Review

For reprint orders, please contact: reprints@futuremedicine.com

Regenerative Medicine

Developing stem cell therapies for juvenile and adult-onset Huntington's disease

Stem cell therapies have been explored as a new avenue for the treatment of neurologic disease and damage within the CNS in part due to their native ability to mimic repair mechanisms in the brain. Mesenchymal stem cells have been of particular clinical interest due to their ability to release beneficial neurotrophic factors and their ability to foster a neuroprotective microenviroment. While early stem cell transplantation therapies have been fraught with technical and political concerns as well as limited clinical benefits, mesenchymal stem cell therapies have been shown to be clinically beneficial and derivable from nonembryonic, adult sources. The focus of this review will be on emerging and extant stem cell therapies for juvenile and adult-onset Huntington's disease.

Keywords: Huntington's disease • regenerative medicine • stem cell • transplantation

Kyle D Fink[1], Peter Deng[1,2], Audrey Torrest[1], Heather Stewart[1], Kari Pollock[1], William Gruenloh[1], Geralyn Annett[1], Teresa Tempkin[3], Vicki Wheelock[3] & Jan A Nolta*[,1]

[1]Stem Cell Program & Institute for Regenerative Cures, University of California Davis Health Systems, 2921 Stockton Blvd. Sacramento, CA 95817, USA

[2]GenomeCenter, Biochemistry & Molecular Medicine, University of California, 451 Health Sciences Dr. Davis, CA 95616, USA

[3]Department of Neurology, University of California Davis Health Systems, 4860 Y Street Sacramento, CA 95817, USA

*Author for correspondence: janolta@ucdavis.edu

Significant advances in stem cell therapies

The clinical use of stem cell therapies has gained approval for a variety of injuries and diseases of the CNS. While much work is still needed before the widespread use of stem cells in a clinical setting can be realized, this mode of therapy may be advantageous to treat neurological disorders than many others because of the ability of stem cells to accurately mimic the normal cell repair and development process in the brain [1]. Although cell transplantation therapies have been fraught with technical and political problems, there are signs that this approach has considerable potential. Early work with Parkinson's disease, where the first clinical trials were performed in the mid-1980s and a total of 300–400 patients have been treated subsequently with fetal cell transplantation and in the open label studies, has yielded evidence of some functional improvement [for review [2,3]] as measured by withdrawal of anti-parkinsonian medications. Patients with Huntington's disease (HD) have received clinical benefits from implants of fetal/embryonic stem cells as well, however, these effects have been shown to be temporal [4–6].

Another type of cells, mesenchymal stem cells (MSCs), have emerged for clinical transplantation studies due to their capacity to release neurotrophic factors and their ability to create a neuroprotective microenvironment through the release of specific ILs and cytokines. Clinical trials using MSCs in the CNS are now also underway, and are focused on the safety of the cells. MSCs have been autologously transplanted into the subventricular zone in patients with advanced Parkinson's disease [7], intravenously in patients that had suffered a stroke [8,9], and umbilical cord MSCs have been administered intravenously in children with cerebral palsy [10] with no adverse side effects from the cells and observed clinical efficacy as measured by improvements in neurological domains and fractional anisotropy values in brain MRI-DTI.

Stem cell clinical trials for stroke, spinal cord injury and amyotrophic lateral sclerosis are already underway while additional studies utilizing adult stem cells are nearing clinical trials for Parkinson's and Alzheimer's and HD.

Future Medicine part of fsg

The goal of stem cell transplantation should focus on providing therapeutic benefit through two main mechanisms. Successful cell transplantation should be able to work synergistically with the endogenous microenvironment to upregulate intrinsic cell proliferation or neuroprotection via trophic factor secretion and immune modulation, potentially enhancing the overall regenerative capacity of the transplanted tissue [11], or by being capable of integrating into the endogenous host network and replacing or repairing the lost neurons. This review will focus on the potential of adult stem cells to provide neuroprotection and immune modulation in adult-onset and juvenile HD.

Huntington's disease

HD is an autosomal-dominant disorder caused by an expanded and unstable CAG trinucleotide repeat that causes a progressive degeneration of neurons, primarily in the putamen, caudate nucleus and cerebral cortex [12]. In the USA, there is estimated to be approximately 30,000 individuals with HD while the Europe Union has a slightly higher prevalence of individuals with symptomatic HD with an estimated 45,000 patients [13]. Juvenile HD (JHD) is defined by disease onset before the age of 20 years and occurs in less than 10% of all HD cases [14]; however, JHD may be further subdivided into patients that have disease onset prior to the age of 10 years or between 10 and 20 years of age as they present with different clinical characteristics [15].

HD occurs when the gene that codes for the htt protein, located on the short arm of chromosome 4, shows an increased number of CAG repeats [16]. Typically, greater than 38 CAG repeats correlate with an onset of the illness in adulthood. JHD is typically transmitted from the paternal allele and usually have more than 60 CAG repeats [14], although there is a reported case of a JHD patient with 250 CAG repeats [17]. Disease onset prior to the age of 20 years is clearly dominated by paternal transmission (about 3:1 paternal–maternal), and paternal transmission is, to date, solely responsible for disease onset prior to the age of 10 years [18].

Adult HD is dominated by chorea and other involuntary movements in the initial and middle stages of the disease, but it is becoming clearer that HD patients have cognitive and emotional deficits including slowing of psychomotor speed, impairment of attention and memory as well as executive and visuospatial functions that eventually degrade into dementia along with depression and apathy, although the emotional features are more variable than the motor or cognitive features [19,20]. Typically, HD eventually culminates in death around 15–20 years after the onset of motor symptoms. The disease progression is more rapid in children than in adults and has been described in three phases: initial phase of behavioural disorder, learning difficulty, gait disturbance and mild chorea; a florid phase with signs of mental deterioration, rigidity, speech disturbance and seizures; and a terminal phase of bed confinement, hypotonia and increasing seizures [15]. JHD patients typically have less chorea than adult onset HD with rigidity reported as the dominant clinical manifestation [14].

Historically, the neuroanatomical changes in the striatum have been the focus of neuropathological and neuroimaging studies, but recently, the presence of abnormalities throughout the cerebellum, specifically in JHD [21], including cortical thinning and decreased white matter volumes, in the prefrontal cortex, have gained significant interest [20,22]. Striatal atrophy as well as white matter loss, as measured by MRI studies, can detect HD-like degeneration 15 years prior to the onset of motor symptoms [23,24], suggesting that once the clinical onset of motor symptoms appear, significant striatal loss has already occurred.

Although HD and JHD have a single genetic cause, HD as a whole has a very complex pathology, with detrimental effects on a wide variety of cellular processes [25]. It has recently been uncovered that while conditional knockout of mutant huntingtin in the striatum of transgenic mice leads to partial motor and psychiatric recovery, silencing of mutant huntingtin in both the cortex and striatum is needed to ameliorate HD-like symptoms [26]. This is suggestive that symptomology is due to widespread dysfunction of the brain and even possibly in other organs as well [27–30].

Currently, only symptomatic treatments are available. Pharmacotherapy is difficult in HD due to the complexity and amount of damage to the brain. The symptomatology of JHD is complex and causes suffering in all domains of life and the pharmacological treatment is difficult as there are no studies to guide the current trial-and-error approach to treating these patients [21]. Clinical outlooks for HD patients and the care given to their family members have improved due to the increased recognition of the disorder, better access to genetic counseling, and more availability to specialized care programs that utilize behavioral, neurological and psychiatric rehabilitation programs [13]. Treatment for patients suffering from HD generally comprises neuroleptics, anticonvulsants [31] or tetrabenazine. The latter of which involves a complicated prescribing process, specialty pharmacies for delivering the drug, strictly managed doses and annual costs exceeding US$70,000 which makes it prohibitively expensive for many patients [32].

Thus, due to the time and nature in diagnosing HD following neuronal loss and motor deficits, restorative therapies should focus on creating a neuroprotective

environment to slow the loss of endogenous neurons as well as replacing lost neurons through either stimulating endogenous neurogenesis or transplanting cells capable of differentiating, integrating and replacing lost cells.

MSCs for HD

At the time of manuscript preparation, 16 published articles have implicated improvement of either behavioral or neuropathological deficits in rodent models of HD following treatment with MSCs (Table 1). These studies have used MSCs from multiple sources including autologous transplantation of unpurified whole bone marrow from rats [33], purified rat MSCs [34–38], mouse bone marrow-derived MSCs [39,40], mouse umbilical cord-derived MSCs [41], human adipose derived MSCs [42–44] and human bone marrow MSCs [45–47].

These studies have demonstrated improvement in motor function [34–36,39–40,42–46,48], cognition [33,40,48], anxiety-like behaviors [42] and the ability to extend the lifespan of these animals [44]. Decreases in the striatal lesion size, less neuronal and medium spiny neuron loss, stimulation of endogenous neurogenesis and reduction of huntingtin aggregation has also been observed following transplantation of MSC [34,37,39–41,43–47].

Several groups have reported that MSCs have the ability to differentiate into neuronal lineages *in vitro* [49–52] and following transplantation into the brain [53–58]. However, the stance that MSCs have the ability to transdifferentiate into mature neuronal phenotypes *in vitro* or *in vivo* remains controversial [59] and none of the aforementioned studies observed neuronal differentiation of the transplanted MSC.

There are several possible mechanisms that MSCs may provide *in lieu* of neuronal differentiation such as trophic support and immunomodulation. These hypotheses are supported from studies of other neurological disorders (Huang *et al.*, [60]; Lin *et al.*, [61]; Han *et al.*, [62] Uccelli *et al.* [63]) and were observed in many HD studies following MSC transplantation (Table 1).

One of the most common mechanism of action postulated following MSC transplantation in HD is that the cells are capable of providing trophic support, specifically BDNF [33–35,37–41,43–44,46,48]. As a reduction in BDNF levels has been noted in HD patients [64,65] and BDNF targeted therapies have shown to ameliorate partial disease pathology [66–93] upregulating BDNF in the HD brain has become a lead therapeutic candidate.

As trophic support is speculated to be the main contributor to behavioral and histological recovery following transplantation of MSC, the potential of MSCs as a delivery vehicle for gene therapy has been examined [94–97]. Due to the nature in which MSC can be engineered *in vitro,* a study tested MSCs that overproduced either BDNF, nerve growth factor or a combination of both [39]. YAC128 transgenic mice that received transplantations of the MSC to overexpress *BDNF* displayed a reduction in motor deficits and had significantly more NeuN- and Darpp32-positive cells (mature and medium spiny neurons, respectively) in the striatum than all other YAC128 groups [39]. The results from this study, along with the previously discussed literature of successful pre-clinical trials has led to translational studies using engineered human MSC in the preparation of a clinical trial [98]. However, many of the successful pre-clinical studies only examine the efficacy of the MSC treatment for a period of days to weeks (refer to Table 1), and the long-term efficacy of this strategy needs to be examined.

Clinical cell transplantation in HD

As mentioned previously, several clinical studies have been conducted to assess the viability of fetal cells as a therapeutic treatment for HD. However, there have been varying results for the long-term viability of fetal cells for HD (Table 2). Bachloud-Levi, *et al.*, found that three out of five patients transplanted with ganglionic eminence cells showed metabolically active graft cells

Table 1. Mesenchymal stem cell transplantation in Huntington's disease.

