med.* **6**, 1477–1490 (2017).
61. Liu, Y. et al. Medial ganglionic eminence-like cells derived from human embryonic stem cells correct learning and memory deficits. *Nat. Biotechnol.* **31**, 440–447 (2013).

62. Zhang, T. et al. Human neural stem cells reinforce hippocampal synaptic network and rescue cognitive deficits in a mouse model of alzheimer's disease. *Stem Cell Rep.* **13**, 1022–1037 (2019).
63. Hardiman, O. et al. Amyotrophic lateral sclerosis. *Nat. Rev. Dis. Primers* **3**, 17071 (2017).
64. Cantara, S., Simoncelli, G. & Ricci, C. Antisense oligonucleotides (ASOs) in motor neuron diseases: a road to cure in light and shade. *Int. J. Mol. Sci.* **25**, 4809 (2024).
65. Yan, J. et al. Extensive neuronal differentiation of human neural stem cell grafts in adult rat spinal cord. *PLoS Med.* **4**, e39 (2007).
66. Xu, L. et al. Human neural stem cell grafts ameliorate motor neuron disease in SOD-1 transgenic rats. *Transplantation* **82**, 865–875 (2006).
67. Feldman, E. L. et al. Intraspinal neural stem cell transplantation in amyotrophic lateral sclerosis: phase 1 trial outcomes. *Ann. Neurol.* **75**, 363–373 (2014).
68. Glass, J. D. et al. Transplantation of spinal cord-derived neural stem cells for ALS: analysis of phase 1 and 2 trials. *Neurology* **87**, 392–400 (2016).
69. Goutman, S. A. et al. Long-term phase 1/2 intraspinal stem cell transplantation outcomes in ALS. *Ann. Clin. Transl. Neurol.* **5**, 730–740 (2018).
70. Mazzini, L. et al. 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.* **8**, 887–897 (2019).
71. Henderson, C. E. et al. GDNF: a potent survival factor for motoneurons present in peripheral nerve and muscle. *Science* **266**, 1062–1064 (1994).
72. Lepore, A. C. et al. Focal transplantation-based astrocyte replacement is neuroprotective in a model of motor neuron disease. *Nat. Neurosci.* **11**, 1294–1301 (2008).
73. Suzuki, M. et al. GDNF secreting human neural progenitor cells protect dying motor neurons, but not their projection to muscle, in a rat model of familial ALS. *PLoS ONE* **2**, e689 (2007).
74. Gowing, G. et al. Glial cell line-derived neurotrophic factor-secreting human neural progenitors show long-term survival, maturation into astrocytes, and no tumor formation following transplantation into the spinal cord of immunocompromised rats. *Neuroreport* **25**, 367–372 (2014).
75. Shelley, B. C., Gowing, G. & Svendsen, C. N. A cGMP-applicable expansion method for aggregates of human neural stem and progenitor cells derived from pluripotent stem cells or fetal brain tissue. *J. Vis. Exp.* **15**, 51219 (2014).
76. Rushton, D. J., Andres, P. L., Allred, P., Baloh, R. H. & Svendsen, C. N. Patients with ALS show highly correlated progression rates in left and right limb muscles. *Neurology* **89**, 196–206 (2017).
77. Baloh, R. H. 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.* **28**, 1813–1822 (2022).
78. Thomsen, G. M. et al. Delayed disease onset and extended survival in the SOD1G93A rat model of amyotrophic lateral sclerosis after suppression of mutant SOD1 in the motor cortex. *J. Neurosci.* **34**, 15587–15600 (2014).
79. Okano, H. Transplantation of neural progenitor cells into the human CNS. *Trends Mol. Med.* **28**, 897–899 (2022).
80. Laperle, A. H. et al. Human iPSC-derived neural progenitor cells secreting GDNF provide protection in rodent models of ALS and retinal degeneration. *Stem Cell Rep.* **18**, 1629–1642 (2023).
