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Cord blood for brain injury

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Abstract

Recovery from neurological injuries is typically incomplete and often results in significant and permanent disabilities. Currently, most available therapies are limited to supportive or palliative measures, aimed at managing the symptoms of the condition. Because restorative therapies targeting the underlying cause of most neurological diseases do not exist, cell therapies targeting anti-inflammatory, neuroprotective and regenerative potential hold great promise. Cord blood (CB) cells can induce repair through mechanisms that involve trophic or cell-based paracrine effects or cellular integration and differentiation. Both may be operative in emerging CB therapies for neurologic conditions, and there are numerous potential applications of CB-based regenerative therapies in neurological diseases, including genetic diseases of childhood, ischemic events such as stroke and neurodegenerative diseases of adulthood. CB appears to hold promise as an effective therapy for patients with brain injuries. In this Review, we describe the state of science and clinical applications of CB therapy for brain injury.

Key Words: *brain injury, cell therapy, regenerative medicine, umbilical cord blood*

Introduction

Neurological injuries can result from any number of insults to the brain, including traumatic, vascular, infectious, genetic and environmental etiologies. Although the cause and mechanism of damage may vary, brain injuries share certain unifying features: as a group they are common, affecting people of all ages and races; they are costly, often causing chronic disabilities that carry significant medical and societal costs; and their current treatment options are extremely limited. Although recovery from a brain injury is typically incomplete, the brain's capacity for self-renewal—albeit limited—has recently been recognized. Concurrently, substantial advancements have been made in the field of stem cell biology. For these reasons, great interest has been generated in developing stem cell therapies as potential treatments to repair damage, regain function and improve quality of life in patients with neurological disorders. In this article, we will review the potential applications of umbilical cord blood (CB) as a source of stem cells for such therapies and some of the brain injuries in which they may be effective.

Umbilical CB as a source of stem cells for neurological applications

Several properties unique to CB make it an attractive source of stem cells for regenerative and restorative purposes. (i) Stem cell characteristics: CB is rich in highly proliferative stem and progenitor cells of the hematopoietic and other lineages mobilized by placental signals promoting homing to developing organs [1,2]. Compared with stem cells obtained from adult bone marrow (BM), CB stem cells are less mature and therefore have longer telomeres and greater proliferating potential [3]. CB-derived cells have been differentiated into numerous cell types throughout the body, including neural cells. Recently, induced pluripotent stem cells (iPS) have also been isolated from CB with simpler methods and greater efficiency as compared with adult cell sources [4–6]. There is also mounting preclinical evidence that cellular therapies act through paracrine and trophic mechanisms of cell signaling to enhance neuroprotection and restoration [7]. (ii) Availability: There are more than 130 million births per year worldwide, so there is ample opportunity to collect CB units for regenerative purposes. Processes are well established

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for the collection, testing, characterization and storage of CB units, which can be cryopreserved for decades for future use. Over the past 20 years, approximately 700,000 unrelated donor CB units have been collected, characterized and banked for public use, and an additional 2 to 3 million CB units have been stored privately for family use. (iii) Safety profile: CB can be collected non-invasively without risk to the mother or infant donor. Compared with adult BM stem cells, CB cells are less immunogenic and less likely to transmit infections through latent viruses. In more than 25 years of use in allogeneic, unrelated hematopoietic stem cell transplantation, CB has not been shown to cause teratomas or solid tumors. (iv) Noncontroversial: Given that cord blood was historically discarded as medical waste with the placenta after birth, it remains a noncontroversial source of stem and progenitor cells. All of these features make CB an attractive source of cells for cellular therapies and regenerative medicine. Of note, umbilical cord tissue is also readily available for harvest at the time of delivery. Mesenchymal stromal cells (MSCs) have been directly isolated or expanded from cord tissue and studied in animal models. These tissues are currently under study in early-phase clinical trials for arthritis, spinal cord injury, Alzheimer's disease and autism. However, the safety and efficacy of these cells is not currently established, and the optimal methods of processing, storing and manufacturing cell products from cord tissue are still the subject of investigation.

Since the first unrelated donor CB transplant in 1988, more than 30,000 CB transplants have been performed, and CB has become a proven source of stem cells for hematopoietic reconstitution for myelo-ablative stem cell transplantation. Additionally, CB also contains non-hematopoietic stem cell populations that are capable of differentiating into numerous cell types throughout the body. In particular, the CB-derived unrestricted somatic stem cell first described by Koegler is a non-hematopoietic multipotent cell with the ability to differentiate into several lineages *in vitro* and *in vivo*, including osteoclasts, hepatocytes and neurons, among others [8–10]. CB-derived cells can also differentiate into MSCs, chondrocytes, osteocytes, adipocytes, cardiac and skeletal muscle myocytes, hepatocytes, pancreatic cells, skin cells, endothelial colony-forming cells and neural cells [11–22]. Though the specific cell of origin that gives rise to neural cells has not yet been identified, neurons, astrocytes, oligodendrocytes and microglia have all repeatedly been derived *in vitro* from CB progenitor cells by means of gene transfection, *ex vivo* culture with and growth factor supplementation, through generation of iPS and/or the use of chemical agents [10,22–30].

Evidence of neural differentiation has also been detected *in vivo*. Donor CB-derived tissue-specific cells have been identified in multiple organs in both animals and humans after HSCT, including the liver, lung, pancreas, skeletal muscle and brain [19,31,32], indicating that CB cells are capable of repopulating more than just the hematopoietic system. This may be due to the presence of a true embryonic-like stem cell in CB and/or small numbers of committed, tissue-specific, non-hematopoietic progenitors. It is important to note that observations of *in vivo* engraftment and differentiation have occurred in immunocompetent, xenogenic animal models, but in humans only after receiving myelo-ablative and immuno-ablative preparative therapies. It is not clear if infusions of CB into an immunocompetent person will produce similar results.

Potential mechanisms of CB-derived therapies in brain injuries

Although CB cells have the ability to differentiate into tissue-specific cells and integrate into host organs, there is growing evidence that their therapeutic effects probably are mediated by an ability to influence tissue damage and repair by signaling and activation of host cells through trophic and/or paracrine effects. Although the exact mechanisms of neural sparing and/or recovery remain the subject of preclinical investigations, several mechanisms have been hypothesized [33]. The survival potential of host neural cells may be enhanced by the delivery of trophic factors from infused and/or transplanted CB cells that provide anti-inflammatory and neuroprotective effects [34–37]. Brain plasticity may be increased by enhancing synaptogenesis, instigating endogenous repair mechanisms, stimulating angiogenesis resulting in neovascularization and inducing migration and proliferation of endogenous neural stem cells [38–40]. To a lesser degree, CB stem cells may also migrate, integrate, proliferate and differentiate into "replacement" neuronal and glial cells and play a role in re-myelination [41]. Additionally, many neurologic diseases involve activation of pro-apoptotic signal transduction, which could be harnessed to attract cells to brain lesions in those diseases. Thus, CB-derived cells could also potentially act as a vehicle to deliver neuroprotective and restorative factors or signal endogenous cells to act in a targeted way toward damaged brain tissue. Given their numerous potential mechanisms of action, CB-derived therapies may be applicable to a wide range of neurological injuries including, but not limited to, genetic diseases of childhood, ischemic damage (acute and/or chronic) and neurodegenerative diseases of adulthood. The remainder of this