Study (year)	Animal model	Type of cell	Behavioral outcome	Histology	Trophic support	Time course	Immunosuppression	Transplantation	Ref.
Mouse animal model									
Dey *et al.* (2010)	YAC128 Mouse	Genetically engineered mouse bone marrow MSCs	YAC128 mice receiving bone marrow transplants demonstrated reduced clasping behavior and longer latencies on the rotarod task	YAC128 mice receiving grafts had significantly more NeuN-positive cells in the striatum compared with untreated YAC128 mice	BDNF-engineered cells had greater behavioral and histological recovery than NGF- or non-engineered cells	Cells were not observed at the conclusion of study, but behavioral and histological effects were still observed	None	Allogeneic	[39]
Im *et al.* (2010)	YAC128 mouse	HD Human adipose MSC	YAC128 mice receiving cell transplants showed a delay in motor deficits up to 4 weeks (measured on the rotarod) following transplantation	Normal adipose cells were able to reduce striatal atrophy while HD adipose cells were unable to prevent atrophy	Cells expressed *BDNF in vitro*	Cells transplanted at 8 or 12 months old. Cells were not detectable 4 months post-transplantation	None	Xenogeneic (hMSC)	[43]
Lee *et al.* (2009)	R6/2 mouse	Human adipose MSC	In R6/2 mice receiving transplants, there was increased life-span, rotarod performance and decreased limb clasping	Grafted R6/2 mice showed a decrease of striatal neuron loss and reduced huntingtin aggregation	Adipose stem cells secreted BDNF, believed to be mechanism of recovery	Cells transplanted at 8 weeks tested for four additional weeks (approximately 13.5% cell survival). Behavioral effects seen after 2 weeks post-operation	None	Xenogeneic (hMSC)	[44]

aNSC: Adult neural stem cell; HD: Huntingdon's disease; hMSC: Human bone marrow mesenchymal stem cell; MSC: Mesenchymal stem cell; QA: Quinolinic acid; tp.: transplantation

Table 1. Mesenchymal stem cell transplantation in Huntington's disease (cont.).

Study (year)	Animal model	Type of cell	Behavioral outcome	Histology	Trophic support	Time course	Immunosuppression	Transplantation	Ref.
Fink *et al.* (2013)	R6/2 mouse	mouse umbilical cord-derived MSC	Transient behavioral sparing was observed following transplantation	MSC transplantation significantly reduced striatal atrophy	UC MSC expressed *BDNF in vitro* and was speculated to promote neuropathological sparing	MSCs survived 6 weeks post-transplantation	None	Allogeneic	[41]
Rossignol *et al.* (2015)	R6/2 mouse	Mouse bone marrow MSC	Delay in the onset of motor and cognitive deficits in rotarod, clasping and Morris Water Maze	MSC transplantation significantly reduced striatal atrophy	MSC transplantation upregulated expression of *BDNF in vivo*.	MSCs survived 6 weeks post-transplantation	None	Allogeneic	[40]
Lin *et al.* (2009)	QA Mouse model, R6/2 mouse model	hMSCs	QA mice receiving MSC transplants demonstrated significant motor recovery on the rotarod task and increased the survivability of the mice	QA mice receiving transplants showed partial striatal recovery in terms of striatal volume	MSC improved neuronal differentiation, motor deficits and cell loss through trophic support	Small number of cells survived up to 8 weeks and could induce endogenous cell proliferation up to 16 weeks	None	Xenogeneic (hMSC)	[45]

aNSC: Adult neural stem cell; HD: Huntingdon's disease; hMSC: Human bone marrow mesenchymal stem cell; MSC: Mesenchymal stem cell; QA: Quinolinic acid; tp.: transplantation

Table 1. Mesenchymal stem cell transplantation in Huntington's disease (cont.).

Study (year)	Animal model	Type of cell	Behavioral outcome	Histology	Trophic support	Time course	Immunosuppression	Transplantation	Ref.
Snyder *et al.* (2012)	N171–82Q (knockin) mouse	hMSCs	No behavioral analysis was performed	Human MSCs were rapidly rejected from the host. However, mice receiving transplants had increased proliferation and neural differentiation of endogenous stem cells. Mice receiving grafts also displayed decreased striatal atrophy and increased neurotrophic signaling	Transplanted MSC stimulated neurotrophic signaling	Transplanted human MSC disappeared over 15 days; however, endogenous cell proliferation, neural differentiation, neurotrophic signaling and decreased atrophy persisted up to 30 days	Cyclosporine A	Xenogeneic (hMSC)	[47]
Rat animal model									
Sadan *et al.* (2008)	QA rat model	Rat MSCs	No behavioral analysis was performed	Cells were capable of migrating toward the lesion site and aided in decreasing the lesion volume	BDNF was the main contributor for migration to lesion site	Cells survived for 19 days *in vivo*	None	Allogeneic	[37]
Lescaudron *et al.* (2003)	QA rat model	Rat whole bone marrow	QA rats receiving bone marrow transplants demonstrated a reduction of cognitive deficits in the radial arm water maze when compared with untreated QA rats	No neuronal differentiation of transplanted cells	Behavioral recovery was speculated to be due to BDNF release	Tested 10 days following bone marrow administration	None	Autologous	[33]

aNSC: Adult neural stem cell; HD: Huntingdon's disease; hMSC: Human bone marrow mesenchymal stem cell; MSC: Mesenchymal stem cell; QA: Quinolinic acid; tp.: transplantation

Table 1. Mesenchymal stem cell transplantation in Huntington's disease (cont.).

Study (year)	Animal model	Type of cell	Behavioral outcome	Histology	Trophic support	Time course	Immunosuppression	Transplantation	Ref.
Lee *et al.* (2009)	QA rat model	Human adipose MSC	In QA rats receiving adipose stem cells, there was a reduction in apomophine-induced rotation behavior	Grafted QA rats had decreased lesion volume and striatal apoptosis	Adipose stem cells secreted BDNF, believed to be mechanism of recovery	Cells transplanted at 8 weeks tested for 4 additional weeks (approximately 13.5% cell survival). Behavioral effects seen after 2 weeks post-operation	None	Xenogeneic (hMSC)	[44]
Edalatmanesh *et al.* (2010)	QA rat model	Rat bone marrow MSCs	In QA rats receiving MSCs, there was a reduction in apomophine-induced rotation behavior, increased performance in the cylinder test, improvement of motor function as measured by beam walking and hanging wire test and memory improvement as measured in the Morris Water Maze when compared with untreated animals	Histological analysis was not performed	Recovery was speculated to be due to the release of neurotrophic factors, specifically BDNF	Cells transplanted 1 week post QA lesion, behavior testing performed one week following transplantation. Behavioral sparing observed immediately	None	Allogeneic	[48]

aNSC: Adult neural stem cell; HD: Huntingdon's disease; hMSC: Human bone marrow mesenchymal stem cell; MSC: Mesenchymal stem cell; QA: Quinolinic acid; tp.: transplantation.

Table 1. Mesenchymal stem cell transplantation in Huntington's disease (cont.).

Study (year)	Animal model	Type of cell	Behavioral outcome	Histology	Trophic support	Time course	Immunosuppression	Transplantation	Ref.
Jiang *et al.* (2010)	QA rat model	Rat bone marrow MSCs	Rats receiving transplants exhibited reduced apomorphine-induced rotational behavior and longer latencies on the rotarod when compared with untreated animals	Grafted cells survived for 8 weeks, significantly reduced the amount of striatal loss observed and elevated the levels of NGF, BDNF, GDNF and CNTF in the brain	Behavioral recovery due to the release of neurotrophic factors, including BDNF	Cells, transplanted 1 week following QA lesion, were detectable for 2 weeks; however, few cells were observed at 8 weeks post	None	Allogeneic	[34]
Sadan *et al.* (2010)	QA rat model	Neurotrophic-factor-treated hMSCs	Reduction in apomorphine-induced rotations	Grafted cells survived for 42 days and reduced lesion size	Neurotrophic factor secreting cells reduce lesion size and behavior abnormalities	Neurotrophic factor-treated MSCs (specifically BDNF) survived better than nontreated cells	Cyclosporin A	Allogeneic	[46]
Serrano Sánchez *et al.* (2014)	QA rat	Rat bone marrow MSC	None performed	Significant reductions of BDNF levels in the cortex and striatum following lesion	MSC transplantation increased brain BDNF levels	MSC transplanted 4 weeks following QA lesion. BDNF levels were measured 30 days post-transplantation and were elevated in the group receiving MSC	None	Allogeneic	[38]

aNSC: Adult neural stem cell; HD: Huntingdon's disease; hMSC: Human bone marrow mesenchymal stem cell; MSC: Mesenchymal stem cell; QA: Quinolinic acid; tp.: transplantation.

Table 1. Mesenchymal stem cell transplantation in Huntington's disease (cont.).

Study (year)	Animal model	Type of cell	Behavioral outcome	Histology	Trophic support	Time course	Immunosuppression	Transplantation	Ref.
Hosseini *et al.* (2015)	QA rat	Human adipose MSC	Improvement in rotarod, hanging wire, reduced apomophine-induced rotations and reduction in anxiety-like behaviors	Cells survived for at least 7 weeks in the brain	Recovery was speculated to be due to the release of neurotrophic factors	Rats were transplanted 7 days following QA lesion. Behavioral testing was conducted over a 10-week period	None	Xenogeneic (hMSC)	[42]
Rossignol *et al.* (2011)	3-NP rat model	Rat bone marrow MSCs	3-NP rats receiving transplants showed reduction of deficits in paw placement, stepping test and hindlimb retraction when compared with untreated animals	Trend toward lesion size reduction in rats receiving transplant. No neuronal differentiation of transplanted cells	Behavioral and histological recovery thought to be due to increase of BDNF immunoreactivity in the area around the transplant	Small transplants were observed 72 days post-transplantation	None	Allogeneic	[35]
Rossignol *et al.* (2013)	tgHD rat	Rat bone marrow MSC and aNSC	Co-transplantation of MSC and aNSC reduced motor dysfunction as measured on the Accelerod	MSC significantly increased aNSC graft survival	MSC likely secreted trophic support and created a local immunomodulatory environment in the striatum	MSCs survived up to 12 weeks post-transplantation	None	Allogeneic	[36]

aNSC: Adult neural stem cell; HD: Huntingdon's disease; hMSC: Human bone marrow mesenchymal stem cell; MSC: Mesenchymal stem cell; QA: Quinolinic acid; tp.: transplantation.

Table 2. Clinical transplantation in Huntington's disease.