81. Du, H. et al. Induced pluripotent stem cells and their applications in amyotrophic lateral sclerosis. *Cells* **12**, 971 (2023).
82. Fujimori, K. et al. Modeling sporadic ALS in iPSC-derived motor neurons identifies a potential therapeutic agent. *Nat. Med.* **24**, 1579–1589 (2018).
83. Huang, X. et al. Human amyotrophic lateral sclerosis excitability phenotype screen: target discovery and validation. *Cell Rep.* **35**, 109224 (2021).
84. Darsalia, V., Kallur, T. & Kokaia, Z. Survival, migration and neuronal differentiation of human fetal striatal and cortical neural stem cells grafted in stroke-damaged rat striatum. *Eur. J. Neurosci.* **26**, 605–614 (2007).
85. Andres, R. H. et al. Human neural stem cells enhance structural plasticity and axonal transport in the ischaemic brain. *Brain* **134**, 1777–1789 (2011).
86. Mine, Y. et al. Grafted human neural stem cells enhance several steps of endogenous neurogenesis and improve behavioral recovery after middle cerebral artery occlusion in rats. *Neurobiol. Dis.* **52**, 191–203 (2013).
87. Sinden, J. D., Hicks, C., Stroemer, P., Vishnubhatla, I. & Corteling, R. Human neural stem cell therapy for chronic ischemic stroke: charting progress from laboratory to patients. *Stem Cells Dev.* **26**, 933–947 (2017).
88. Pollock, K. et al. A conditionally immortal clonal stem cell line from human cortical neuroepithelium for the treatment of ischemic stroke. *Exp. Neurol.* **199**, 143–155 (2006).
89. Stroemer, P. et al. The neural stem cell line CTX0E03 promotes behavioral recovery and endogenous neurogenesis after experimental stroke in a dose-dependent fashion. *Neurorehabil. Neural Repair* **23**, 895–909 (2009).
90. Kalladka, D. et al. Human neural stem cells in patients with chronic ischaemic stroke (PISCES): a phase 1, first-in-man study. *Lancet* **388**, 787–796 (2016).
91. Muir, K. W. et al. Intracerebral implantation of human neural stem cells and motor recovery after stroke: multicentre prospective single-arm study (PISCES-2). *J. Neurol. Neurosurg. Psychiatry* **91**, 396–401 (2020).
92. Zhang, G. et al. Stable intracerebral transplantation of neural stem cells for the treatment of paralysis due to ischemic stroke. *Stem Cells Transl. Med.* **8**, 999–1007 (2019).
93. Jin, K. et al. Transplantation of human neural precursor cells in Matrigel scaffolding improves outcome from focal cerebral ischemia after delayed postischemic treatment in rats. *J. Cereb. Blood Flow. Metab.* **30**, 534–544 (2010).
94. Hicks, A. U. et al. Transplantation of human embryonic stem cell-derived neural precursor cells and enriched environment after cortical stroke in rats: cell survival and functional recovery. *Eur. J. Neurosci.* **29**, 562–574 (2009).
95. Kim, H. -S. et al. PSA-NCAM$^+$ neural precursor cells from human embryonic stem cells promote neural tissue integrity and behavioral performance in a rat stroke model. *Stem Cell Rev. Rep.* **10**, 761–771 (2014).
96. Wendling, P. Stem cell therapy improves post-stroke motor function. *Medscape* https://www.medscape.com/viewarticle/stem-cell-therapy-improves-post-stroke-motor-function-2024a10008ve#:~:text=Significant%20gains%20were%20also%20seen,or%20stroke%20volume%2C%20Steinberg%20said (2024).
97. Dudek, F. E. Loss of GABAergic interneurons in seizure-induced epileptogenesis-two decades later and in a more complex world. *Epilepsy Curr.* **20**, 70S–72S (2020).
98. Franz, J. et al. Differential vulnerability of neuronal subpopulations of the subiculum in a mouse model for mesial temporal lobe epilepsy. *Front. Cell. Neurosci.* **17**, 1142507 (2023).
