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Treating childhood traumatic brain injury with autologous stem cell therapy

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Abstract

Introduction—Neonatal traumatic brain injury (TBI) is a significant cause of developmental disorders. Autologous stem cell therapy may enhance neonatal brain plasticity towards repair of the injured neonatal brain.

Areas Covered—The endogenous neonatal anti-inflammatory response can be enhanced by biological treatments. Stem cell therapy stands as a robust approach for sequestering the inflammation-induced cell death in the injured brain. Here, we discuss the use of umbilical cord blood cells and bone marrow stromal cells for acute and chronic treatment of experimental neonatal TBI. Autologous stem cell transplantation may retard and possibly even halt this neuroinflammation-plagued secondary cell death. Clinical translation of this stem cell therapy will require identifying the therapeutic window post-injury and harvesting ample supply of transplantable autologous stem cells. Stem cell banking with access to cryopreserved cells may allow readily available transplantable cells in addressing the unpredictable nature of neonatal TBI. Harnessing the anti-inflammatory properties of stem cells is key in combating the progressive neurodegeneration after the initial injury.

Expert Opinion—Combination treatments, such as with hypothermia, may enhance the therapeutic effects of stem cells. Stem cell therapy has potential as stand-alone or adjunctive therapy for treating neuroinflammation associated with acute and progressive stages of neonatal TBI.

Keywords

Traumatic brain injury; Neuroinflammation; Neuroplasticity; Hypoxic ischemic encephalopathy; Neonatal; Stem cells; Umbilical cord blood cells; Bone marrow stromal cells; Autologous

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Declaration of Interest

CV Borlongan has patent applications related to stem cell therapy with Athersys Inc., Saneron CCEL, and SanBio Inc. The authors have no other 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 apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose

1. Introduction to traumatic brain injury and stem cells

Traumatic brain injury (TBI) causes abnormal neurological function and may involve a direct blow to the head, but TBI-like pathology may present following indirect injury to the head (as in blast wave insults), as well as in impaired vascular injuries arising from genetic, environmental, viral and toxin-mediated alterations, such as that found in neonatal hypoxia-ischemic encephalopathy (HIE). One major landmark of TBI is neuroinflammation, a process known to impact natural repair mechanisms and cause secondary cell death. TBI is often caused by acceleration (a process that occurs when the head moves and the brain is hit by the moving skull) deceleration (where the skull is stopped while the brain continues to move forward and collides with the skull). While TBI is most common in children (ages 0–4) and the elderly (65 and older), most research has focused on treating TBI in adults. Compared to adults or the elderly, neural plasticity (the innate ability of a developing brain to recover) of young children provides a natural remedy to TBI. However, recent studies show that childhood TBI often significantly impacts developing brains. The most common causes of childhood TBI are falls or drops (64% of ER visits), car crashes (40% of deaths in young children), and shaken baby syndrome (in infants 6 months or younger) [1]. A serious condition that may result from TBI is HIE, which presents as a malfunction of or damage to the brain caused by the obstruction of oxygenated blood flow and occurs in about 2.5/1000 normal births [1, 2]. With newborns, HIE causes severe neurological deficits and may prompt doctors to subject the babies to hypothermia [3]. While this treatment has shown some success in term births, it is chiefly effective only up to 6 hours after birth, associated with some adverse effects, and only decreases death or disability in babies by about 11% [3], thereby prompting investigations into novel treatments, such as stem cell therapy.

Stem cells are undifferentiated cells that can replicate even after periods of inactivity and can be induced to become cells with specific functions such as tissue cells and organ-specific cells [4,5]. The unique properties of stem cells provide the basis for their use as transplantable cells in treating many conditions and diseases. The most common form of stem cell therapy is the use of blood stem cells derived from the bone marrow to treat diseases and conditions of the blood and immune system [4]. Types of stem cells include embryonic, fetal, neonatal (e.g., placenta, umbilical cord blood and tissues, amnion fluid and tissues, Wharton jelly), and adult tissues [1–3]. Embryonic stem cells are derived from the inner cell mass of a blastocyst, an early stage of embryonic development [4]. Adult stem cells are undifferentiated somatic cells found throughout the body that remain undifferentiated to replenish dying and damaged tissues, an example is cells in the bone marrow [4]. Induced pluripotent stem cells are produced from differentiated somatic cells, which when exposed to stem cell inducing elements (i.e., oncogenic factors) can revert to naive cells with stem cell properties [4]. Stem cells can also fall into the categories of totipotent, pluripotent, and multipotent. Totipotent stem cells can divide and specialize into any body cell, while pluripotent stem cells can differentiate into any of the three germ layers: endoderm, mesoderm, and ectoderm [4, 5]. Multipotent stem cells have more limited differentiation potential, able to differentiate into many cells of one tissue, such as differentiation into multiple blood cells or different nervous cells [4]. Additionally, different approaches to transplant stem cells in CNS disorders have been investigated. Autologous

transplantation refers to a process by which stem cells are harvested from a patient than later returned to the patient for treatment [1, 4]. Allogeneic transplants differ in that stem cells are harvested from a donor (with similar immune system markers to the recipient) and transplanted to the recipient [1, 4]. Closely related family members are often the most effective allogeneic donors because their immune systems are the most similar to the recipients [1, 4]. Xenogeneic transplants are similar to allogeneic transplants in that there is a mismatch in the donor and the recipient, but xenogeneic transplants involve a donor of a different species than the recipient [1, 4].