Study (year)	Clinical size	Type of cell	Clinical outcome	Negative effects	Ref.
Bachoud-Levi *et al.* (2006, 2009, 2000)	Five patients	Whole ganglionic eminence	Three of five patients showed stability of symptoms or clinical improvement for 4–6 years	One patient showed development of a putaminial cyst	[4,99,108]
Capetian *et al.* (2009)	One patient	Whole ganglionic eminence	UHDRS score stability for 6 months. Survival and differentiation of grafted cells	None reported (patient died from unrelated causes)	[109]
Cicchetti *et al.* (2009, 2014)	Three patients	Lateral ventricular eminence containing striatal primordia	Improvement of UHDRS in two of three patients for up to 18 months before returning to presurgical levels	Grafts underwent disease-like neuronal degeneration. Cortical hemorrhage, subdural hematoma following surgery	[5,100]
Freeman *et al.* (2000)	One patient	Lateral ventricular eminence containing striatal primordia	Stability of UHDRS 15 months following transplantation. Transplants integrated into the host tissue	None reported	[110]
Furtado *et al.* (2005)	Seven patients	Fetal striatal tissue	Transplants failed to restore fluorodeoxyglucose uptake and D1 and D2 receptor binding in subjects	Possible technical issues with regards to the ganglionic eminence and in targeting the striatum	[111]
Hauser *et al.* (2002)	Seven patients	Fetal striata	Grafts developed striatal morphology, UHDRS improved significantly 12 months following surgery	Three subjects developed subdural hemorrhages, one patient died 18 months following surgery from probable cardiac arrhythmia	[112]
Keene *et al.* (2007)	Two patients	Fetal lateral ganglionic eminence	Improved ambulation 3 months following transplant in one patient. In both patients, transplanted cells displayed morphology of neurons and astrocytes	One patient reported chronic headaches following surgery and was treated for bilateral subdural hematomas. Reported that transplants did not have an effect on the course of HD	[113]
Keene *et al.* (2009)	One patient	Fetal neuronal tissue	Clinical improvement for UHDRS for 2 years. Patient died 121 months following surgery from complications of advanced HD	Three mass lesions and one large cyst were present on the left caudate and putamen. Five mass lesions and two cysts were present on the right caudate and putamen	[6]
Kopyov *et al.* (1998)	Three patients	Lateral ganglionic eminence	Clinical improvement for UHDRS for all three patients 12 months following surgery. Graft survival and growth within the striatum without displacing host tissue	None reported	[114]
Krystkowiak *et al.* (2007)	13 patients	Fetal neuronal tissue	Pre- and post-UHDRS were not reported. Four of the 13 patients had grafts that did not display signs of rejection	Biological, radiological and clinical rejection of grafts in other subjects (reversible under immunosuppressive treatment)	[115]

HD: Huntingdon's disease; UHDRS: Unified Huntington's disease rating scale.

Table 2. Clinical transplantation in Huntington's disease (cont.).

Study (year)	Clinical size	Type of cell	Clinical outcome	Negative effects	Ref.
Reuter *et al.* (2008)	Two patients	Whole ganglionic eminence	Clinical improvement for UHDRS over 5-year period for one patient. Increased striatal D2 receptor binding, suggesting long-term survival and efficacy of grafts	None reported	[101]
Rosser *et al.* (2002)	Four patients	Whole ganglionic eminence	Stability of UHDRS as well as cognitive ability up to 6 months following surgery. Graft survival without overgrowth	None reported	[116]
Philpott *et al.* (1997)	Three patients	Lateral ganglionic eminence	Increased cognitive functioning 6 months following surgery	None reported	[117]
Gallina *et al.* (2010)	Four patients	Whole ganglionic eminence	Stability or improvement in motor, behavioral and functional scores up to 24 months following surgery	None reported	[104]
Madrazo *et al.* (1995)	Two patients	Whole ganglionic eminence	Stability or improvement on functional capacity for up to 25 months following surgery when a slow progression of HD was observed	None reported	[118]

HD: Huntingdon's disease; UHDRS: Unified Huntington's disease rating scale.

10 years following transplantation [99] and these results correlated with a slowing of the progressive nature of the disease, with even some functional recovery observed at the early time points; however, in another study the transplanted ganglionic eminence underwent a similar neurodegeneration associated with HD [5], likely due to accumulation of mutant huntingtin in the neuronal graft [100,101]. It has since been postulated that mutant huntingtin is transneuronally propagated along neuronal networks, likely contributing to the pathophysiology of HD [102]. This theory has been reported in other disease models and it is thought that the mutant protein is transferred from the host into the transplanted fetal neurons via retrograde transfer [103]. Even in studies where the transplanted cells were still viable, their effect on behavioral recovery began to diminish between 2 and 4 years following the treatment [99,101,104]. While ganglionic eminence transplantations into HD patients have shown considerable promise as a treatment for HD there are many problems with the continued use of fetal cells for transplantation therapies such as ethical, logistical and availability issues [105–107].

Embryonic cell transplantation in HD

Preclinical research using ganglionic eminence transplanted into rodent models of HD has yielded similar results in that the cells can differentiate into mature neurons and astrocytes [119], rescue the behavioral deficits [120], but that these effects are not long lasting [121]. It has been observed that HD animals receiving pluripotent embryonic stem cells (ESCs) show transient recovery of motor deficits, but this effect rarely extends beyond 8 weeks [121]. Similar to what is observed in animals receiving transplants of fetal tissue, ESCs are either rejected by the host immune system or overproliferate, disrupting the host cytoarchitechure and causing teratoma formation [122]. This short-term effect of the cells is likely due to a failure of the graft to successfully rebuild or replace the lost cellular connections, or due to the grafts being systematically rejected by the host immune system. Induced pluripotent stem cells have recently been transplanted into a 3-nitropropionic acid (3-NP) toxic lesion models of HD [123] and in the transgenic YAC128 [124] with both studies reporting significant behavioral improvement and that the transplanted cells were capable of differentiating into neuronal phenotypes. However, more work is still needed to characterize the safety and immunological profile of these cells following transplantation before they could be considered for clinical use.

Neuronal cell transplantation in HD

Another stem cell type that has been shown to be a potential avenue for cell replacement therapy in

Table 3. Cell transplantation in Huntington's disease.

Study (year)	Animal model	Type of cell	Behavioral outcome	Histology	Ref.
Mouse animal model					
Yang & Yu (2009)	R6/2 mouse	Mouse NSCs	R6/2 mice receiving cells had increased life spans and improved motor function on the beam walking and rotarod task when compared with untreated animals	NSCs transplanted into R6/2 mice differentiated into neurons, reduced striatal loss and reduced ubiquitin-positive aggregation in the striatum	[126]
Dunnett *et al.* (1998)	R6/2 mouse	Mouse lateral ganglionic eminence	R6/2 mice receiving transplants demonstrated increased locomotion in the open field test	Grafts were capable of survival, integration and differentiation into neurons	[119]
Yang & Yu (2009)	R6/2 mouse	Mouse NSCs	R6/2 mice receiving cells had increased life spans and improved motor function on the beam walking and rotarod task when compared with untreated animals	NSCs transplanted into R6/2 mice differentiated into neurons, reduced striatal loss and reduced ubiquitin-positive aggregation in the striatum	[126]
Johann *et al.* (2007)	QA mouse model, R6/2 mouse	Mouse embryonic NSCs	No behavioral analysis was performed	Cells differentiated into astrocytes and were rejected after 14 (QA mouse) and 28 days (R6/2)	[131]
Bernreuther *et al.* (2006)	QA mouse model	Mouse ESCs	Mice receiving transplants of cells exhibited reduced amphetamine-induced rotational behavior when compared with untreated animals up to 4 weeks following surgery, but returned to sham levels at 8 weeks	Transplanted mice showed an increase in the number of neurons in the striatum and differentiated into astrocytes and GABAergic neurons	[121]
Pineda *et al.* (2007)	QA mouse model	Genetically engineered mouse NSCs	Mice receiving transplants of cells exhibited reduced amphetamine-induced rotational behavior when compared with untreated animals	Cells were able to survive and proliferate in the mouse brain. Mice receiving transplants showed less striatal loss when compared with untreated animals	[129]
Shin *et al.* (2012)	QA mouse model	Mouse embryonic NSCs	No behavioral analysis was performed	Grafted cells survived for 28 days and differentiated into mature neurons expressing DARPP32	[133]
Rat animal model					
Aubry *et al.* (2008)	QA rat model	Striatal progenitors derived from human ESCs	No behavioral analysis was performed.	Cells transplanted at the ganglionic eminence stage were capable of survival, differentiation into striatal neurons, but resulted in tumor-like overproliferation	[122]
Song *et al.* (2007)	QA rat model	Human ESC neural precursors	Rats receiving transplants exhibited reduced apomorhine-induced rotational behavior when compared with untreated animals	Cells were positive for early neuronal markers and no tumor formation was observed at 3 weeks post-transplantation	[130]
Kordower *et al.* (1997)	QA rat model	Genetically engineered mouse embryonic NSCs	No behavioral analysis was performed	Rats receiving grafts displayed sparing of striatal neurons after QA injection	[134]

3-NP: 3-nitropropionic acid; ESC: Embryonic stem cell; NSC: Nueral stem cell; QA: Quinolinic acid.

Table 3. Cell transplantation in Huntington's disease (cont.).

Study (year)	Animal model	Type of cell	Behavioral outcome	Histology	Ref.
Rat animal model (cont.)					
Hurlbert *et al.* (1999)	QA rat model	Human teratocarcinoma neural precursors	Rats receiving transplants exhibited reduced methamphetamine-induced rotational behavior and improved forelimb use in a staircase task when compared with untreated animals	Cells survived for 12 weeks and displayed markers of mature neurons but did not differentiate into medium spiny neurons (DARPP32)	[135]
Armstrong *et al.* (2000)	QA rat model	Rat embryonic NSCs	No behavioral analysis was performed	Grafted cells survived for 12 weeks following surgery and some differentiated into mature phenotypes expressing DARPP32. It was also observed that grafts exhibited neuronal fibers outgrowth	[136]
Vazey *et al.* (2006)	QA rat model	Rat adult NSCs	Rats receiving transplants exhibited reduced apomorhine-induced rotational behavior and increased forelimb exploratory behavior when compared with untreated animals	Cells survived for up to 8 weeks following surgery, migrated throughout the striatum and differentiated into astrocytes, mature neurons and striatal medium spiny neurons	[127]
Visnyei *et al.* (2006)	QA rat model	Rat embryonic NSCs	No behavioral recovery was observed in QA rats receiving cells in apomorphine-induced rotation tests	Cells survived, migrated toward the lesion site and olfactory bulbs and differentiated into astrocytes and neurons	[137]
Bosch *et al.* (2004)	QA rat model	Immortalized NSCs	Rats receiving transplants exhibited reduced apomorhine-induced rotational behavior when compared with untreated animals	Transplanted cells maintained a GABAergic phenotype, had elaborate neurite processes and formed synaptic connections with endogenous neurons	[128]
Ryu *et al.* (2004)	3-NP rat model	Immortalized human embryonic NSCs	Rats that received cell transplantation prior to administration of 3-NP demonstrated improved motor function on a rotarod task when compared with 3-NP animals not receiving cells	Transplanted cells expressed primarily immature neuronal markers with few cells expressing intermediate neurons or astrocytes	[120]

3-NP: 3-nitropropionic acid; ESC: Embryonic stem cell; NSC: Nueral stem cell; QA: Quinolinic acid.