99. Miller, K. J. & Fine, A. L. Decision-making in stereotactic epilepsy surgery. *Epilepsia* **63**, 2782–2801 (2022).
100. Pereira Dalio, M. T. R. et al. Long-term outcome of temporal lobe epilepsy surgery in 621 patients with hippocampal sclerosis: clinical and surgical prognostic factors. *Front. Neurol.* **13**, 833293 (2022).

101. Southwell, D. G. Interneuron transplantation for drug-resistant epilepsy. *Neurosurg. Clin. N. Am.* **35**, 151–160 (2024).
102. Alayli, A. et al. Stem cells: recent developments redefining epilepsy therapy. *Cell Transplant.* **32**, 9636897231158968 (2023).
103. Gonzalez-Ramos, A. et al. Human stem cell-derived GABAergic neurons functionally integrate into human neuronal networks. *Sci. Rep.* **11**, 22050 (2021).
104. Waloschková, E. et al. Human stem cell-derived GABAergic interneurons establish efferent synapses onto host neurons in rat epileptic hippocampus and inhibit spontaneous recurrent seizures. *Int. J. Mol. Sci.* **22**, 13243 (2021).
105. Bershteyn, M. et al. Human pallial MGE-type GABAergic interneuron cell therapy for chronic focal epilepsy. *Cell Stem Cell* **30**, 1331–1350 (2023).
106. Neurona Therapeutics. Neurona Therapeutics presents positive clinical update from NRTX-1001 cell therapy trial in adults with drug-resistant focal epilepsy at American Academy of Neurology (AAN) 2024 Annual Meeting. https://www.neuronatherapeutics.com/news/press-releases/041524/ (2024).
107. Upadhya, D. et al. Human induced pluripotent stem cell-derived MGE cell grafting after status epilepticus attenuates chronic epilepsy and comorbidities via synaptic integration. *Proc. Natl Acad. Sci. USA* **116**, 287–296 (2019).
108. Upadhya, D. et al. Grafted hPSC-derived GABA-ergic interneurons regulate seizures and specific cognitive function in temporal lobe epilepsy. *NPJ Regen. Med.* **7**, 38 (2022).
109. Alizadeh, A., Dyck, S. M. & Karimi-Abdolrezaee, S. Myelin damage and repair in pathologic CNS: challenges and prospects. *Front. Mol. Neurosci.* **8**, 35 (2015).
110. Christodoulou, M. V. et al. Cell replacement therapy with stem cells in multiple sclerosis, a systematic review. *Hum. Cell* **37**, 9–53 (2024).
111. Goldman, S. A., Mariani, J. N. & Madsen, P. M. Glial progenitor cell-based repair of the dysmyelinated brain: progression to the clinic. *Semin. Cell Dev. Biol.* **116**, 62–70 (2021).
112. Windrem, M. S. et al. Human glial progenitor cells effectively remyelinate the demyelinated adult brain. *Cell Rep.* **31**, 107658 (2020).
113. Genchi, A. et al. Neural stem cell transplantation in patients with progressive multiple sclerosis: an open-label, phase 1 study. *Nat. Med.* **29**, 75–85 (2023).
114. Leone, M. A. et al. Phase I clinical trial of intracerebroventricular transplantation of allogeneic neural stem cells in people with progressive multiple sclerosis. *Cell Stem Cell* **30**, 1597–1609 (2023).
115. Osorio, M. J. & Goldman, S. A. Glial progenitor cell-based treatment of the childhood leukodystrophies. *Exp. Neurol.* **283**, 476–488 (2016).
116. Gupta, N. et al. Neural stem cell engraftment and myelination in the human brain. *Sci. Transl. Med.* **4**, 155ra137 (2012).
117. Gupta, N. et al. Long-term safety, immunologic response, and imaging outcomes following neural stem cell transplantation for Pelizaeus–Merzbacher disease. *Stem Cell Rep.* **13**, 254–261 (2019).