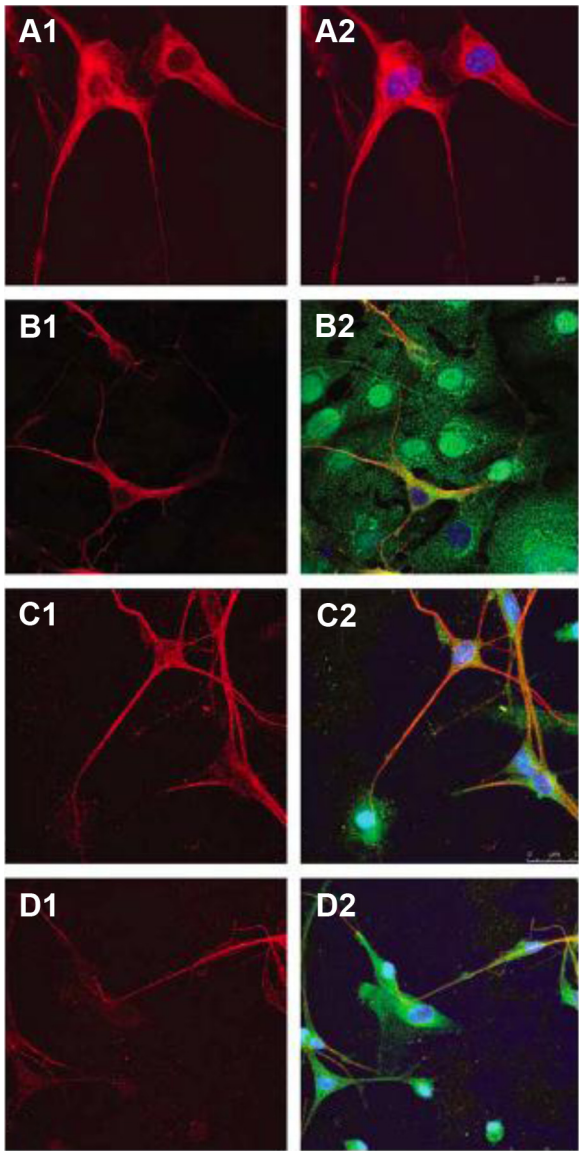

Figure 1. *In vitro* functional assay of myelination of shiverer mouse neurons by cryopreserved CB-derived oligodendrocyte-like cells (DUOC-01). Shiverer neurons co-cultured with O-cells were co-stained for BT3 (Texas red) and MBP (fluorescein isothiocyanate). Controls stained positive for BT3 (A1) but not MBP (A2). When co-cultured with DUOC-01 for 1 week, BT3 (B1) and MBP (B2) were expressed. Z-stacked projection after 3 weeks in culture demonstrated BT3 expression (C1, D1) and close association between BT3-expressing neuronal cells and MBP-expressing cells (C2), with MBP expression along axonal processes (D2) (reprinted from Tracy et al [22] with permission from Elsevier © 2011).

article will review the rationale, preclinical models and early clinical experience of CB and related therapies for some of these neurological conditions.

Childhood genetic brain diseases

The potential of CB cells to differentiate into non-hematopoietic lineages in humans was initially identified in children undergoing unrelated donor CB transplantation for certain inherited metabolic diseases (IMDs), a heterogeneous group of genetic diseases. In many IMDs, patients lack a critical enzyme necessary for the production and maintenance of myelin or other cellular-based structural parts of the nervous system, resulting in progressive neurological deterioration caused by absent or abnormal brain myelination. Affected babies may appear normal at birth but develop symptoms in the first months to years of life, ultimately resulting in death in childhood.

When donor CB cells engraft in a patient with particular genetic lysosomal and peroxisomal storage diseases, they serve as a constant source of enzyme replacement, thereby slowing or halting the natural progression of disease [42–45]. When patients with these diseases, ranging in age from newborns to young adults, are transplanted early in the course of their disease, they derive extensive benefits from the transplant procedure, which both extends life for decades and greatly improves neurologic functioning [46–48]. High pre-transplant performance status, a marker of disease progression, is associated with a much higher rate of survival than transplants performed in children with lower performance scores [43]. Clinical and pathological observations from these patients provide additional support for the concept that CB cells can repair non-hematopoietic tissues.

Autopsy studies in humans who died after intravenously administered, sex-mismatched BM and CB transplant have confirmed the engraftment of donor cells throughout the brain months after transplantation [49–51]. Most engrafting cells were non-neuronal microglial cells, but donor-derived neurons, astrocytes and oligodendrocytes have been identified. Globoid bodies, the pathological perivascular signature of Krabbe disease, were not detected in the brain of a patient transplanted for early infantile Krabbe disease at 3 weeks of age who died of unrelated causes at 5 years of age [51]. On the basis of these observations, our group hypothesized that CB contained cells capable of differentiating into oligodendrocyte- and microglial-like cells. We subsequently cultured and expanded oligodendrocyte-like cells from fresh and cryopreserved CB after 3 to 4 weeks in tissue culture supplemented with neurotrophic growth factors [22,24]. These cells (DUOC-01 or "O-cells") grow as an adherent population that, after 21 days in culture, express surface antigens found on oligodendrocytes (O1, O4, PLP, MBP) and microglia (CD45, CD11b), make corresponding RNAs and myelinate shiverer neuron axons in an *in vitro* potency assay (Figure 1). They also constitutively

produce interleukin-6 and interleukin-10 and retain the ability to produce lysosomal enzymes in culture after manufacturing. Although the exact cell of origin for the DUOC-01 cell is not known, a starting culture of 200 $\times$ 10^6 CB mononuclear cells yields approximately 2 to 3 million DUOC-01 cells after 21 days in culture. DUOC-01 doubling time is slow and estimated at one-doubling every 3 to 4 days. The cells have been shown in brain slice models to mediate repair of oxidative injury and to promote re-myelination. Intrathecal dosing in immunodeficient newborn mice showed the best distribution of DUOC-01 in the central nervous system as compared with intravenous or intracranial delivery routes.

Results of CB transplantation for IMDs suggest that greater benefit is likely when the transplant is performed early in the disease course before the development of clinical neurologic and other manifestations [48,52,53]. However, damage to the central nervous system occurs prenatally in some of these disorders. In addition, neurologic progression often occurs during and in the early months after transplant before sufficient numbers of donor cells engraft in the brain and produce adequate levels of the deficient enzyme. As a result, patients often have a progressive loss of neurologic function for the first few months after transplantation before the disease stabilizes, and most patients are left with some residual and irreversible neurologic impairment. To address this delay in engraftment, a phase I trial is underway in which the DUOC-01 described above are administered intrathecally 1 month after a standard allogeneic CB transplant from the same CB donor. The goal of this therapy is to accelerate delivery of donor cells to the central nervous system, thereby bridging the gap between systemic transplantation and engraftment of cells in the brain, resulting in an earlier arrest of disease progression. This trial is one example that the availability of well-characterized, screened and HLA-typed CB, coupled with its vast differentiation potential, makes it an attractive source of stem cells for applications in tissue repair and regeneration, particularly in the central nervous system.