HD is neuronal stem cells (NSCs). Immortalized human [125], mouse [126] and rat [127] embryonic NSCs have all shown considerable promise when transplanted into various models of HD. In both transgenic mice and toxic lesion rat models of HD, NSCs have been shown to survive up to 8 weeks following transplantation, differentiate into mature neurons and astrocytes and show behavioral recovery, specifically in apomorphine-induced rotational tests [121,127–130], beam walking [126] and in the amount of time on the rotarod [120]. However, Johann *et al.*, found that NSCs were rapidly rejected after 28 days in the R6/2 and after 14 days in a quinolinic acid (QA) mouse model of HD [131]. A large inflammatory immune response was observed following NSCs transplantation in a transgenic rat model of HD 40 weeks following transplantation [36], suggesting that these cells elicit an extended immune response. While it is possible to globally suppress the immune system with cyclosporine or other immunesuppressors to enhance the graft survival, there are several side effects associated with long-term immunosuppressive treatments [132]. For pluripotent or adult NSCs to be a viable therapeutic option for HD, local immune suppression or genetically engineering the cells to avoid rejection from the host is necessary along with the ability to direct the cells into the correct lineage following transplantation (Table 3).

While transplantation of embryonic, neural and mesenchymal stem cells have shown to be effective both clinically and experimentally, they are not effective cures for the natural progression of HD due to the gene mutation and the ability of the mutant protein to propagate into the transplanted cells, specifically neuronal linages and are thought to only delay the onset or change the trajectory of the disease.

Ongoing challenges

An ongoing challenge to the clinical development of stem cell therapies for HD and JHD is navigating the immune response to the transplant. Although the brain has often been considered an 'immune privileged' organ, there are several reported cases suggesting a strong immune response with the brain that can lead to the rejection of the graft and the subsequent halting of beneficial effects [138] While it has been suggested in previous work that MSC provide immune modulation in the area around the transplant, many of these studies use an allotransplantation paradigm, thus reducing the extent of neuroinflammation [139]. While this can be addressed by using species-specific cells to avoid rejection of the xenograft, this strategy includes several caveats that impede the clinical relevancy of these studies. It is known that mouse stem cells express many different surface expression markers than human cells [140], and behave differently following *in vitro* expansion protocols [141–143].

The challenge of the immune response following transplantation into the brain raises an interesting dichotomy when developing stem cell therapies for clinical trials. While the ideal candidate for preclinical studies would be the type of cell planned to be used in a theoretical trial, the immune response following xenotransplantation may potentially mask some of the beneficial effects. On the contrary, conducting studies using an allotransplantation paradigm to avoid the immune response to the xenograft may lead to false discovery as cells isolated from mice or rats may be inherently different than human cells.

A second challenge that exists with translating successful stem cell therapies for HD or any other neurodegenerative disease is the accuracy of the animal model in recapitulating the human disease phenotypes. HD is a unique disease in that it is caused by a single gene mutation that can be mimicked in transgenic animals (Table 4). Transgenic mouse models can be useful tools for the study of biochemical, morphological and functional changes associated with the mutant *htt* [16]. The R6/2, with the N-terminal portion of human htt, containing a highly expanded glutamine repeat (145–155; [144], the yeast artificial chromosome (YAC) with the full-length human mutant *htt* gene carrying 128 CAG repeats [16,25] and knock-in (KI) mice, typically with 92–140 CAG repeats generated by the insertion in the endogenous *htt* gene, mimic the disease manifestation and show several phenotypical alterations, resembling those observed in HD patients [16]. While these mouse models capture some of the phenotypes of HD, none of the mouse models recapitulates the substantial striatal neuronal cell loss that is characteristic in HD patients, thereby limiting the effectiveness of translational research [145]. Specifically in the human disease, approximately 50% atrophy of the caudate and putamen is observed prior to the onset of clinically classified motor dysfunction [146,147]. 3-NP crosses the blood–brain–barrier and can be administered systematically to induce cell death in the brain, through excitatory mechanisms closely correlated with HD [148] and create the neuropathology and behavioral abnormalities of HD [149]. QA administration recapitulates many histopathological and neurochemical features of HD neuropathy and also causes memory deficits, leading many researchers to use QA models to explore striatal neurodegeneration as well as to evaluate neuroprotective strategies against HD [48,150–152]. The 3-NP and QA models of HD are useful tools for studying the motor dysfunction associated with clinical or late stage HD, but may not be appropriate to study the early cogni-

Table 4. Common animal models of Huntington's disease.

Animal model	Name	CAG repeat length	Strengths	Weaknesses	Ref.
Mouse	R6/2	144	Rapid, progressive behavioral deficits	Limited neuropathology, short lifespan	[157]
	N171-Q82	82	Accumulation of mutant *Htt* aggregates	Subtle motor changes	[158]
	YAC128	128	Striatal atrophy	Late onset, subtle and transient behavior deficits	[159]
	BACHD	97	Striatal atrophy and behavioral deficits	Weight gain, late onset	[160]
	Hdh (CAG)150	150	Striatal atrophy and behavioral deficits	Late onset	[161]
Rat	TgHD51	51	Progressive behavior deficits	Late-onset and limited neuropathology	[155]
	BACHD	97	Striatal atrophy and behavioral deficits	Limited availability and late onset	[156]
	Quinolinic acid	N/A	Reproducible behavioral deficits and striatal cell loss	Not progressive, does not have the mutant *Htt* gene or produce mutant protein	[162]
	3-nitropropionic acid	N/A	Reproducible behavioral deficits and striatal cell loss	Does not have the mutant *Htt* gene or produce mutant protein	[163]
Mini-pig	N208	105	HD-like apoptotic neurons and DNA fragmentation	Limited behavioral tests and availability	[164]
Sheep	OVT73	73	Reduction in striatal GABA A receptor	Limited behavioral tests and availability	[165]
Nonhuman primate	Exon 1 *HTT*	84	Dystonia, chorea, neuronal inclusions and neuropil aggregates	Extremely limited availability	[166]

HD: Huntingdon's disease.

tive deficits and presymptomatic pathology associated with HD patients. The number of transgenic rat models recapitulating key pathological hallmarks of HD is still limited [153–156] and these models have many of the same limitations of the transgenic mice.

While these models can provide a great deal of information on the behavioral-, histological- and molecular-level abnormalities associated with HD, no singular model can fully capture the diverse phenotypes associated with the disease. Many of the transgenic models currently available are unable to recapitulate both behavioral deficits and the associated neuropathology. While it is possible to study the progressive behavioral deficits in several of the transgenic mouse models, typically these models do not display neuronal loss that correlates to the human condition. Alternatively, the animal models that provide reproducible neuronal cell loss and striatal atrophy are either toxic lesion models not carrying the mutant gene or transgenic animals that have late disease onset (greater than 12 months) and display subtle motor deficits. The usefulness of rodent models is also limited by other translational constraints. Namely, the brains of rodents differ significantly from humans in both their small size and their neuroanatomical organization [167]. The second major concern using a transgenic animal model to study a prodromal disease that extends over a long period of time is that the animals have a significantly shorter lifespan [167]. Due to these specific shortfalls, large animal models of HD have been created and are now being studied. A transgenic minipig carrying 105 CAG repeats displays some neuropathology associated with HD, specifically apoptotic neurons in the striatum [164]. However, behavioral testing for minipigs has not been well established. Transgenic sheep have also been created carrying 73 CAG repeats. These animals showed reduction of GABA A receptors and expression of medium spiny neuron marker DARPP-32 in the striatum but behavior deficits have not been reported and are not well established in ovine models [165]. The use of large animals raises housing issues and a limited number of labs are capable of performing studies on sheep or minipigs, but they do present relevant large animal models for studying distribution and pharmacokinetics of therapeutic modalities.

Transgenic nonhuman primates have also been created by microinjection of a lentivirus carrying the human exon 1 fragment with 84 CAG repeats [166]. These nonhuman primates have shown behavioral deficits similar to the human condition such as chorea and dystonia and evidence of widespread mutant htt inclusions upon histological analysis. Furthermore, nonhuman primates have established cognitive and motor tests, albeit these have not been optimized for HD. However, the availability of these animals is at a premium and would prove to be cost prohibitive for most studies.

While HD is advanced in terms of creating rodent and large-scale models that recapitulate the genetic mutation known to cause the disease, the models need to be refined to better mimic the cognitive, motor and emotional phenotypes along with the associated neuropathology. As more therapies near clinical trials for HD, the need for animal models that more accurately predict clinical efficacy in humans is needed. While the initial costs of nonhuman primate studies may be prohibitive, they may prove more valuable for predicting promising therapeutics to take forward to clinical trials.

Unmet needs

Translational research for HD could benefit by having standardized tests and endpoints, agreed upon by the HD research community, for the different animal models on what would constitute a promising therapeutic study. While several behavioral tests, such as the rotarod, are generally accepted as a reliable measure of motor dysfunction in HD, other tests such as the limb clasping response are vague in their external validity to HD. Other histological and molecular analyses also differ between various animal models and the relative effect size observed is often difficult to extrapolate to the human condition. The rate of disease progression also plays a large role to the extent in which the respective animal model can be used to test therapeutic products. For example, many studies utilize the R6/2 mouse model to characterize behavioral deficits and the ability of a target therapy or compound to extend the lifespan of these animals; however it is widely accepted that this mouse recapitulates JHD and as such, therapies aimed at preventing neuronal loss would be unsuccessful due to the lack of neuropathology in this model. Conversely, therapies aimed at the metabolic dysfunction or at extending the lifespan of the mice might be unsuccessful in either the YAC128 or bacteria artificial chromosome HD mouse models as they exhibit weight gain uncharacteristic of the human condition and have a normal lifespan when compared with nongene carrying littermates.

As mentioned above, many genetic large animal models of HD are being developed. These new animal models should create an avenue for large animal safety and toxicology studies. The rodent brain lacks some of the major neuroanatomical characteristics relevant to the human HD brain; specifically mice and rats do not have separate caudate and putamen or the dark pigment, neuromelanin, in the substantia nigra [167]. Mice also have smooth (lisencephalic) cortices whereas the human cortex has convoluted (gyrencephalic)

anatomy [167], which contributes to targeting difficulties if the planned therapeutic involving intracranial transplantation. These issues indicate a need to conduct large animal safety studies to accurately assess the delivery of the stem cells and to perform long-term toxicology studies.

Conclusion

In conclusion, stem cell therapies, particularly engineered MSC transplantation, holds great promise to slow the progression of HD. While many advances are being made in the field of stem cell research, the strong clinical safety profile of MSC make them a strong candidate to move forward with clinical trials for this devastating disease.

Future perspective

With the initiation of several clinical trials for the use of MSC in the CNS, the future of this therapy will focus on the clinical follow-up of these patients to demonstrate the safety and feasibility of such a trial. If these cells follow the same safety profile that they have demonstrated preclinically, the initiation of Phase II and III trials will hopefully be underway with larger cohorts of patients to test the efficacy of these treatments. It is likely that following the initial trials of MSC treatments that the preclinical focus will be on the development and optimization to improve the efficacy of these cells. The ease in which MSC can be engineered will likely shape the transplantation field in the next 5–10 years. The ability for MSCs to act as a biological delivery system will enable researchers to test different therapeutic targets for gene delivery using a reliable delivery platform. Several clinical trials have initiated testing the potential safety of adult stem cells in the CNS.