118. Keirstead, H. S. et al. Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury. *J. Neurosci.* **25**, 4694–4705 (2005).
119. Ceto, S., Sekiguchi, K. J., Takashima, Y., Nimmerjahn, A. & Tuszynski, M. H. Neural stem cell grafts form extensive synaptic networks that integrate with host circuits after spinal cord injury. *Cell Stem Cell* **27**, 430–440 (2020).
120. Kawai, M. et al. Long-term selective stimulation of transplanted neural stem/progenitor cells for spinal cord injury improves locomotor function. *Cell Rep.* **37**, 110019 (2021).
121. Shibata, T., Tashiro, S., Nakamura, M., Okano, H. & Nagoshi, N. A review of treatment methods focusing on human induced pluripotent stem cell-derived neural stem/progenitor cell transplantation for chronic spinal cord injury. *Medicina* **59**, 1235 (2023).
122. Curtis, E. et al. A first-in-human, phase I study of neural stem cell transplantation for chronic spinal cord injury. *Cell Stem Cell* **22**, 941–950.e6 (2018).
123. Levi, A. D. et al. Clinical outcomes from a multi-center study of human neural stem cell transplantation in chronic cervical spinal cord injury. *J. Neurotrauma* **36**, 891–902 (2019).
124. Temple, S. & Studer, L. Lessons learned from pioneering neural stem cell studies. *Stem Cell Rep.* **8**, 191–193 (2017).
125. Anderson, A. J., Piltti, K. M., Hooshmand, M. J., Nishi, R. A. & Cummings, B. J. Preclinical efficacy failure of human CNS-derived stem cells for use in the pathway study of cervical spinal cord injury. *Stem Cell Rep.* **8**, 249–263 (2017).
126. Shin, J. C. et al. Clinical trial of human fetal brain-derived neural stem/progenitor cell transplantation in patients with traumatic cervical spinal cord injury. *Neural Plast.* **2015**, 630932 (2015).
127. Manley, N. C., Priest, C. A., Denham, J., Wirth, E. D. & Lebkowski, J. S. Human embryonic stem cell-derived oligodendrocyte progenitor cells: preclinical efficacy and safety in cervical spinal cord injury. *Stem Cells Transl. Med.* **6**, 1917–1929 (2017).
128. Scott, C. T. & Magnus, D. Wrongful termination: lessons from the Geron clinical trial. *Stem Cells Transl. Med.* **3**, 1398–1401 (2014).
129. McKenna, S. L. et al. Ten-year safety of pluripotent stem cell transplantation in acute thoracic spinal cord injury. *J. Neurosurg. Spine* **37**, 321–330 (2022).
130. Fessler, R. G. et al. A phase 1/2a dose-escalation study of oligodendrocyte progenitor cells in individuals with subacute cervical spinal cord injury. *J. Neurosurg. Spine* **37**, 812–820 (2022).
131. Kobayashi, Y. et al. Pre-evaluated safe human iPSC-derived neural stem cells promote functional recovery after spinal cord injury in common marmoset without tumorigenicity. *PLoS ONE* **7**, e52787 (2012).
132. Nori, S. et al. Grafted human-induced pluripotent stem-cell-derived neurospheres promote motor functional recovery after spinal cord injury in mice. *Proc. Natl Acad. Sci. USA* **108**, 16825–16830 (2011).
133. Nagoshi, N. & Okano, H. iPSC-derived neural precursor cells: potential for cell transplantation therapy in spinal cord injury. *Cell. Mol. Life Sci.* **75**, 989–1000 (2018).
134. Sugai, K. et al. First-in-human clinical trial of transplantation of iPSC-derived NS/PCs in subacute complete spinal cord injury: study protocol. *Regen. Ther.* **18**, 321–333 (2021).
135. Proulx, S. T. & Engelhardt, B. Central nervous system zoning: How brain barriers establish subdivisions for CNS immune privilege and immune surveillance. *J. Intern. Med.* **292**, 47–67 (2022).