Ischemic injuries

Observations of CB used to treat children with genetic conditions led to the hypothesis that CB might also be beneficial in patients with brain injury. Numerous animal models have demonstrated both neurological and survival benefits of CB cells in the setting of stroke, ischemia and intracranial hemorrhage [54–57]. These injuries differ in that some are focal (ie, stroke) and others are global (ie, hypoxia), but all are typically characterized by immediate damage to all neural cell types within the affected region, accelerating a cascade of events that lead to demyelination and necrosis of brain tissue. Inflammation, apoptosis, neuronal and oligodendrocyte death and astrocytosis are all operative in mediating damage resulting from these insults. Therefore, therapeutic strategies might involve methods to promote cell survival and repair or regeneration of the affected areas, potentially through anti-inflammatory effects, neurogenesis, synaptogenesis and/or angiogenesis after the injury has been sustained. Neuroprotection, neovascularization and neuronal regeneration have all been demonstrated in various models [40,54]. The most extensively studied models involve brain damage resulting from permanent middle cerebral artery occlusion (MCAO) in adult rats or transient occlusion accompanied with hypoxia in neonatal rats or mice. Intravenous injection of CB can greatly mitigate the damage caused by such acute hypoxic/ischemic brain injury [58].

In addition to evaluating treatment response and further elucidating mechanism of action, many preclinical studies have attempted to address other critical aspects of cell administration, including dose, timing and route of delivery. In addition to functional outcomes, Vendrame *et al.* [54] examined anatomic measures of infarct volume after MCAO in the presence of increasing doses of CB cells. At 4 weeks after infusion, infarct volume measurements revealed an inverse relationship between CB cell dose and damage volume, reaching significance at a dose of 10^7 cells, thereby demonstrating a dose-dependent relationship between CB cell dose, behavioral improvement and neuronal sparing. Also in an MCAO model, Chen *et al.* [55] showed a greater improvement in somatosensory behavior and neurologic dysfunction when CB or bone marrow stromal cells were administered at 1 day versus 7 days after the injury, which suggests that earlier may be better. In fact, the majority of stroke models have evaluated stem cell therapy in the acute or subacute setting, immediately to several days after the insult. However, Shen *et al.* [59] demonstrated improvement in functional outcomes in rats treated intravenously with bone marrow stromal cells 1 month after MCAO stroke. In this model, scar tissue was reduced and the number of proliferating cells and oligodendrocyte precursors in the area of injury were increased, possibly indicating neurogenesis and myelination. This suggests that although the ideal timing of cellular therapy for stroke or other brain injury is still unknown, benefits may be attainable long after the injury is sustained. Models delivering cells through the intravenous, intra-arterial and

intracerebral routes have not demonstrated that any one mode of delivery is significantly superior in terms of functional outcomes [60,61]. In animal models, delivery of MSCs and neural stem cells to the brain has also been accomplished through intranasal administration, an attractive alternative because of its noninvasiveness [62,63].

CB therapy has also been studied in models of hypoxic ischemic encephalopathy. In a neonatal rat model that results in severe cerebral damage and contralateral spastic paresis after unilateral carotid artery ligation on day 7 of life, intraperitoneal CB mononuclear cells administered 1 day after the hypoxic event migrate to the area of brain damage and persist for at least 2 weeks. Although the extent of morphologic injury on gross pathology was not altered, animals that received CB mononuclear cells did not develop spastic paresis, which indicates functional recovery [56]. In a baby rabbit model of ischemic encephalopathy, Derrick *et al.* [64] demonstrated that labeled human CB cells reached the brain within 24 hours, persisted for at least 1 week and decreased the degree of brain damage on magnetic resonance imaging (MRI). In severely affected animals, CB administration improved gross motor function in a short-term functional assay [65]. Additionally, Ballabh *et al.* [66] developed a rabbit model of intraventricular hemorrhage (IVH) by administering glycerol intraperitoneally to premature rabbit pups. In this model, IVH is followed by the development of hydrocephalus and subsequent white matter demyelination. Intraventricular administration of human CB cells 24 and 72 hours after glycerol failed to prevent the hydrocephalus but did reduce subsequent demyelination (Ballabh, personal communication, 2014).

In summary, xenogenic infusion of CB cells in animals after ischemic injury results in improved survival and functional outcomes. Optimal dose, timing and route of administration as well as specifics regarding mechanism of action are not fully understood and may vary on the basis of type, degree and time interval since the insult.

Clinical experience

Intravenous infusion of CB is currently under investigation in clinical trials for a variety of ischemic-related conditions, including neonatal hypoxic ischemic encephalopathy, cerebral palsy and stroke. Of note, intrathecal administration of allogeneic CB-derived cells, mostly MSCs, has been performed for a variety of neurologic conditions in a few small studies, primarily in China. In general, side effects are reported to be minor and transient, most commonly including fever, headache and dizziness [67–70]. Efficacy cannot be determined at this time, and further safety studies are needed.

Perinatal brain injury

The fetal and neonatal brain is uniquely susceptible to injury from a variety of causes, most frequently caused by ischemia in full-term babies, but also commonly including periventricular leukomalacia and IVH in preterm neonates.

In a phase I trial of newborns with hypoxic ischemic brain injury at birth conducted at Duke, fresh, non-cryopreserved, volume-reduced and red blood cell–reduced autologous CB was infused in one, two or four doses of 1 to 5×10^7 nucleated cells/kg within the first 48 to 72 hours of life in babies with moderate-to-severe encephalopathy qualifying for systemic hypothermia [71]. Initial infusions were administered an average of 6.5 hours after birth, with a second infusion before 48 hours of life. Babies who received CB infusions were compared with a concomitant group of babies treated at Duke who were cooled but did not receive CB cells. Infusions were found to be safe in these critically ill babies, and babies receiving cells had increased survival rates to discharge (100% versus 85%, $P = 0.20$) and improved function at 1 year of age (74% versus 41% with development in the normal range, $P = 0.05$). A phase II randomized trial is currently in development. If this therapy improves the outcome of babies with significant birth trauma, the current model of CB collection and banking may need to adapt to make this therapy available to all eligible babies. It may also be necessary to develop safe and effective therapies through the use of allogeneic CB donors because many of these babies and/or mothers will be too sick at birth to prioritize autologous CB collection.

Repeated autologous CB infusions are also being studied in young babies born with congenital hydrocephalus. In this condition, excessive accumulation of cerebral spinal fluid (CSF) within the ventricular system of the brain results in a progressive increase in ventricular volume and intracranial pressure, leaving the brain limited space to develop and expand. The increased pressure damages the developing brain through a crush injury that causes mechanical distortion and impaired blood flow as well as extravasation of CSF into the brain parenchyma that causes demyelination and loss of axons. Although some white matter changes may be reversible after ventriculo-peritoneal shunt placement to divert the flow of CSF after birth, most affected children are left with a myriad of motor, sensory and cognitive deficits caused by their early brain injury. At Duke University, more than 80 patients ages 6 days to 4 years with congenital hydrocephalus have received autologous CB infusions.