Conversely, the sustained engraftment of MSCs may be a potential obstacle in development of long-term cellular therapy. Allogeneic MSC engraftments in macaque monkeys have been shown to have varying success as a result of immunogenicity. Special care must be taken into account for future MSC engraftment studies in this regard. Transient engraftment of MSCs may prove to be a potential boon rather than a limitation insofar as a potential safeguard from a prolonged immune response [168–170].

As adult and juvenile HD have subtle but significant differences in disease progression and symptoms, it is important to consider these when developing a stem cell therapy. This review has focused mainly on the concept of neuroprotection in adult HD with the use of genetically engineered MSC, but in specific cases of juvenile HD, where the disease progression is too rapid; there may be too widespread neuronal loss for neuroprotection to be effective. It is likely that a polytherapy or multiple types of cell transplantation would be needed to address the multifaceted nature of the disease.

The company Brain-Storm Cell Therapeutics, Inc., based at the Hadassah University Medical Center in Jerusalem, reported in early 2015 that it treated the first patients with amyotrophic lateral sclerosis with a modified stem cell (NurOwn) isolated from the bone marrow and enhanced to resemble glial-derived neurotrophic factor astrocyte-like cells by exposure to specific growth factors [171].

In December 2014, Athersys concluded patient enrolment of a Phase IIa clinical study for ischemic

Executive summary

Significant advances in stem cell therapies

- Stem cell therapies for diseases of the CNS are underway and hold significant clinical benefit.

Huntington's disease

- Stem cell therapies hold great potential for adult and juvenile Huntington's disease (HD).

Mesenchymal stem cells for HD

- Mesenchymal stem cells (MSCs) have a long, robust history in animal models of HD for providing behavioral and histological benefits.

Ongoing challenges

- A major hurdle in developing stem cell therapies is addressing/managing the immune response following transplantation.

Unmet needs

- Transgenic animal models need to be improved to help facilitate translational research to get to clinical trials.
- MSCs have long displayed promising therapeutic effects and strong safety profiles in preclinical studies and are now gaining US FDA approval to clinically test for diseases and disorders of the CNS. Intrastriatal transplantation of MSCs in rodent models of HD has led to improvements of behavioral function and has proven capable of slowing the rate of neurodegeneration by creating a neuroprotective environment, likely through the release of trophic factors. These positive results have led to the proposed clinical use of MSCs engineered to release BDNF. However, more work is needed to optimize the safety and delivery of these cells in large animal models that more closely resemble the human brain.

stroke patients treated with an MSC-like stem cell therapy referred to as MultiStem. This stem cell trial has the potential to substantially improve neurological and functional recovery following ischemic stroke by providing neuroprotection to the damaged host neurons, immune-modulation, releasing factors that support neuronal recovery and regrowth and restoring immune system homeostasis [172].

Asterias Biotherapeutics, Inc. received approval by the US FDA in 2014 to begin a Phase I/IIa clinical trial to test the safety and efficacy of oligodendrocyte progenitor cells (AST-OPC1) for patients who have suffered spinal cord injuries. This study is an extension of a trial started by Geron in 2010, in which five patients treated showed no serious side effects [173].

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 Dutta S, Singh G, Sreejith S *et al.* Cell therapy: the final frontier for treatment of neurological diseases. *CNS Neurosci. Ther.* 19(1), 5–11 (2013).

2 Barker RA. Stem cells and neurodegenerative diseases: where is it all going? *Regen. Med.* 7(6 Suppl), 26–31 (2012).

3 Karussis D, Petrou P, Kassis I. Clinical experience with stem cells and other cell therapies in neurological diseases. *J. Neurol. Sci.* 324(1–2), 1–9 (2013).

4 Bachoud-Lévi A-C, Gaura V, Brugières P *et al.* Effect of fetal neural transplants in patients with Huntington's disease 6 years after surgery: a long-term follow-up study. *Lancet Neurol.* 5(4), 303–309 (2006).

5 Cicchetti F, Saporta S, Hauser RA *et al.* Neural transplants in patients with Huntington's disease undergo disease-like neuronal degeneration. *Proc. Natl Acad. Sci. USA* 106(30), 12483–12488 (2009).

6 Keene CD, Chang RC, Leverenz JB *et al.* A patient with Huntington's disease and long-surviving fetal neural transplants that developed mass lesions. *Acta Neuropathol. (Berl.).* 117(3), 329–338 (2009).

7 Venkataramana NK, Kumar SKV, Balaraju S *et al.* Open-labeled study of unilateral autologous bone-marrow-derived mesenchymal stem cell transplantation in Parkinson's disease. *Transl. Res. J. Lab. Clin. Med.* 155(2), 62–70 (2010).

8 Boncoraglio GB, Bersano A, Candelise L, Reynolds BA, Parati EA. Stem cell transplantation for ischemic stroke. *Cochrane Database Syst. Rev. Online* (9), CD007231 (2010).

9 Lee JS, Hong JM, Moon GJ *et al.* A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. *Stem Cells Dayt. Ohio* 28(6), 1099–1106 (2010).

10 Lee Y-H, Choi KV, Moon JH *et al.* Safety and feasibility of countering neurological impairment by intravenous administration of autologous cord blood in cerebral palsy. *J. Transl. Med.* 10, 10 (2012).

11 Madhavan L, Collier TJ. A synergistic approach for neural repair: cell transplantation and induction of endogenous precursor cell activity. *Neuropharmacology* 58(6), 835–844 (2010).

12 The Huntington's Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. *Cell* 72(6), 971–983 (1993).

13 Shoulson I, Young AB. Milestones in huntington disease. *Mov. Disord.* 26(6), 1127–1133 (2011).

• **Excellent review of the major progress in the treatment, drug development, therapeutic targets and etiology of Hungtington's disease (HD).**

14 Ribaï P, Nguyen K, Hahn-Barma V *et al.* Psychiatric and cognitive difficulties as indicators of juvenile huntington disease onset in 29 patients. *Arch. Neurol.* 64(6), 813–819 (2007).

15 Gonzalez-Alegre P, Afifi AK. Clinical characteristics of childhood-onset (juvenile) Huntington disease: report of 12 patients and review of the literature. *J. Child Neurol.* 21(3), 223–229 (2006).

16 Estrada Sánchez AM, Mejía-Toiber J, Massieu L. Excitotoxic neuronal death and the pathogenesis of Huntington's disease. *Arch. Med. Res.* 39(3), 265–276 (2008).

17 Nance MA, Mathias-Hagen V, Breningstall G, Wick MJ, McGlennen RC. Analysis of a very large trinucleotide repeat in a patient with juvenile Huntington's disease. *Neurology* 52(2), 392–394 (1999).

18 Biglan K, Shoulson I. Juvenile-onset huntington disease: a matter of perspective. *Arch. Neurol.* 64(6), 783–784 (2007).

19 Klempír J, Klempírová O, Stochl J, Spacková N, Roth J. The relationship between impairment of voluntary movements and cognitive impairment in Huntington's disease. *J. Neurol.* 256(10), 1629–1633 (2009).

20 Ross CA, Aylward EH, Wild EJ *et al.* Huntington disease: natural history, biomarkers and prospects for therapeutics. *Nat. Rev. Neurol.* 10(4), 204–216 (2014).

21 Douglas I, Evans S, Rawlins MD, Smeeth L, Tabrizi SJ, Wexler NS. Juvenile Huntington's disease: a population-based study using the General Practice Research Database. *BMJ Open* doi:10.1136/bmjopen-2012-002085 (2013) (Epub ahead of print).

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

22 Stout JC, Weaver M, Solomon AC *et al.* Are cognitive changes progressive in prediagnostic HD? *Cogn. Behav. Neurol.* 20(4), 212–218 (2007).

23 Aylward EH, Rosenblatt A, Field K *et al.* Caudate volume as an outcome measure in clinical trials for Huntington's disease: a pilot study. *Brain Res. Bull.* 62(2), 137–141 (2003).

• **One of the first to establish robust clinical measurements to track the progression of HD. The results from this study help to design clinical trials aimed at slowing or at tenuating disease progression.**

24 Tabrizi SJ, Langbehn DR, Leavitt BR *et al.* Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *Lancet Neurol.* 8(9), 791–801 (2009).

25 Southwell AL, Ko J, Patterson PH. Intrabody gene therapy ameliorates motor, cognitive, and neuropathological symptoms in multiple mouse models of Huntington's disease. *J. Neurosci.* 29(43), 13589–13602 (2009).

• **One of the first to report significant *in vivo* data in transgenic mouse models of HD supporting the hypothesis that if mutant huntingtin was reduced the behavioral and neuropathological deficits would also be reduced.**

26 Wang N, Gray M, Lu X-H *et al.* Neuronal targets for reducing mutant huntingtin expression to ameliorate disease in a mouse model of Huntington's disease. *Nat. Med.* 20(5), 536–541 (2014).

27 Mielcarek M, Inuabasi L, Bondulich MK *et al.* Dysfunction of the CNS-heart axis in mouse models of Huntington's disease. *PLoS Genet.* 10(8), e1004550 (2014).

28 Buonincontri G, Wood NI, Puttick SG *et al.* Right ventricular dysfunction in the R6/2 transgenic mouse model of Huntington's disease is unmasked by dobutamine. *J. Huntingt. Dis.* 3(1), 25–32 (2014).

29 Mihm MJ, Amann DM, Schanbacher BL, Altschuld RA, Bauer JA, Hoyt KR. Cardiac dysfunction in the R6/2 mouse model of Huntington's disease. *Neurobiol. Dis.* 25(2), 297–308 (2007).

30 Zielonka D, Piotrowska I, Marcinkowski JT, Mielcarek M. Skeletal muscle pathology in Huntington's disease. *Front. Physiol.* 5, 5 (2014).

31 Sari Y. Potential drugs and methods for preventing or delaying the progression of Huntington's disease. *Recent Patents CNS Drug Discov.* 6(2), 80–90 (2011).

32 Venuto CS, McGarry A, Ma Q, Kieburtz K. Pharmacologic approaches to the treatment of Huntington's disease. *Mov. Disord.* 27(1), 31–41 (2012).

33 Lescaudron L, Unni D, Dunbar GL. Autologous adult bone marrow stem cell transplantation in an animal model of huntington's disease: behavioral and morphological outcomes. *Int. J. Neurosci.* 113(7), 945–956 (2003).

34 Jiang Y, Lv H, Huang S, Tan H, Zhang Y, Li H. Bone marrow mesenchymal stem cells can improve the motor function of a Huntington's disease rat model. *Neurol. Res.* 33(3), 331–337 (2011).

35 Rossignol J, Boyer C, Lévèque X *et al.* Mesenchymal stem cell transplantation and DMEM administration in a 3NP rat model of Huntington's disease: morphological and behavioral outcomes. *Behav. Brain Res.* 217(2), 369–378 (2011).