136. Marchetti, L. & Engelhardt, B. Immune cell trafficking across the blood–brain barrier in the absence and presence of neuroinflammation. *Vasc. Biol.* **2**, H1–H18 (2020).
137. Freed, C. R. et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N. Engl. J. Med.* **344**, 710–719 (2001).
138. Kordower, J. H. et al. Fetal grafting for Parkinson's disease: expression of immune markers in two patients with functional fetal nigral implants. *Cell Transplant.* **6**, 213–219 (1997).
139. Krystkowiak, P. et al. Alloimmunisation to donor antigens and immune rejection following foetal neural grafts to the brain in patients with Huntington's disease. *PLoS ONE* **2**, e166 (2007).
140. Li, W. et al. Extensive graft-derived dopaminergic innervation is maintained 24 years after transplantation in the degenerating parkinsonian brain. *Proc. Natl Acad. Sci. USA* **113**, 6544–6549 (2016).

141. Jha, B. S., Farnoodian, M. & Bharti, K. Regulatory considerations for developing a phase I investigational new drug application for autologous induced pluripotent stem cells-based therapy product. *Stem Cells Transl. Med.* **10**, 198–208 (2021).
142. Zhao, T., Zhang, Z. -N., Rong, Z. & Xu, Y. Immunogenicity of induced pluripotent stem cells. *Nature* **474**, 212–215 (2011).
143. Kuebler, B. et al. Generation of a bank of clinical-grade, HLA-homozygous iPSC lines with high coverage of the Spanish population. *Stem Cell Res. Ther.* **14**, 366 (2023).
144. Yoshida, S. et al. A clinical-grade HLA haplobank of human induced pluripotent stem cells matching approximately 40% of the Japanese population. *Med* **4**, 51–66 (2023).
145. Morizane, A. et al. MHC matching improves engraftment of iPSC-derived neurons in non-human primates. *Nat. Commun.* **8**, 385 (2017).
146. Aron Badin, R. et al. MHC matching fails to prevent long-term rejection of iPSC-derived neurons in non-human primates. *Nat. Commun.* **10**, 4357 (2019).
147. Xu, H. et al. Targeted disruption of HLA genes via CRISPR-Cas9 generates iPSCs with enhanced immune compatibility. *Cell Stem Cell* **24**, 566–578 (2019).
148. Han, X. et al. Generation of hypoimmunogenic human pluripotent stem cells. *Proc. Natl Acad. Sci. USA* **116**, 10441–10446 (2019).
149. Sung, T. -C. et al. Universal and hypoimmunogenic pluripotent stem cells for clinical usage. *Prog. Mol. Biol. Transl. Sci.* **199**, 271–296 (2023).
150. Hotta, A., Schrepfer, S. & Nagy, A. Genetically engineered hypoimmunogenic cell therapy. *Nat. Rev. Bioeng.* https://doi.org/10.1038/s44222-024-00219-9 (2024).
151. Hu, X. et al. Hypoimmune induced pluripotent stem cells survive long term in fully immunocompetent, allogeneic rhesus macaques. *Nat. Biotechnol.* **42**, 413–423 (2024).
152. Greene, P. E. et al. Persistent dyskinesias in patients with fetal tissue transplantation for Parkinson disease. *NPJ Parkinsons Dis.* **7**, 38 (2021).
153. Kordower, J. H. et al. Robust graft survival and normalized dopaminergic innervation do not obligate recovery in a Parkinson disease patient. *Ann. Neurol.* **81**, 46–57 (2017).
154. Politis, M. et al. Serotonergic neurons mediate dyskinesia side effects in Parkinson's patients with neural transplants. *Sci. Transl. Med.* **2**, 38ra46 (2010).
155. Williams-Gray, C. H., Foltynie, T., Lewis, S. J. G. & Barker, R. A. Cognitive deficits and psychosis in Parkinson's disease: a review of pathophysiology and therapeutic options. *CNS Drugs* **20**, 477–505 (2006).