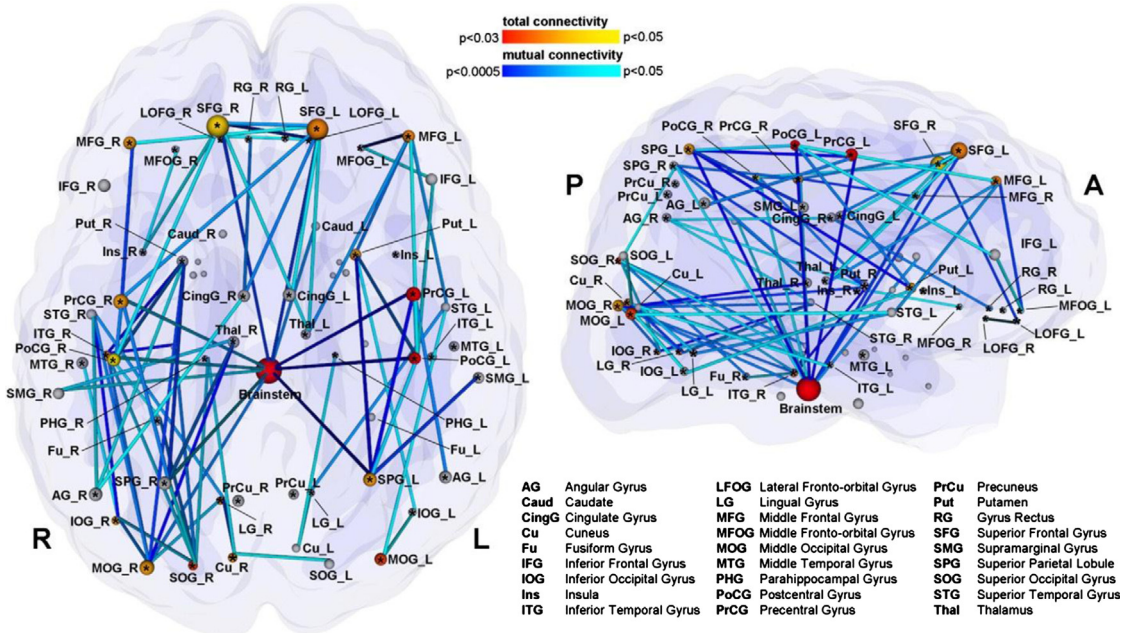

Figure 2. Inter-regional whole-brain connectivity analysis of 17 children with cerebral palsy. Red-yellow nodes indicate significantly reduced total connectivity to all other brain regions in severe versus moderate cerebral palsy. Cool-colored connections between nodes indicate significantly reduced mutual connectivities in the severely affected group compared with the moderately affected group (reprinted with permission from Englander et al [76]). R, right; L, left; A, anterior; P, posterior.

Because these babies are identified prenatally, CB collection can be planned in advance of delivery. Because of their small size, and perhaps their delivery by cesarean section, most autologous CB units were large enough to supply multiple doses. Thus, patients received up to four doses of autologous CB at approximately 2- to 6-month intervals (unpublished data). Although the efficacy of this approach is still under investigation, there have been no safety concerns. This indicates that repeated dosing of autologous CB is safe even in very young babies, and such a dosing scheme could be potentially advantageous for other neurologic conditions as well.

Cerebral palsy

Clinical studies evaluating the use of CB in children with cerebral palsy are ongoing in both the United States and Korea. In a safety study, we treated 184 infants and children with cerebral palsy (76%), congenital hydrocephalus (12%) and other brain injuries (12%) with intravenous autologous CB infusions [72]. Patients were treated in the outpatient clinic through a peripheral intravenous injection after a single dose of Tylenol, Benadryl and Solumedrol. Infusions contained a median of 2.0×10^7 total nucleated cells/kg (range, $0.1-13.3 \times 10^7$) and 0.7×10^5 CD34+ cells/kg (range, $0.04\text{-}6.4 \times 10^5$). Approximately 1.5% of patients had hypersensitivity reactions (ie, hives and/or wheezing) during the CB infusion that resolved after discontinuation of the infusion and outpatient medical management. With more than 3 years of follow-up, no additional adverse events have been reported, indicating that the procedure is safe. A randomized, double-blind, placebo-controlled study is in process to determine the efficacy of this approach. In this study, children ages 1 to 6 years are randomly assigned to the order in which they receive CB and placebo infusions, each given 1 year apart. Motor, cognitive and imaging studies are performed at baseline and 1 and 2 years to evaluate any differences between CB and placebo groups. Within each group, patients are stratified by age to determine if the time interval between injury and infusion affects response. The primary end point is improvement in motor function on standardized scales. Preliminarily, studies with the MRI biomarker of white matter connectivity have shown that clinical functional phenotype correlated with MRI findings through the use of whole-brain connectivity analysis (Figure 2) [73]. A similar study of allogeneic CB and erythropoietin was conducted in Korean children with cerebral palsy [74]. The investigators reported greater improvements in cognitive and select motor functions in children who received CB and erythropoietin versus control patients. There was no CB-only group for comparison.

Stroke

Most human studies of stem cells in adults who have had a stroke have used autologous BM cells [75,76]. Although no safety concerns have been identified, the

studies are too small to reliably assess efficacy. However, because the majority of adult stroke victims are elderly and critically ill after their injury, a CB-derived off-the-shelf therapy is an attractive alternative to autologous BM because it would avoid the need for a potentially risky BM harvest in these critically ill patients. Trials that use allogeneic cell sources are planned or underway. In these studies, cell sources will include MSCs derived from adipose tissue, bone marrow or umbilical cord, fetal neural stem cells and CB; patients may be treated in the acute or chronic setting (up to 5 years after stroke); and cells will be administered intravenously, intra-arterially or intracranially. In the only published series of four stroke patients (three ischemic, one hemorrhagic) treated with allogeneic MSCs isolated from umbilical cord, the procedure was safe and produced no adverse events [77]. In the patients with ischemic stroke, but not those with hemorrhagic stroke, MSC therapy was associated with improved neurological function as assessed by use of the modified Rankin scale.

Autism

The cause of autism is still the subject of much investigation, though a multifactorial etiology involving both genetic (ie, Rett syndrome, Fragile X, pathogenic copy number variants) and environmental factors is likely. The mechanism by which these factors interact and affect the developing brain, causing social, communication and, in some cases, cognitive impairment, are also unknown. With stem cell therapy emerging as potential treatment for other neurological conditions, the question of whether it might have a role in the treatment of autism has also been raised. In a mouse model of autism, animals that received intraventricular injections of human adipose-derived stem cells had decreased repetitive movements and improved social activity [78]. This finding, in conjunction with early observations of increased brain connectivity in young children with cerebral palsy receiving autologous CB infusions [73], generated the hypothesis that CB infusion may aid in the restoration of faulty neural connections in children with autism, thereby improving the clinical symptoms. Autologous CB and/or bone marrow treatment in children with autism is currently under investigation in several countries [70,79]. The manifestations of autism vary in both quality and severity in any given patient. Therefore, identifying both suitable subjects and reliable outcome measures that can objectively measure response to therapeutic interventions is both challenging and critical to conducting valid clinical trials of cell therapy in autism. Event-related potentials of word processing, obtained from EEG readings, have been correlated with receptive language, cognitive ability and adaptive behavior [80] and may be useful as an objective outcome. Functional MRI findings have also been associated with the autistic traits of auditory target detection, social target detection and executive deficits, which indicates that functional MRI may be useful as a biomarker of clinical response [81–83]. Clinical studies evaluating CB in children with autism are underway at Duke University in North Carolina, the Sutter Institute in California and in China. The first Duke study will focus on identifying the most appropriate outcome measures to be used as study end points in clinical trials of cellular therapies in children with autism.