36 Rossignol J, Fink K, Davis K *et al.* Transplants of adult mesenchymal and neural stem cells provide neuroprotection and behavioral sparing in a transgenic rat model of Huntington's disease. *Stem Cells Dayt. Ohio* 32(2), 500–509 (2013).

• **Provided evidence for the use of mesenchymal stem cells to both modulate the host microenvironment to increase survival of normally rejected transplanted cells and to provide functional and histological benefits by themselves.**

37 Sadan O, Shemesh N, Barzilay R *et al.* Migration of neurotrophic factors-secreting mesenchymal stem cells toward a quinolinic acid lesion as viewed by magnetic resonance imaging. *Stem Cells Dayt. Ohio* 26(10), 2542–2551 (2008).

38 Serrano Sánchez T, Alberti Amador E, Lorigados Pedre L, Blanco Lezcano L, Diaz Armesto I, Bergado JA. BDNF in quinolinic acid lesioned rats after bone marrow cells transplant. *Neurosci. Lett.* 559, 147–151 (2014).

39 Dey ND, Bombard MC, Roland BP *et al.* Genetically engineered mesenchymal stem cells reduce behavioral deficits in the YAC 128 mouse model of Huntington's disease. *Behav. Brain Res.* 214(2), 193–200 (2010).

•• **A proof-of-concept study that demonstrated the role of BDNF released from mesenchymal stem cells to provide significant recovery or prevention of deficits in a transgenic mouse model of HD.**

40 Rossignol J, Fink KD, Crane AT *et al.* Reductions in behavioral deficits and neuropathology in the R6/2 mouse model of Huntington's disease following transplantation of bone-marrow-derived mesenchymal stem cells is dependent on passage number. *Stem Cell Res. Ther.* doi:10.1186/scrt545 (2015) (Epub ahead of print).

41 Fink KD, Rossignol J, Crane AT *et al.* Transplantation of umbilical cord-derived mesenchymal stem cells into the striata of R6/2 mice: behavioral and neuropathological analysis. *Stem Cell Res. Ther.* 4(5), 130 (2013).

42 Hosseini M, Moghadas M, Edalatmanesh MA, Hashemzadeh MR. Xenotransplantation of human adipose derived mesenchymal stem cells in a rodent model of Huntington's disease: motor and non-motor outcomes. *Neurol. Res.* 37(4), 309–319 (2015).

43 Im W, Lee S-T, Park JE *et al.* Transplantation of patient-derived adipose stem cells in YAC128 Huntington's disease transgenic mice. *PLoS Curr.* 2 (2010).

44 Lee S-T, Chu K, Jung K-H *et al.* Slowed progression in models of Huntington disease by adipose stem cell transplantation. *Ann. Neurol.* 66(5), 671–681 (2009).

45 Lin Y-T, Chern Y, Shen C-KJ *et al.* Human mesenchymal stem cells prolong survival and ameliorate motor deficit through trophic support in Huntington's disease mouse models. *PLoS ONE* 6(8), e22924 (2011).

• **Further evidence of mesenchymal stem cells' ability to release neurotrophic factors and reduce motor deficits and increase the lifespan following transplantation into transgenic mouse models of HD.**

46 Sadan O, Shemesh N, Barzilay R *et al.* Mesenchymal stem cells induced to secrete neurotrophic factors attenuate

quinolinic acid toxicity: a potential therapy for Huntington's disease. *Exp. Neurol.* 234(2), 417–427 (2012).

47 Snyder BR, Chiu AM, Prockop DJ, Chan AWS. Human multipotent stromal cells (MSCs) increase neurogenesis and decrease atrophy of the striatum in a transgenic mouse model for Huntington's disease. *PLoS ONE* 5(2), e9347 (2010).

48 Edalatmanesh M-A, Matin MM, Neshati Z, Bahrami A-R, Kheirabadi M. Systemic transplantation of mesenchymal stem cells can reduce cognitive and motor deficits in rats with unilateral lesions of the neostriatum. *Neurol. Res.* 32(2), 166–172 (2010).

49 Bae KS, Park JB, Kim HS, Kim DS, Park DJ, Kang SJ. Neuron-like differentiation of bone marrow-derived mesenchymal stem cells. *Yonsei Med. J.* 52(3), 401–412 (2011).

50 Black IB, Woodbury D. Adult rat and human bone marrow stromal stem cells differentiate into neurons. *Blood Cells. Mol. Dis.* 27(3), 632–636 (2001).

51 Sanchez-Ramos J, Song S, Cardozo-Pelaez F *et al.* Adult bone marrow stromal cells differentiate into neural cells *in vitro*. *Exp. Neurol.* 164(2), 247–256 (2000).

52 Woodbury D, Schwarz EJ, Prockop DJ, Black IB. Adult rat and human bone marrow stromal cells differentiate into neurons. *J. Neurosci. Res.* 61(4), 364–370 (2000).

53 Brazelton TR, Rossi FM, Keshet GI, Blau HM. From marrow to brain: expression of neuronal phenotypes in adult mice. *Science* 290(5497), 1775–1779 (2000).

54 Hung S-C, Cheng H, Pan C-Y, Tsai MJ, Kao L-S, Ma H-L. *In vitro* differentiation of size-sieved stem cells into electrically active neural cells. *Stem Cells Dayt. Ohio* 20(6), 522–529 (2002).

55 Jiang Y, Jahagirdar BN, Reinhardt RL *et al.* Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* 418(6893), 41–49 (2002).

56 Kopen GC, Prockop DJ, Phinney DG. Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. *Proc. Natl Acad. Sci. USA* 96(19), 10711–10716 (1999).

57 Mezey E, Chandross KJ, Harta G, Maki RA, McKercher SR. Turning blood into brain: cells bearing neuronal antigens generated *in vivo* from bone marrow. *Science* 290(5497), 1779–1782 (2000).

58 Muñoz-Elias G, Marcus AJ, Coyne TM, Woodbury D, Black IB. Adult bone marrow stromal cells in the embryonic brain: engraftment, migration, differentiation, and long-term survival. *J. Neurosci.* 24(19), 4585–4595 (2004).

59 Hardy SA, Maltman DJ, Przyborski SA. Mesenchymal stem cells as mediators of neural differentiation. *Curr. Stem Cell Res. Ther.* 3(1), 43–52 (2008).

60 Huang W *et al*. Transplantation of differentiated bone marrow stromal cells promotes motor functional recovery in rats with stroke. Neurol. Res. 35, 320– 328 (2013).

61 Lin Q-M. Mesenchymal stem cells transplantation suppresses inflammatory responses in global cerebral ischemia: contribution of TNF-α-induced protein 6. *Acta Pharmacol. Sin.*doi:10.1038/aps.2012.199 (2013).

62 Han EY, Chun MH, Kim ST, Lin D. Injection time-dependent effect of adult human bone marrow stromal cell transplantation in a rat model of severe traumatic brain injury. *Curr. Stem Cell Res. Ther.* 8, 172–181 (2013).

63 Uccelli A, Benvenuto F, Laroni A Giunti D *et al.* Neuroprotective features of mesenchymal stem cells. *Best Pract. Res. Clin. Haematol.* 24, 59–64 (2011).

64 Zuccato C, Ciammola A, Rigamonti D *et al.* Loss of huntingtin-mediated *BDNF* gene transcription in Huntington's disease. *Science* 293(5529), 493–498 (2001).

65 Zuccato C, Marullo M, Vitali B *et al.* Brain-derived neurotrophic factor in patients with Huntington's disease. *PLoS ONE* 6(8), e22966 (2011).

•• **An all-encompassing manuscript over the role of brain-derived neurotrophic factor's role in HD. This study provides evidence that BDNF is decreased in Huntington's patients and that BDNF is highly correlative with disease progression and decreases as the severity increases.**

66 Almeida S, Laço M, Cunha-Oliveira T, Oliveira CR, Rego AC. BDNF regulates BIM expression levels in 3-nitropropionic acid-treated cortical neurons. *Neurobiol. Dis.* 35(3), 448–456 (2009).

67 Arregui L, Benítez JA, Razgado LF, Vergara P, Segovia J. Adenoviral astrocyte-specific expression of *BDNF* in the striata of mice transgenic for Huntington's disease delays the onset of the motor phenotype. *Cell. Mol. Neurobiol.* 31(8), 1229–1243 (2011).

68 Bemelmans AP, Horellou P, Pradier L, Brunet I, Colin P, Mallet J. Brain-derived neurotrophic factor-mediated protection of striatal neurons in an excitotoxic rat model of Huntington's disease, as demonstrated by adenoviral gene transfer. *Hum. Gene Ther.* 10(18), 2987–2997 (1999).

69 Benraiss A, Bruel-Jungerman E, Lu G, Economides AN, Davidson B, Goldman SA. Sustained induction of neuronal addition to the adult rat neostriatum by AAV4-delivered noggin and BDNF. *Gene Ther.* 19(5), 483–493 (2012).

70 Benraiss A, Toner MJ, Xu Q *et al.* Sustained mobilization of endogenous neural progenitors delays disease progression in a transgenic model of Huntington's disease. *Cell Stem Cell* 12(6), 787–799 (2013).

• **It further strengthens the hypothesis that if BDNF can be increased in the brain of transgenic HD mice, behavioral deficits and neuropathology will be decreased. The manuscript also presents a mechanism by which BDNF increases endogenous neurogenesis.**

71 Canals JM, Pineda JR, Torres-Peraza JF *et al.* Brain-derived neurotrophic factor regulates the onset and severity of motor dysfunction associated with enkephalinergic neuronal degeneration in Huntington's disease. *J. Neurosci.* 24(35), 7727–7739 (2004).

72 Cepeda C, Starling AJ, Wu N *et al.* Increased GABAergic function in mouse models of Huntington's disease: reversal by BDNF. *J. Neurosci. Res.* 78(6), 855–867 (2004).

73 Gharami K, Xie Y, An JJ, Tonegawa S, Xu B. Brain-derived neurotrophic factor over-expression in the forebrain ameliorates Huntington's disease phenotypes in mice. *J. Neurochem.* 105(2), 369–379 (2008).

74 Giampà C, Montagna E, Dato C, Melone MAB, Bernardi G, Fusco FR. Systemic delivery of recombinant brain derived neurotrophic factor (*BDNF*) in the R6/2 mouse model of Huntington's disease. *PLoS ONE* 8(5), e64037 (2013).

75 Giralt A, Friedman HC, Caneda-Ferrón B *et al. BDNF* regulation under GFAP promoter provides engineered astrocytes as a new approach for long-term protection in Huntington's disease. *Gene Ther.* 17(10), 1294–1308 (2010).

76 Giralt A, Carretón O, Lao-Peregrin C, Martín ED, Alberch J. Conditional BDNF release under pathological conditions improves Huntington's disease pathology by delaying neuronal dysfunction. *Mol. Neurodegener.* 6(1), 71 (2011).

77 Jiang M, Peng Q, Liu X *et al.* Small-molecule TrkB receptor agonists improve motor function and extend survival in a mouse model of Huntington's disease. *Hum. Mol. Genet.* 22(12), 2462–2470 (2013).