156. Sagar, S., Rick, J., Chandra, A., Yagnik, G. & Aghi, M. K. Functional brain mapping: overview of techniques and their application to neurosurgery. *Neurosurg. Rev.* **42**, 639–647 (2019).
157. Silvestrini, M. T. et al. Interventional magnetic resonance imaging-guided cell transplantation into the brain with radially branched deployment. *Mol. Ther.* **23**, 119–129 (2015).
158. Lee, J. -P. et al. Chemical mutagenesis of a GPCR ligand: detoxifying "inflammo-attraction" to direct therapeutic stem cell migration. *Proc. Natl Acad. Sci. USA* **117**, 31177–31188 (2020).
159. Wang, Z. et al. Enabling survival of transplanted neural precursor cells in the ischemic brain. *Adv. Sci.* **10**, e2302527 (2023).
160. Park, T. -Y. et al. Co-transplantation of autologous T_{reg} cells in a cell therapy for Parkinson's disease. *Nature* **619**, 606–615 (2023).
161. Ahmed, N., Gandhi, D., Melhem, E. R. & Frenkel, V. MRI guided focused ultrasound-mediated delivery of therapeutic cells to the brain: a review of the state-of-the-art methodology and future applications. *Front. Neurol.* **12**, 669449 (2021).
162. Lamanna, J. J. et al. Ferumoxytol labeling of human neural progenitor cells for diagnostic cellular tracking in the porcine spinal cord with magnetic resonance imaging. *Stem Cells Transl. Med.* **6**, 139–150 (2017).
163. Bulte, J. W. M. & Daldrup-Link, H. E. Clinical tracking of cell transfer and cell transplantation: trials and tribulations. *Radiology* **289**, 604–615 (2018).
164. Bernau, K. et al. In vivo tracking of human neural progenitor cells in the rat brain using magnetic resonance imaging is not enhanced by ferritin expression. *Cell Transplant.* **25**, 575–592 (2016).
165. Yarjanli, Z., Ghaedi, K., Esmaeili, A., Rahgozar, S. & Zarrabi, A. Iron oxide nanoparticles may damage to the neural tissue through iron accumulation, oxidative stress, and protein aggregation. *BMC Neurosci.* **18**, 51 (2017).
166. Cisbani, G. et al. Presence of tau pathology within foetal neural allografts in patients with Huntington's and Parkinson's disease. *Brain* **140**, 2982–2992 (2017).
167. Olanow, C. W., Savolainen, M., Chu, Y., Halliday, G. M. & Kordower, J. H. Temporal evolution of microglia and α-synuclein accumulation following foetal grafting in Parkinson's disease. *Brain* **142**, 1690–1700 (2019).
168. Salem, S. et al. Evidence of mutant huntingtin and tau-related pathology within neuronal grafts in Huntington's disease cases. *Neurobiol. Dis.* **198**, 106542 (2024).
169. Sison, S. L., Vermilyea, S. C., Emborg, M. E. & Ebert, A. D. Using patient-derived induced pluripotent stem cells to identify Parkinson's disease-relevant phenotypes. *Curr. Neurol. Neurosci. Rep.* **18**, 84 (2018).
170. Zygogianni, O. et al. In vivo phenotyping of familial Parkinson's Disease with human induced pluripotent stem cells: a proof-of-concept study. *Neurochem. Res.* **44**, 1475–1493 (2019).
171. Jeon, I. et al. Human-to-mouse prion-like propagation of mutant huntingtin protein. *Acta Neuropathol.* **132**, 577–592 (2016).
172. An, M. C. et al. Genetic correction of Huntington's disease phenotypes in induced pluripotent stem cells. *Cell Stem Cell* **11**, 253–263 (2012).
173. Kurzrock, R. et al. Moving beyond 3+3: the future of clinical trial design. *Am. Soc. Clin. Oncol. Educ. Book* **41**, e133–e144 (2021).