Neurodegenerative diseases

As opposed to acute or developmental brain injuries, chronic neurodegenerative diseases are often characterized by preferential loss of a specific cell population. These diseases follow a slowly progressive course, typically preceded by an asymptomatic period during which damage is already occurring. In this class of diseases, neuroprotective therapies given early in the course of disease could potentially slow or halt disease progression, and neurorestorative therapies might ultimately focus on replacement of a specific cell type through regeneration techniques.

Cellular approaches to neurodegenerative diseases have been studied most extensively in Parkinson's disease, in which degeneration of primarily nigrostriatal dopaminergic neurons results in motor symptoms such as resting tremors, rigidity and hypokenisia. Cell replacement strategies have been attempted in more than 300 patients with Parkinson's disease through the use of intrastriatal implantation of fetal mesencephalic tissue, and several open-label trials suggest clinical benefit [84,85]. Given the limitations of the use of human fetal tissue, however, interest has grown in generating dopaminergic neurons from other cell sources. Neurons that express dopamine-related genes and demonstrate the ability to synthesize and release dopamine have been successfully derived from CB stem cells *in vitro* [25]. In hemi-parkinsonian rats, unmodified human umbilical cord MSCs injected into the striatum can improve behavioral symptoms, and this effect is enhanced by adenovirus-mediated vascular endothelial growth factor modification of the cells [86]. These studies indicate that CB has potential as a source of stem cells for cellular replacement strategies in Parkinson's disease.

CB cells have been evaluated in *in vitro* and *in vivo* models of Alzheimer's disease. Transgenic mice treated with CB-MSCs show a reduction in both microglial activation and β-amyloid deposits,

the pathologic signature of the disease [87]. CB-treated mice also demonstrate decreased cognitive impairment in functional assays [88] and an extended lifespan [89]. Although the mechanism is not entirely clear, it is possible that the CB cells mediate the microglial response to β-amyloid deposits, promote β-amyloid phagocytosis and/or prevent apoptosis of host cells. Neurostem, a CB-MSC product, has been investigated in a phase I trial in Korea, although results of that study have not yet been published.

Amyotrophic lateral sclerosis (ALS), a neurodegenerative disease characterized by a loss of upper and lower motor neurons, is another condition that may be responsive to cellular therapy. Although the exact mechanism of neuronal loss has not been identified, neuro-inflammation, including astrocyte and microglial activation, has been shown to play a role. In ALS, cellular therapies could potentially act as modifiers of the inflammatory state, thereby promoting longer survival of motor neurons. CB has been investigated in a mouse model of ALS. Given as a single large (25×10^6 cells) dose, CB mononuclear cells delivered intravenously delayed the onset of disease in presymptomatic mice and extended survival by 20% to 25% [90]. When smaller doses (1 or 2.5×10^6 cells/dose) were administered to presymptomatic or early symptomatic animals at weekly intervals, disease progression was again delayed and survival was prolonged [91]. CB cells were detected throughout the brain and spinal cord but concentrated in the ventral horn gray matter of the spinal cord, an area known to be affected by ALS. In the ventral horns, the number of microglia and reactive astrocytes were decreased in mice treated with CB cells, and the number of motor neurons were increased in mice who began treatment presymptomatically or at the higher dose (2.5×10^6 cells/dose) once symptoms had developed. In addition to demonstrating that CB cells can modulate neuro-inflammation and prolong host neuron survival, the experiment also highlights the fact that cell dose and timing are important factors to optimize the effectiveness of cellular therapies for neurological conditions.

Summary

Until recently, the mature human brain was thought to be static. We now know that the adult human brain retains some capacity for self-renewal, though it is intrinsically quite limited. In the context of brain injuries, stem cell therapy may play both a neuroprotective role by dampening the inflammatory response, particularly in the acute setting, as well as a reconstructive role by enhancing the brain's repair mechanisms. A cellular therapy that could reduce the neurological sequelae of brain injury in adults would be truly revolutionary and have public health ramifications, given the high prevalence of these conditions. Because of its relative availability, favorable safety profile and pluripotential nature, CB is a prime source of stem cells for such therapies.

Unlike the adult brain, the exponential growth and continued development of a child's brain from the fetal period through early childhood has long been recognized. The developing brain exhibits remarkable plasticity, as evidenced by the rapidity and propensity with which young children can acquire and hone new skills. Although this ongoing development makes the immature brain particularly susceptible to injury, it may also provide a greater opportunity to affect repair. In the acute setting, mechanisms of neural protection and early repair are likely to be similar in children and adults. However, if stem cell therapy can be harnessed to modulate the developing brain's intrinsic plasticity, then the therapeutic window may be much wider in children, extending the potential benefits to the many children who do not exhibit neurological symptoms of their brain injury until months to years after the injury occurred. As the mechanisms by which cells affect brain plasticity are further defined, they may also be applicable to injuries in the adult brain, providing additional tools to further enhance recovery and/or extend the therapeutic window for repair.

For many of the conditions discussed in this article, long-term engraftment of CB cells may not be necessary to produce the desired effects. There is mounting preclinical evidence that cellular therapies act through paracrine and trophic mechanisms of cell signaling to enhance neuroprotection and restoration. In that case, allogeneic CB cells provide a readily available source of well-characterized cells for such applications. The use of allogeneic cells, however, does raise some additional questions regarding how long donor cells must survive in the patient to exert their effects, whether immunosuppression is necessary to enable donor cell survival for that duration and what the risk of graft-versus-host disease would be in these scenarios. Observations in immunocompetent, xenogeneic models are encouraging in this regard.

Neurological injuries are typically associated with permanent and life-long disabilities, hefty expenses and a lack of therapeutic options to prevent or repair tissue damage. Much work remains to be done in preclinical and clinical studies to further define efficacy, dose, route, timing and need for immunosuppression before cell-based therapies can be routinely

used in the clinic. Nonetheless, cellular therapies, particularly those that use CB cells, have great potential to significantly advance the treatment of patients with acquired and genetic brain diseases.

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References

[1] Broxmeyer HE, Douglas GW, Hangoc G, Cooper S, Bard J, English D, et al. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. Proc Natl Acad Sci U S A 1989;86:3828–32.

[2] Broxmeyer HE, Srour EF, Hangoc G, Cooper S, Anderson SA, Bodine DM. High-efficiency recovery of functional hematopoietic progenitor and stem cells from human cord blood cryopreserved for 15 years. Proc Natl Acad Sci U S A 2003;100:645–50.