78 Kells AP, Fong DM, Dragunow M, During MJ, Young D, Connor B. AAV-mediated gene delivery of *BDNF* or *GDNF* is neuroprotective in a model of Huntington disease. *Mol. Ther. J. Am. Soc. Gene Ther.* 9(5), 682–688 (2004).

79 Kells AP, Henry RA, Connor B. *AAV–BDNF* mediated attenuation of quinolinic acid-induced neuropathology and motor function impairment. *Gene Ther.* 15(13), 966–977 (2008).

80 Lynch G, Kramar EA, Rex CS *et al.* Brain-derived neurotrophic factor restores synaptic plasticity in a knock-in mouse model of Huntington's disease. *J. Neurosci.* 27(16), 4424–4434 (2007).

81 Martire A, Pepponi R, Domenici MR, Ferrante A, Chiodi V, Popoli P. BDNF prevents NMDA-induced toxicity in models of Huntington's disease: the effects are genotype specific and adenosine A(2A) receptor is involved. *J. Neurochem.* doi:10.1111/jnc.12177 (2013) (Epub ahead of print).

82 Pérez-Navarro E, Alberch J, Neveu I, Arenas E. Brain-derived neurotrophic factor, neurotrophin-3 and neurotrophin-4/5 differentially regulate the phenotype and prevent degenerative changes in striatal projection neurons after excitotoxicity *in vivo*. *Neuroscience* 91(4), 1257–1264 (1999).

83 Pérez-Navarro E, Canudas AM, Akerund P, Alberch J, Arenas E. Brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4/5 prevent the death of striatal projection neurons in a rodent model of Huntington's disease. *J. Neurochem.* 75(5), 2190–2199 (2000).

84 Petersén A A, Larsen KE, Behr GG *et al.* Brain-derived neurotrophic factor inhibits apoptosis and dopamine-induced free radical production in striatal neurons but does not prevent cell death. *Brain Res. Bull.* 56(3–4), 331–335 (2001).

85 Reiner A, Wang HB, Del Mar N, Sakata K, Yoo W, Deng YP. BDNF may play a differential role in the protective effect of the mGluR2/3 agonist LY379268 on striatal projection neurons in R6/2 Huntington's disease mice. *Brain Res.* 1473, 161–172 (2012).

86 Saylor AJ, McGinty JF. An intrastriatal brain-derived neurotrophic factor infusion restores striatal gene expression in *Bdnf* heterozygous mice. *Brain Struct. Funct.* 215(2), 97–104 (2010).

87 Simmons DA, Rex CS, Palmer L *et al.* Up-regulating BDNF with an ampakine rescues synaptic plasticity and memory in Huntington's disease knockin mice. *Proc. Natl Acad. Sci. USA* 106(12), 4906–4911 (2009).

88 Simmons DA, Belichenko NP, Yang T *et al.* A small molecule TrkB ligand reduces motor impairment and neuropathology in R6/2 and BACHD mouse models of Huntington's disease. *J. Neurosci.* 33(48), 18712–18727 (2013).

89 Todd D, Gowers I, Dowler SJ *et al.* A monoclonal antibody TrkB receptor agonist as a potential therapeutic for Huntington's disease. *PLoS ONE* 9(2), e87923 (2014).

90 Volpe BT, Wildmann J, Altar CA. Brain-derived neurotrophic factor prevents the loss of nigral neurons induced by excitotoxic striatal-pallidal lesions. *Neuroscience* 83(3), 741–748 (1998).

91 Wu C-L, Hwang C-S, Yang D-I. Protective effects of brain-derived neurotrophic factor against neurotoxicity of 3-nitropropionic acid in rat cortical neurons. *Neurotoxicology* 30(4), 718–726 (2009).

92 Xie Y, Hayden MR, Xu B. *BDNF* overexpression in the forebrain rescues Huntington's disease phenotypes in YAC128 mice. *J. Neurosci.* 30(44), 14708–14718 (2010).

93 Zuccato C, Liber D, Ramos C *et al.* Progressive loss of BDNF in a mouse model of Huntington's disease and rescue by BDNF delivery. *Pharmacol. Res.* 52(2), 133–139 (2005).

94 Barzilay R, Ben-Zur T, Bulvik S, Melamed E, Offen D. Lentiviral delivery of LMX1a enhances dopaminergic phenotype in differentiated human bone marrow mesenchymal stem cells. *Stem Cells Dev.* 18(4), 591–601 (2009).

95 Bauer G, Dao MA, Case SS *et al. In vivo* biosafety model to assess the risk of adverse events from retroviral and lentiviral vectors. *Mol. Ther. J. Am. Soc. Gene Ther.* 16(7), 1308–1315 (2008).

96 Joyce N, Annett G, Wirthlin L, Olson S, Bauer G, Nolta JA. Mesenchymal stem cells for the treatment of neurodegenerative disease. *Regen. Med.* 5(6), 933–946 (2010).

97 Meyerrose T, Olson S, Pontow S *et al.* Mesenchymal stem cells for the sustained *in vivo* delivery of bioactive factors. *Adv. Drug Deliv. Rev.* 62(12), 1167–1174 (2010).

98 Pollock K, Stewart H, Cary W *et al.* Mesenchymal stem cells engineered to produce BDNF for the treatment of Huntington's disease. *Cell Transplant.* 23(6), 780 (2014).

99 Bachoud-Lévi A-C. Neural grafts in Huntington's disease: viability after 10 years. *Lancet Neurol.* 8(11), 979–981 (2009).

100 Cicchetti F, Lacroix S, Cisbani G *et al.* Mutant huntingtin is present in neuronal grafts in Huntington disease patients. *Ann. Neurol.* 76(1), 31–42 (2014).

101 Reuter I, Tai YF, Pavese N *et al.* Long-term clinical and positron emission tomography outcome of fetal striatal transplantation in Huntington's disease. *J. Neurol. Neurosurg. Psychiatry* 79(8), 948–951 (2008).

102 Pecho-Vrieseling E, Rieker C, Fuchs S *et al.* Transneuronal propagation of mutant huntingtin contributes to non-cell autonomous pathology in neurons. *Nat. Neurosci.* 17(8), 1064–1072 (2014).

103 Kordower JH, Dodiya HB, Kordower AM *et al.* Transfer of host-derived α synuclein to grafted dopaminergic neurons in rat. *Neurobiol. Dis.* 43(3), 552–557 (2011).

104 Gallina P, Paganini M, Lombardini L *et al.* Human striatal neuroblasts develop and build a striatal-like structure into the brain of Huntington's disease patients after transplantation. *Exp. Neurol.* 222(1), 30–41 (2010).

105 Brundin P, Barker RA, Parmar M. Neural grafting in Parkinson's disease problems and possibilities. *Prog. Brain Res.* 184, 265–294 (2010).

106 Mathews DJH, Sugarman J, Bok H *et al.* Cell-based interventions for neurologic conditions: ethical challenges for early human trials. *Neurology* 71(4), 288–293 (2008).

107 Pullicino PM, Burke WJ. Cell-based interventions for neurologic conditions: ethical challenges for early human trials. *Neurology* 72(19), 1709 (2009).

108 Bachoud-Lévi AC, Rémy P, Nguyen JP *et al.* Motor and cognitive improvements in patients with Huntington's disease after neural transplantation. *Lancet* 356(9246), 1975–1979 (2000).

109 Capetian P, Knoth R, Maciaczyk J *et al.* Histological findings on fetal striatal grafts in a Huntington's disease patient early after transplantation. *Neuroscience* 160(3), 661–675 (2009).

110 Freeman TB, Cicchetti F, Hauser RA *et al.* Transplanted fetal striatum in Huntington's disease: phenotypic development and lack of pathology. *Proc. Natl Acad. Sci. USA* 97(25), 13877–13882 (2000).

111 Furtado S, Sossi V, Hauser RA *et al.* Positron emission tomography after fetal transplantation in Huntington's disease. *Ann. Neurol.* 58(2), 331–337 (2005).

112 Hauser RA, Furtado S, Cimino CR *et al.* Bilateral human fetal striatal transplantation in Huntington's disease. *Neurology* 58(5), 687–695 (2002).

113 Keene CD, Sonnen JA, Swanson PD *et al.* Neural transplantation in Huntington disease: long-term grafts in two patients. *Neurology* 68(24), 2093–2098 (2007).

114 Kopyov OV, Jacques S, Lieberman A, Duma CM, Eagle KS. Safety of intrastriatal neurotransplantation for Huntington's disease patients. *Exp. Neurol.* 149(1), 97–108 (1998).

115 Krystkowiak P, Gaura V, Labalette M *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(1), e166 (2007).

116 Rosser AE, Barker RA, Harrower T *et al.* Unilateral transplantation of human primary fetal tissue in four patients with Huntington's disease: NEST-UK safety report ISRCTN no 36485475. *J. Neurol. Neurosurg. Psychiatry* 73(6), 678–685 (2002).

117 Philpott LM, Kopyov OV, Lee AJ *et al.* Neuropsychological functioning following fetal striatal transplantation in Huntington's chorea: three case presentations. *Cell Transplant* 6(3), 203–212 (1997).

118 Madrazo I, Franco-Bourland RE, Castrejon H, Cuevas C, Ostrosky-Solis F. Fetal striatal homotransplantation for Huntington's disease: first two case reports. *Neurol. Res.* 17(4), 312–315 (1995).

119 Dunnett SB, Carter RJ, Watts C *et al.* Striatal transplantation in a transgenic mouse model of Huntington's disease. *Exp. Neurol.* 154(1), 31–40 (1998).

120 Ryu JK, Kim J, Cho SJ *et al.* Proactive transplantation of human neural stem cells prevents degeneration of striatal neurons in a rat model of Huntington disease. *Neurobiol. Dis.* 16(1), 68–77 (2004).

121 Bernreuther C, Dihné M, Johann V *et al.* Neural cell adhesion molecule L1-transfected embryonic stem cells promote functional recovery after excitotoxic lesion of the mouse striatum. *J. Neurosci.* 26(45), 11532–11539 (2006).

122 Aubry L, Bugi A, Lefort N, Rousseau F, Peschanski M, Perrier AL. Striatal progenitors derived from human ES cells mature into DARPP32 neurons *in vitro* and in quinolinic acid-lesioned rats. *Proc. Natl Acad. Sci. USA* 105(43), 16707–16712 (2008).

123 Fink KD, Crane AT, Lévêque X *et al.* Intrastriatal transplantation of adenovirus-generated induced pluripotent stem cells for treating neuropathological and functional deficits in a rodent model of Huntington's disease. *Stem Cells Transl. Med.* 3(5), 620–631 (2014).

124 Jeon I, Choi C, Lee N *et al. In vivo* roles of a patient-derived induced pluripotent stem cell line (HD72-iPSC) in the YAC128 model of Huntington's disease. *Int. J. Stem Cells.* 7(1), 43–47 (2014).

125 Lee S-T, Chu K, Park J-E *et al.* Intravenous administration of human neural stem cells induces functional recovery in Huntington's disease rat model. *Neurosci. Res.* 52(3), 243–249 (2005).