174. Clark, P. A. Placebo surgery for Parkinson's disease: do the benefits outweigh the risks? *J. Law Med. Ethics* **30**, 58–68 (2002).
175. Tabar, V. & Barker, R. A. Sham surgery for the trialing of cell-based therapies to the CNS may not be necessary. *Cell Stem Cell* **31**, 158–160 (2024).
176. Lewis, R. G., Florio, E., Punzo, D. & Borrelli, E. The brain's reward system in health and disease. *Adv. Exp. Med. Biol.* **1344**, 57–69 (2021).
177. Goetz, C. G. et al. Placebo response in Parkinson's disease: comparisons among 11 trials covering medical and surgical interventions. *Mov. Disord.* **23**, 690–699 (2008).
178. de la Fuente-Fernández, R. et al. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. *Science* **293**, 1164–1166 (2001).
179. Eisenman, D. & Swindle, S. Food and Drug Administration guidance on design of clinical trials for gene therapy products with potential for genome integration or genome editing and associated long-term follow-up of research subjects. *Appl. Biosaf.* **27**, 201–209 (2022).
180. Suvarna, V. Phase IV of drug development. *Perspect. Clin. Res.* **1**, 57–60 (2010).
181. Stroke Therapy Academic Industry Roundtable II (STAIR-II). Recommendations for clinical trial evaluation of acute stroke therapies. *Stroke* **32**, 1598–1606 (2001).
182. Kobold, S. et al. History and current status of clinical studies using human pluripotent stem cells. *Stem Cell Rep.* **18**, 1592–1598 (2023).
183. Mullard, A. Pfizer exits neuroscience. *Nat. Rev. Drug Discov.* **17**, 86 (2018).
184. Vieira, R. et al. Young glial progenitor cells competitively replace aged and diseased human glia in the adult chimeric mouse brain. *Nat. Biotechnol.* **42**, 719–730 (2024).

185. Var, S. R. et al. Transplanting microglia for treating CNS injuries and neurological diseases and disorders, and prospects for generating exogenic microglia. *Cell Transplant.* **32**, 9636897231171000 (2023).
186. Schaukowitch, K., Janas, J. A. & Wernig, M. Insights and applications of direct neuronal reprogramming. *Curr. Opin. Genet. Dev.* **83**, 102128 (2023).
187. Palmer, T. D., Takahashi, J. & Gage, F. H. The adult rat hippocampus contains primordial neural stem cells. *Mol. Cell. Neurosci.* **8**, 389–404 (1997).
188. Doetsch, F., Caillé, I., Lim, D. A., García-Verdugo, J. M. & Alvarez-Buylla, A. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell* **97**, 703–716 (1999).
189. Sorrells, S. F. et al. Positive controls in adults and children support that very few, if any, new neurons are born in the adult human hippocampus. *J. Neurosci.* **41**, 2554–2565 (2021).
190. Janeckova, L. et al. Astrocyte-like subpopulation of NG2 glia in the adult mouse cortex exhibits characteristics of neural progenitor cells. *Glia* **72**, 245–273 (2024).
191. Dimou, L. & Gallo, V. NG2-glia and their functions in the central nervous system. *Glia* **63**, 1429–1451 (2015).
192. Zhang, L., Wang, Y., Liu, T., Mao, Y. & Peng, B. Novel microglia-based therapeutic approaches to neurodegenerative disorders. *Neurosci. Bull.* **39**, 491–502 (2023).
193. Chen, Y. -C. et al. A NeuroD1 AAV-based gene therapy for functional brain repair after ischemic injury through in vivo astrocyte-to-neuron conversion. *Mol. Ther.* **28**, 217–234 (2020).
194. Puls, B. et al. Regeneration of functional neurons after spinal cord injury via in situ NeuroD1-mediated astrocyte-to-neuron conversion. *Front. Cell Dev. Biol.* **8**, 591883 (2020).