[3] van de Ven C, Collins D, Bradley MB, Morris E, Cairo MS. The potential of umbilical cord blood multipotent stem cells for nonhematopoietic tissue and cell regeneration. Exp Hematol 2007;35:1753–65.

[4] Broxmeyer HE, Lee MR, Hangoc G, Cooper S, Prasain N, Kim YJ, et al. Hematopoietic stem/progenitor cells, generation of induced pluripotent stem cells, and isolation of endothelial progenitors from 21- to 23.5-year cryopreserved cord blood. Blood 2011;117:4773–7.

[5] Takenaka C, Nishishita N, Takada N, Jakt LM, Kawamata S. Effective generation of iPS cells from CD34+ cord blood cells by inhibition of p53. Exp Hematol 2010;38:154–62.

[6] Zaehres H, Kogler G, Arauzo-Bravo MJ, Bleidissel M, Santourlidis S, Weinhold S, et al. Induction of pluripotency in human cord blood unrestricted somatic stem cells. Exp Hematol 2010;38:809–18.e801–2.

[7] Chen N, Newcomb J, Garbuzova-Davis S, Davis Sanberg C, Sanberg PR, Willing AE. Human Umbilical Cord Blood Cells Have Trophic Effects on Young and Aging Hippocampal Neurons in Vitro. Aging Disease 2010;1:173–90.

[8] Kogler G, Sensken S, Airey JA, Trapp T, Muschen M, Feldhahn N, et al. A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. J Exp Med 2004;200:123–35.

[9] Waclawczyk S, Buchheiser A, Flogel U, Radke TF, Kogler G. In vitro differentiation of unrestricted somatic stem cells into functional hepatic-like cells displaying a hepatocyte-like glucose metabolism. J Cell Physiol 2010;225:545–54.

[10] Greschat S, Schira J, Kury P, Rosenbaum C, de Souza Silva MA, Kogler G, et al. Unrestricted somatic stem cells from human umbilical cord blood can be differentiated into neurons with a dopaminergic phenotype. Stem Cells Dev 2008;17:221–32.

[11] Bieback K, Kern S, Kluter H, Eichler H. Critical parameters for the isolation of mesenchymal stem cells from umbilical cord blood. Stem Cells 2004;22:625–34.

[12] Lee OK, Kuo TK, Chen WM, Lee KD, Hsieh SL, Chen TH. Isolation of multipotent mesenchymal stem cells from umbilical cord blood. Blood 2004;103:1669–75.

[13] Kang XQ, Zang WJ, Bao LJ, Li DL, Xu XL, Yu XJ. Differentiating characterization of human umbilical cord blood-derived mesenchymal stem cells in vitro. Cell Biol Int 2006;30:569–75.

[14] Lu LL, Liu YJ, Yang SG, Zhao QJ, Wang X, Gong W, et al. Isolation and characterization of human umbilical cord mesenchymal stem cells with hematopoiesis-supportive function and other potentials. Haematologica 2006;91:1017–26.

[15] Lu FZ, Fujino M, Kitazawa Y, Uyama T, Hara Y, Funeshima N, et al. Characterization and gene transfer in mesenchymal stem cells derived from human umbilical-cord blood. J Lab Clin Med 2005;146:271–8.

[16] Park KS, Lee YS, Kang KS. In vitro neuronal and osteogenic differentiation of mesenchymal stem cells from human umbilical cord blood. J Vet Sci 2006;7:343–8.

[17] Bosch J, Houben AP, Radke TF, Stapelkamp D, Bunemann E, Balan P, et al. Distinct differentiation potential of "MSC" derived from cord blood and umbilical cord: are cord-derived cells true mesenchymal stromal cells? Stem Cells Dev 2012;21:1977–88.

[18] de Mara CS, Duarte AS, Sartori-Cintra AR, Luzo AC, Saad ST, Coimbra IB. Chondrogenesis from umbilical cord blood cells stimulated with BMP-2 and BMP-6. Rheumatol Int 2013;33:121–8.

[19] Hess DA, Craft TP, Wirthlin L, Hohm S, Zhou P, Eades WC, et al. Widespread nonhematopoietic tissue distribution by transplanted human progenitor cells with high aldehyde dehydrogenase activity. Stem Cells 2008;26:611–20.

[20] Gang EJ, Jeong JA, Hong SH, Hwang SH, Kim SW, Yang IH, et al. Skeletal myogenic differentiation of mesenchymal stem cells isolated from human umbilical cord blood. Stem Cells 2004;22:617–24.

[21] Gao F, Wu DQ, Hu YH, Jin GX, Li GD, Sun TW, et al. In vitro cultivation of islet-like cell clusters from human umbilical cord blood-derived mesenchymal stem cells. Transl Res 2008;151:293–302.

[22] Tracy E, Aldrink J, Panosian J, Beam D, Thacker J, Reese M, et al. Isolation of oligodendrocyte-like cells from human umbilical cord blood. Cytotherapy 2008;10:518–25.

[23] Jeong JA, Gang EJ, Hong SH, Hwang SH, Kim SW, Yang IH, et al. Rapid neural differentiation of human cord blood-derived mesenchymal stem cells. Neuroreport 2004;15:1731–4.

[24] Tracy ET, Zhang CY, Gentry T, Shoulars KW, Kurtzberg J. Isolation and expansion of oligodendrocyte progenitor cells from cryopreserved human umbilical cord blood. Cytotherapy 2011;13:722–9.

[25] Fallahi-Sichani M, Soleimani M, Najafi SM, Kiani J, Arefian E, Atashi A. In vitro differentiation of cord blood unrestricted somatic stem cells expressing dopamine-associated genes into neuron-like cells. Cell Biol Int 2007;31:299–303.

[26] Sun W, Buzanska L, Domanska-Janik K, Salvi RJ, Stachowiak MK. Voltage-sensitive and ligand-gated channels in differentiating neural stem-like cells derived from the nonhematopoietic fraction of human umbilical cord blood. Stem Cells 2005;23:931–45.

[27] Lee MW, Moon YJ, Yang MS, Kim SK, Jang IK, Eom YW, et al. Neural differentiation of novel multipotent progenitor cells from cryopreserved human umbilical cord blood. Biochem Biophys Res Commun 2007;358:637–43.

[28] Lee OK, Ko YC, Kuo TK, Chou SH, Li HJ, Chen WM, et al. Fluvastatin and lovastatin but not pravastatin induce neuroglial differentiation in human mesenchymal stem cells. J Cell Biochem 2004;93:917–28.

[29] Jin W, Xing YQ, Yang AH. Epidermal growth factor promotes the differentiation of stem cells derived from human umbilical cord blood into neuron-like cells via taurine induction in vitro. In Vitro Cell Dev Biol Anim 2009;45:321–7.