126 Yang C-R, Yu RK. Intracerebral transplantation of neural stem cells combined with trehalose ingestion alleviates pathology in a mouse model of Huntington's disease. *J. Neurosci. Res.* 87(1), 26–33 (2009).

127 Vazey EM, Chen K, Hughes SM, Connor B. Transplanted adult neural progenitor cells survive, differentiate and reduce motor function impairment in a rodent model of Huntington's disease. *Exp. Neurol.* 199(2), 384–396 (2006).

128 Bosch M, Pineda JR, Suñol C *et al.* Induction of GABAergic phenotype in a neural stem cell line for transplantation in an excitotoxic model of Huntington's disease. *Exp. Neurol.* 190(1), 42–58 (2004).

129 Pineda JR, Rubio N, Akerud P *et al.* Neuroprotection by GDNF-secreting stem cells in a Huntington's disease model: optical neuroimage tracking of brain-grafted cells. *Gene Ther.* 14(2), 118–128 (2007).

130 Song J, Lee S-T, Kang W *et al.* Human embryonic stem cell-derived neural precursor transplants attenuate apomorphine-induced rotational behavior in rats with unilateral quinolinic acid lesions. *Neurosci. Lett.* 423(1), 58–61 (2007).

131 Johann V, Schiefer J, Sass C *et al.* Time of transplantation and cell preparation determine neural stem cell survival in a mouse model of Huntington's disease. *Exp. Brain Res.* 177(4), 458–470 (2007).

132 Kawakami M, Yoshimoto T, Nakagata N, Yamamura K-I, Siesjo BK. Effects of cyclosporin A administration on gene expression in rat brain. *Brain Inj.* 25(6), 614–623 (2011).

133 Shin E, Palmer MJ, Li M, Fricker RA. GABAergic neurons from mouse embryonic stem cells possess functional properties of striatal neurons *in vitro*, and develop into striatal neurons *in vivo* in a mouse model of Huntington's disease. *Stem Cell Rev.* 8(2), 513–531 (2012).

134 Kordower JH, Chen EY, Winkler C *et al.* Grafts of EGF-responsive neural stem cells derived from GFAP-hNGF transgenic mice: trophic and tropic effects in a rodent model of Huntington's disease. *J. Comp. Neurol.* 387(1), 96–113 (1997).

135 Hurlbert MS, Gianani RI, Hutt C, Freed CR, Kaddis FG. Neural transplantation of hNT neurons for Huntington's disease. *Cell Transplant.* 8(1), 143–151 (1999).

136 Armstrong RJ, Watts C, Svendsen CN, Dunnett SB, Rosser AE. Survival, neuronal differentiation, and fiber outgrowth of propagated human neural precursor grafts in an animal model of Huntington's disease. *Cell Transplant.* 9(1), 55–64 (2000).

137 Visnyei K, Tatsukawa KJ, Erickson RI *et al.* Neural progenitor implantation restores metabolic deficits in the brain following striatal quinolinic acid lesion. *Exp. Neurol.* 197(2), 465–474 (2006).

138 Leveque X, Fink KD, Rossignol J, Dunbar GL, Lescaudron L. The use of xenotransplantation in neurodegenerative diseases: a way to go? *Xenotransplantation* 7, 93–107 (2012).

139 Lévêque X, Mathieux E, Nerrière-Daguin V *et al.* Local control of the host immune response performed with mesenchymal stem cells: perspectives for functional intracerebral xenotransplantation. *J. Cell. Mol. Med.* 19(1), 124–134 (2014).

140 Chamberlain G, Wright K, Rot A, Ashton B, Middleton J. Murine mesenchymal stem cells exhibit a restricted repertoire of functional chemokine receptors: comparison with human. *PLoS ONE* 3(8), e2934 (2008).

141 Leten C, Roobrouck VD, Struys T *et al.* Controlling and monitoring stem cell safety *in vivo* in an experimental rodent model. *Stem Cells Dayt. Ohio* 32(11), 2833–2844 (2014).

142 Liu AM, Qu WW, Liu X, Qu C-K. Chromosomal instability in *in vitro* cultured mouse hematopoietic cells associated with oxidative stress. *Am. J. Blood Res.* 2(1), 71–76 (2012).

143 Zhou YF, Bosch-Marce M, Okuyama H *et al.* Spontaneous transformation of cultured mouse bone marrow-derived stromal cells. *Cancer Res.* 66(22), 10849–10854 (2006).

144 Murphy KP, Carter RJ, Lione LA *et al.* Abnormal synaptic plasticity and impaired spatial cognition in mice transgenic for exon 1 of the human Huntington's disease mutation. *J. Neurosci.* 20(13), 5115–5123 (2000).

145 Franich NR, Fitzsimons HL, Fong DM, Klugmann M, During MJ, Young D. AAV vector-mediated RNAi of mutant huntingtin expression is neuroprotective in a novel genetic rat model of Huntington's disease. *Mol. Ther.* 16(5), 947–956 (2008).

146 Paulsen JS, Langbehn DR, Stout JC *et al.* Detection of Huntington's disease decades before diagnosis: the predict-HD study. *J. Neurol. Neurosurg. Psychiatry* 79(8), 874–880 (2008).

147 Aylward EH. Change in MRI striatal volumes as a biomarker in preclinical Huntington's disease. *Brain Res. Bull.* 72(2–3), 152–158 (2007).

148 Túnez I, Tasset I, Pérez-De La Cruz V, Santamaría A. 3-nitropropionic acid as a tool to study the mechanisms involved in Huntington's disease: past, present and future. *Mol. Basel Switz.* 15(2), 878–916 (2010).

149 Shear DA, Haik KL, Dunbar GL. Creatine reduces 3-nitropropionic-acid-induced cognitive and motor abnormalities in rats. *Neuroreport* 11(9), 1833–1837 (2000).

150 Ayalon L, Doron R, Weiner I, Joel D. Amelioration of behavioral deficits in a rat model of Huntington's disease by an excitotoxic lesion to the globus pallidus. *Exp. Neurol.* 186(1), 46–58 (2004).

151 Kalonia H, Kumar P, Nehru B, Kumar A. Neuroprotective effect of MK-801 against intra-striatal quinolinic acid induced behavioral, oxidative stress and cellular alterations in rats. *Indian J. Exp. Biol.* 47(11), 880–892 (2009).

152 Velloso NA, Dalmolin GD, Gomes GM *et al.* Spermine improves recognition memory deficit in a rodent model of Huntington's disease. *Neurobiol. Learn. Mem.* 92(4), 574–580 (2009).

153 Fink KD, Rossignol J, Crane AT *et al.* Early cognitive dysfunction in the HD 51 CAG transgenic rat model of Huntington's disease. *Behav. Neurosci.* 126(3), 479–487 (2012).

154 Jansson EKH, Clemens LE, Riess O, Nguyen HP. Reduced motivation in the BACHD rat model of Huntington disease is dependent on the choice of food deprivation strategy. *PLoS ONE* 9(8), e105662 (2014).

155 Von HÃ¶rsten S, Schmitt I, Nguyen HP *et al.* Transgenic rat model of Huntington's disease. *Hum. Mol. Genet.* 12(6), 617–624 (2003).

156 Yu-Taeger L, Petrasch-Parwez E, Osmand AP *et al.* A novel BACHD transgenic rat exhibits characteristic neuropathological features of Huntington disease. *J. Neurosci.* 32(44), 15426–15438 (2012).

157 Carter RJ, Lione LA, Humby T *et al.* Characterization of progressive motor deficits in mice transgenic for the human Huntington's disease mutation. *J. Neurosci.* 19(8), 3248–3257 (1999).

158 Schilling G, Becher MW, Sharp AH *et al.* Intranuclear inclusions and neuritic aggregates in transgenic mice expressing a mutant N-terminal fragment of huntingtin. *Hum. Mol. Genet.* 8(3), 397–407 (1999).

159 Slow EJ, van Raamsdonk J, Rogers D *et al.* Selective striatal neuronal loss in a YAC128 mouse model of Huntington disease. *Hum. Mol. Genet.* 12(13), 1555–1567 (2003).

160 Gray M, Shirasaki DI, Cepeda C *et al.* Full-length human mutant huntingtin with a stable polyglutamine repeat can elicit progressive and selective neuropathogenesis in BACHD mice. *J. Neurosci.* 28(24), 6182–6195 (2008).

161 Lin CH, Tallaksen-Greene S, Chien WM *et al.* Neurological abnormalities in a knock-in mouse model of Huntington's disease. *Hum. Mol. Genet.* 10(2), 137–144 (2001).

162 Beal MF, Kowall NW, Ellison DW, Mazurek MF, Swartz KJ, Martin JB. Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid. *Nature* 321(6066), 168–171 (1986).

163 Hamilton BF, Gould DH. Nature and distribution of brain lesions in rats intoxicated with 3-nitropropionic acid:

a type of hypoxic (energy deficient) brain damage. *Acta Neuropathol. (Berl.).* 72(3), 286–297 (1987).

164 Yang D, Wang C-E, Zhao B *et al.* Expression of Huntington's disease protein results in apoptotic neurons in the brains of cloned transgenic pigs. *Hum. Mol. Genet.* 19(20), 3983–3994 (2010).

165 Jacobsen JC, Bawden CS, Rudiger SR *et al.* An ovine transgenic Huntington's disease model. *Hum. Mol. Genet.* 19(10), 1873–1882 (2010).

166 Yang S-H, Cheng P-H, Banta H *et al.* Towards a transgenic model of Huntington's disease in a non-human primate. *Nature* 453(7197), 921–924 (2008).

167 Morton AJ, Howland DS. Large genetic animal models of Huntington's Disease. *J. Huntingt. Dis.* 2(1), 3–19 (2013).

168 Isakova IA, Baker K, Dufour J, Gaupp D, Phinney DG. Preclinical evaluation of adult stem cell engraftment and toxicity in the CNS of rhesus macaques. *Mol. Ther. J. Am. Soc. Gene Ther.* 13(6), 1173–1184 (2006).

169 Isakova IA, Dufour J, Lanclos C, Bruhn J, Phinney DG. Cell-dose-dependent increases in circulating levels of immune effector cells in rhesus macaques following intracranial injection of allogeneic MSCs. *Exp. Hematol.* 38(10), 957–967.e1 (2010).

170 Isakova IA, Lanclos C, Bruhn J *et al.* Allo-reactivity of mesenchymal stem cells in rhesus macaques is dose and haplotype dependent and limits durable cell engraftment *in vivo*. *PLoS ONE* 9(1), e87238 (2014).

171 Gothelf Y, Abramov N, Harel A, Offen D. Safety of repeated transplantations of neurotrophic factors-secreting human mesenchymal stromal stem cells. *Clin. Transl. Med.* 3, 3 (2014).

172 Hess DC, Sila CA, Furlan AJ, Wechsler LR, Switzer JA, Mays RW. A double-blind placebo-controlled clinical evaluation of MultiStem for the treatment of ischemic stroke. *Int. J. Stroke* 9(3), 381–386 (2014).

173 Alper J. Geron gets green light for human trial of ES cell-derived product. *Nat. Biotechnol.* 27(3), 213–214 (2009).