195. Guo, Z. et al. In vivo direct reprogramming of reactive glial cells into functional neurons after brain injury and in an Alzheimer's disease model. *Cell Stem Cell* **14**, 188–202 (2014).
196. Xie, Y., Zhou, J., Wang, L. -L., Zhang, C. -L. & Chen, B. New AAV tools fail to detect Neurod1-mediated neuronal conversion of Müller glia and astrocytes in vivo. *EBioMedicine* **90**, 104531 (2023).
197. Svendsen, C. N. & Sofroniew, M. V. Lineage tracing: the gold standard to claim direct reprogramming in vivo. *Mol. Ther.* **30**, 988–989 (2022).
198. Liang, S., Zhou, J., Yu, X., Lu, S. & Liu, R. Neuronal conversion from glia to replenish the lost neurons. *Neural Regen. Res.* **19**, 1446–1453 (2024).
199. O'Shea, T. M. et al. Lesion environments direct transplanted neural progenitors towards a wound repair astroglial phenotype in mice. *Nat. Commun.* **13**, 5702 (2022).
200. Lindvall, O. et al. Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's disease. A detailed account of methodology and a 6-month follow-up. *Arch. Neurol.* **46**, 615–631 (1989).
201. Spencer, D. D. et al. Unilateral transplantation of human fetal mesencephalic tissue into the caudate nucleus of patients with Parkinson's disease. *N. Engl. J. Med.* **327**, 1541–1548 (1992).
202. Freed, C. R. et al. Transplantation of human fetal dopamine cells for Parkinson's disease. Results at 1 year. *Arch. Neurol.* **47**, 505–512 (1990).
203. Kordower, J. H. et al. Neuropathological evidence of graft survival and striatal reinnervation after the transplantation of fetal mesencephalic tissue in a patient with Parkinson's disease. *N. Engl. J. Med.* **332**, 1118–1124 (1995).
204. Hauser, R. A. et al. Long-term evaluation of bilateral fetal nigral transplantation in Parkinson disease. *Arch. Neurol.* **56**, 179–187 (1999).
205. Olanow, C. W. et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. *Ann. Neurol.* **54**, 403–414 (2003).
206. Freed, C. R., Zhou, W. & Breeze, R. E. Dopamine cell transplantation for Parkinson's disease: the importance of controlled clinical trials. *Neurotherapeutics* **8**, 549–561 (2011).
207. Hauser, R. A. et al. Bilateral human fetal striatal transplantation in Huntington's disease. *Neurology* **58**, 687–695 (2002).
208. Freeman, T. B. et al. Transplanted fetal striatum in Huntington's disease: phenotypic development and lack of pathology. *Proc. Natl Acad. Sci. USA* **97**, 13877–13882 (2000).
209. Keene, C. D. et al. Neural transplantation in Huntington disease: long-term grafts in two patients. *Neurology* **68**, 2093–2098 (2007).
210. Barker, R. A. et al. The long-term safety and efficacy of bilateral transplantation of human fetal striatal tissue in patients with mild to moderate Huntington's disease. *J. Neurol. Neurosurg. Psychiatr.* **84**, 657–665 (2013).
211. Bachoud-Lévi, A. -C. 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.* **5**, 303–309 (2006).
212. Bachoud-Lévi, A. -C., Massart, R. & Rosser, A. Cell therapy in Huntington's disease: taking stock of past studies to move the field forward. *Stem Cells* **39**, 144–155 (2021).
213. Barker, R. A. & TRANSEURO consortium Designing stem-cell-based dopamine cell replacement trials for Parkinson's disease. *Nat. Med.* **25**, 1045–1053 (2019).
214. Drew, C. J. G. et al. Protocol for an open label: phase I trial within a cohort of foetal cell transplants in people with Huntington's disease. *Brain Commun.* **3**, fcaa230 (2021).

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Competing interests

C.N.S. has patents associated with the production, differentiation and transplantation of iPS cell-derived neural cells and is on the board of Coya Therapeutics.

Additional information

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