[30] Naujock M, Stanslowsky N, Reinhardt P, Stemeckert J, Haase A, Martin U, et al. Molecular and functional analyses of motor neurons generated from humad cord blood derived inducted pluripotent stem cells. Stem Cells Dev 2014;23: 3011–20.
[31] Huang CJ, Butler AE, Moran A, Rao PN, Wagner JE, Blazar BR, et al. A low frequency of pancreatic islet insulin-expressing cells derived from cord blood stem cell allografts in humans. Diabetologia 2011;54:1066–74.
[32] Gussoni E, Bennett RR, Muskiewicz KR, Meyerrose T, Nolta JA, Gilgoff I, et al. Long-term persistence of donor nuclei in a Duchenne muscular dystrophy patient receiving bone marrow transplantation. J Clin Invest 2002;110: 807–14.
[33] Bliss T, Guzman R, Daadi M, Steinberg GK. Cell transplantation therapy for stroke. Stroke 2007;38(2 Suppl):817–26.
[34] Llado J, Haenggeli C, Maragakis NJ, Snyder EY, Rothstein JD. Neural stem cells protect against glutamate-induced excitotoxicity and promote survival of injured motor neurons through the secretion of neurotrophic factors. Mol Cell Neurosci 2004;27:322–31.
[35] Vendrame M, Gemma C, de Mesquita D, Collier L, Bickford PC, Sanberg CD, et al. Anti-inflammatory effects of human cord blood cells in a rat model of stroke. Stem Cells Dev 2005;14:595–604.
[36] Borlongan CV, Hadman M, Sanberg CD, Sanberg PR. Central nervous system entry of peripherally injected umbilical cord blood cells is not required for neuroprotection in stroke. Stroke 2004;35:2385–9.
[37] Arien-Zakay H, Lecht S, Bercu MM, Tabakman R, Kohen R, Galski H, et al. Neuroprotection by cord blood neural progenitors involves antioxidants, neurotrophic and angiogenic factors. Exp Neurol 2009;216:83–94.
[38] Carmichael ST. Plasticity of cortical projections after stroke. Neuroscientist 2003;9:64–75.
[39] Chen J, Zhang ZG, Li Y, Wang L, Xu YX, Gautam SC, et al. Intravenous administration of human bone marrow stromal cells induces angiogenesis in the ischemic boundary zone after stroke in rats. Circ Res 2003;92:692–9.
[40] Taguchi A, Soma T, Tanaka H, Kanda T, Nishimura H, Yoshikawa H, et al. Administration of CD34+ cells after stroke enhances neurogenesis via angiogenesis in a mouse model. J Clin Invest 2004;114:330–8.
[41] Shen LH, Li Y, Chen J, Zhang J, Vanguri P, Borneman J, et al. Intracarotid transplantation of bone marrow stromal cells increases axon-myelin remodeling after stroke. Neuroscience 2006;137:393–9.
[42] Beam D, Poe MD, Provenzale JM, Szabolcs P, Martin PL, Prasad V, et al. Outcomes of unrelated umbilical cord blood transplantation for X-linked adrenoleukodystrophy. Biol Blood Marrow Transplant 2007;13:665–74.
[43] Prasad VK, Mendizabal A, Parikh SH, Szabolcs P, Driscoll TA, Page K, et al. Unrelated donor umbilical cord blood transplantation for inherited metabolic disorders in 159 pediatric patients from a single center: influence of cellular composition of the graft on transplantation outcomes. Blood 2008;112:2979–89.
[44] Boelens JJ. Trends in haematopoietic cell transplantation for inborn errors of metabolism. J Inherit Metab Dis 2006;29: 413–20.
[45] Staba SL, Escolar ML, Poe M, Kim Y, Martin PL, Szabolcs P, et al. Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. N Engl J Med 2004;350:1960–9.
[46] Provenzale JM, Escolar M, Kurtzberg J. Quantitative analysis of diffusion tensor imaging data in serial assessment of Krabbe disease. Ann N Y Acad Sci 2005;1064:220–9.
[47] Martin PL, Carter SL, Kernan NA, Sahdev I, Wall D, Pietryga D, et al. Results of the cord blood transplantation study (COBLT): outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with lysosomal and peroxisomal storage diseases. Biol Blood Marrow Transplant 2006;12:184–94.
[48] Escolar ML, Poe MD, Provenzale JM, Richards KC, Allison J, Wood S, et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med 2005;352:2069–81.
[49] Mezey E, Key S, Vogelsang G, Szalayova I, Lange GD, Crain B. Transplanted bone marrow generates new neurons in human brains. Proc Natl Acad Sci U S A 2003;100: 1364–9.
[50] Cogle CR, Yachnis AT, Laywell ED, Zander DS, Wingard JR, Steindler DA, et al. Bone marrow transdifferentiation in brain after transplantation: a retrospective study. Lancet 2004;363:1432–7.
[51] Kurtzberg JKB, Stephens C, Snyder EY. Umbilical cord blood cells engraft and differentiate in neural tissues after human transplantation. Biol Blood Marrow Transplant 2003;9:128–9.
[52] Boelens JJ, Wynn RF, O'Meara A, Veys P, Bertrand Y, Souillet G, et al. Outcomes of hematopoietic stem cell transplantation for Hurler's syndrome in Europe: a risk factor analysis for graft failure. Bone Marrow Transplant 2007; 40:225–33.
[53] Martin HR, Poe MD, Provenzale JM, Kurtzberg J, Mendizabal A, Escolar ML. Neurodevelopmental outcomes of umbilical cord blood transplantation in metachromatic leukodystrophy. Biol Blood Marrow Transplant 2013;19: 616–24.
[54] Vendrame M, Cassady J, Newcomb J, Butler T, Pennypacker KR, Zigova T, et al. Infusion of human umbilical cord blood cells in a rat model of stroke dose-dependently rescues behavioral deficits and reduces infarct volume. Stroke 2004;35:2390–5.
[55] Chen J, Sanberg PR, Li Y, Wang L, Lu M, Willing AE, et al. Intravenous administration of human umbilical cord blood reduces behavioral deficits after stroke in rats. Stroke 2001; 32:2682–8.
[56] Meier C, Middelanis J, Wasielewski B, Neuhoff S, Roth-Haerer A, Gantert M, et al. Spastic paresis after perinatal brain damage in rats is reduced by human cord blood mononuclear cells. Pediatr Res 2006;59:244–9.
[57] Nan Z, Grande A, Sanberg CD, Sanberg PR, Low WC. Infusion of human umbilical cord blood ameliorates neurologic deficits in rats with hemorrhagic brain injury. Ann N Y Acad Sci 2005;1049:84–96.
[58] Li Y, Chen J, Wang L, Lu M, Chopp M. Treatment of stroke in rat with intracarotid administration of marrow stromal cells. Neurology 2001;56:1666–72.
[59] Shen LH, Li Y, Chen J, Zacharek A, Goa Q, Kapke A, et al. Therapeutic benefit of bone marrow stromal cells administered 1 month after stroke. J Cereb Blood Flow Metab 2007;27:6–13.
[60] Willing AE, Lixian J, Milliken M, Poulos S, Zigova T, Song S, et al. Intravenous versus intrastriatal cord blood administration in a rodent model of stroke. J Neurosci Res 2003;73:296–307.
[61] Yang B, Migliati E, Parsha K, Schaar K, Xi X, Aronowski J, et al. Intra-arterial delivery is not superior to intravenous delivery of autologous bone marrow mononuclear cells in acute ischemic stroke. Stroke 2013;44:3463–72.
[62] Reitz M, Demestre M, Sedlacik J, Meissner H, Fiehler J, Kim SU, et al. Intranasal delivery of neural stem/progenitor cells: a noninvasive passage to target intracerebral glioma. Stem Cells Transl Med 2012;1:866–73.

[63] Wei N, Yu SP, Gu X, Taylor TM, Song D, Liu XF, et al. Delayed intranasal delivery of hypoxic-preconditioned bone marrow mesenchymal stem cells enhanced cell homing and therapeutic benefits after ischemic stroke in mice. Cell Transplant 2013;22:977–91.
[64] Derrick M, Drobyshevsky A, Ji X, Tan S. A model of cerebral palsy from fetal hypoxia-ischemia. Stroke 2007;38 (2 Suppl):731–5.
[65] Ji XTE, Drobyshevsky A, Derrick M, Yu L, Liu A, Cotten M, et al. Do Human Umbilical Cord Blood Cells Improve Outcome in a Fetal Rabbit Model of Cerebral Palsy? Pediatric Academic Society 2009. EPAS2009:3455.11.
[66] Chua CO, Chahboune H, Braun A, Dummula K, Chua CE, Yu J, et al. Consequences of intraventricular hemorrhage in a rabbit pup model. Stroke 2009;40:3369–77.
[67] Yang WZ, Zhang Y, Wu F, Min WP, Minev B, Zhang M, et al. Safety evaluation of allogeneic umbilical cord blood mononuclear cell therapy for degenerative conditions. J Transl Med 2010;8:75.
[68] Dongmei H, Jing L, Mei X, Ling Z, Hongmin Y, Zhidong W, et al. Clinical analysis of the treatment of spinocerebellar ataxia and multiple system atrophy-cerebellar type with umbilical cord mesenchymal stromal cells. Cytotherapy 2011;13:913–7.
[69] Jin JL, Liu Z, Lu ZJ, Guan DN, Wang C, Chen ZB, et al. Safety and efficacy of umbilical cord mesenchymal stem cell therapy in hereditary spinocerebellar ataxia. Curr Neurovasc Res 2013;10:11–20.
[70] Lv YT, Zhang Y, Liu M, Qiuwaxi JN, Ashwood P, Cho SC, et al. Transplantation of human cord blood mononuclear cells and umbilical cord-derived mesenchymal stem cells in autism. J Transl Med 2013;11:196.
[71] Cotten CM, Murtha AP, Goldberg RN, Grotegut CA, Smith PB, Goldstein RF, et al. Feasibility of Autologous Cord Blood Cells for Infants with Hypoxic-Ischemic Encephalopathy. J Pediatr 2014;164:973–9.
[72] Sun J, Allison J, McLaughlin C, Sledge L, Waters-Pick B, Wease S, et al. Differences in quality between privately and publicly banked umbilical cord blood units: a pilot study of autologous cord blood infusion in children with acquired neurologic disorders. Transfusion 2010;50:1980–7.
[73] Englander ZA, Pizoli CE, Batrachenko A, Sun J, Worley G, Mikati MA, et al. Diffuse reduction of white matter connectivity in cerebral palsy with specific vulnerability of long range fiber tracts. Neuroimage Clin 2013;2:440–7.
[74] Min K, Song J, Kang JY, Ko J, Ryu JS, Kang MS, et al. Umbilical cord blood therapy potentiated with erythropoietin for children with cerebral palsy: a double-blind, randomized, placebo-controlled trial. Stem Cells 2013;31:581–91.
[75] Bang OY, Lee JS, Lee PH, Lee G. Autologous mesenchymal stem cell transplantation in stroke patients. Ann Neurol 2005;57:874–82.
[76] Mendonca ML, Freitas GR, Silva SA, Manfrim A, Falcao CH, Gonzales C, et al. [Safety of intra-arterial autologous bone marrow mononuclear cell transplantation for acute ischemic stroke]. Arq Bras Cardiol 2006;86:52–5.
[77] Jiang Y, Zhu W, Zhu J, Wu L, Xu G, Liu X. Feasibility of delivering mesenchymal stem cells via catheter to the proximal end of the lesion artery in patients with stroke in the territory of the middle cerebral artery. Cell Transplant 2013; 22:2291–8.
[78] Ha S, Kim HJ, Joo Y, Suh YH, Chang KA. Therapeutic effects of human adipose-derived stem cells in VPA-induced autism mouse model. Neuroscience. 2013. Poster 50.01/Q57.
[79] Sharma A, Gokulchandran N, Sane H, Nagrajan A, Paranjape A, Kulkarni P, et al. Autologous bone marrow mononuclear cell therapy for autism: an open label proof of concept study. Stem Cells Int 2013;2013:623875.
[80] Kuhl PK, Coffey-Corina S, Padden D, Munson J, Estes A, Dawson G. Brain responses to words in 2-year-olds with autism predict developmental outcomes at age 6. PLoS One 2013;8:e64967.
[81] Dichter GS, Felder JN, Bodfish JW. Autism is characterized by dorsal anterior cingulate hyperactivation during social target detection. Soc Cogn Affect Neurosci 2009;4:215–26.
[82] Gomot M, Belmonte MK, Bullmore ET, Bernard FA, Baron-Cohen S. Brain hyper-reactivity to auditory novel targets in children with high-functioning autism. Brain 2008; 131(Pt 9):2479–88.
[83] Shafritz KM, Dichter GS, Baranek GT, Belger A. The neural circuitry mediating shifts in behavioral response and cognitive set in autism. Biological Psychiatry 2008;63:974–80.
[84] Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. N Engl J Med 2001;344: 710–9.
[85] Olanow CW, Goetz CG, Kordower JH, Stoessl AJ, Sossi V, Brin MF, et al. A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease. Ann Neurol 2003;54:403–14.
[86] Xiong N, Zhang Z, Huang J, Chen C, Jia M, Xiong J, et al. VEGF-expressing human umbilical cord mesenchymal stem cells, an improved therapy strategy for Parkinson's disease. Gene Ther 2011;18:394–402.
[87] Nikolic WV, Hou H, Town T, Zhu Y, Giunta B, Sanberg CD, et al. Peripherally administered human umbilical cord blood cells reduce parenchymal and vascular beta-amyloid deposits in Alzheimer mice. Stem Cells Dev 2008;17:423–39.
[88] Darlington D, Deng J, Giunta B, Hou H, Sanberg CD, Kuzmin-Nichols N, et al. Multiple low-dose infusions of human umbilical cord blood cells improve cognitive impairments and reduce amyloid-beta-associated neuropathology in Alzheimer mice. Stem Cells Dev 2013;22: 412–21.
[89] Ende N, Chen R, Ende-Harris D. Human umbilical cord blood cells ameliorate Alzheimer's disease in transgenic mice. J Med 2001;32:241–7.
[90] Garbuzova-Davis S, Sanberg CD, Kuzmin-Nichols N, Willing AE, Gemma C, Bickford PC, et al. Human umbilical cord blood treatment in a mouse model of ALS: optimization of cell dose. PLoS One 2008;3:e2494.
[91] Garbuzova-Davis S, Rodrigues MC, Mirtyl S, Turner S, Mitha S, Sodhi J, et al. Multiple intravenous administrations of human umbilical cord blood cells benefit in a mouse model of ALS. PLoS One 2012;7:e31254.