Stem cell therapy is emerging as a promising treatment for many diseases and conditions, prominently brain injury and neurodegeneration. A major area of stem cell research is conducted around Traumatic Brain injury because of its general clinical prevalence and increased prevalence amongst military members. Stem cell therapy is being researched as a method of repairing neuronal loss caused by traumatic brain injury as well as a means of limiting the secondary cell death cascade that follows the injury. There is significant research in stem cell therapy for treatment of adult traumatic brain injury, but treatment of neonatal traumatic brain injury remains relatively underexplored.

2. Pathophysiology of neonatal TBI

Traumatic brain injury (TBI) occurs in neonates when a force to the head or brain impairs proper neurological function [1,2], although as noted above indirect insults may present with TBI-like pathology. The most common cause of neonatal TBI is shaken baby syndrome in which rapid acceleration and deceleration cause damage at the point of impact and at the opposite pole of the brain [1–3]. Sparse research on the topic of neonatal TBI shows that the neonates' young age allows for increased recovery due to the plasticity of the young brain. However, despite the neuroplastic immature brain, TBI at a young age can still produce negative effects on brain development with symptoms that can become evident during adulthood [6].

A well-documented characteristic of adult TBI is an increased inflammatory response following injury, a pathological feature not shared by neonatal TBI. Whereas in adult rodents the trend of inflammation post experimental TBI is associated with an increase in pro-inflammatory cytokines, neonatal animals exposed to a similar TBI model display a significant suppression of these cytokines [1]. The study examined the levels of 23 cytokines before and after TBI in neonatal rats, and a downregulation of 18 of 23 of the cytokines was observed. In the study, this downregulation of cytokines was proven to be localized to the brain because cytokine levels were not altered in the plasma. The downregulation of cytokines and resulting lack of inflammation in neonatal rats following TBI allows for an unhindered brain repair response.

Another study examined the effects of resveratrol in TBI inflicted mice in which the resveratrol group saw a decrease in IL-6 and IL-12 over a placebo group [7]. The study also found that the resveratrol treated mice showed decreased microglial activation over the placebo group. Microglia have been shown to play an important role in the inflammatory response following TBI as well as in the cascading secondary cell death [8]. Therefore, a

decrease in inflammatory cytokines, such as IL-6, as well as a decrease in microglial expression could help ameliorate the effects of secondary cell death following TBI. The neonatal “anti-inflammatory” response displayed in rats could lead to more successful cell proliferation and differentiation to reduce the effects of TBI [1]. In the adult rat TBI brain, the inflammatory response causes neuronal loss and limits the endogenous repair mechanisms [9].

The decrease in inflammation may explain why greater recovery can be seen in younger humans post TBI when compared to older counterparts. While improved outcomes have been shown for children who have sustained TBI over their adult counterparts, it has also been shown that increased age amongst children is correlated with improved outcomes [10]. The observed therapeutic effects of an anti-inflammatory response in neonatal rats following TBI could lead to the development of therapies assisting the repair mechanism in neonatal TBI patients. Further study of the anti-inflammatory response in neonates following TBI could assist in the treatment of adult TBI. Since TBI rat neonates exhibit dampened “pro-inflammatory cytokines,” further enhancing such neuroprotective response may lead to robust acute and stable chronic functional benefits during development and in adulthood. In contrast, adult rats display a heightened inflammatory response, a pathological condition that would be more difficult to arrest compared to neonates [1].

Based on the observed endogenous anti-inflammatory response, further enhancing this regenerative process by exogenous delivery of anti-inflammatory agents may improve the therapeutic outcome. One such agent, pomalidomide was shown to mitigate TNF-α generation as well as significantly lowering numbers of degenerating neurons when compared to a control in a rat model of TBI [11]. Similarly, Minocycline and Exendin-4 had ameliorating effects on thalamic and hippocampal degeneration respectively [12–13]. When Exendin-4 was examined in a TBI rat model as a treatment pre-and post-injury, it prevented TBI induced impairments in object recognition memory 7 days post injury, as well as thirty days, post injury. The experimenters concluded that the Exendin-4 treatment ameliorated damages to the mouse brain circuits caused by the secondary effects of tissue damage triggered by the blast shockwave. Additionally, signaling/pathological events triggered by TBI were amenable to beneficial manipulation by treatment with Extendin-4 [13]. Minocycline, which has been shown to exert anti-inflammatory properties, had positive effects on recognition memory in a rat model of TBI nine weeks post injury [14]. Minocycline treatment was able to successfully attenuate the ensuing cognitive decline following TBI in a lasting manner [15], which may be mediated by reduced corpus callosum and striatal atrophy, ventriculomegaly, astrogliosis, and microglial activation. These anti-inflammatory agents have potential as TBI treatment, with a focus on hindering the secondary cell death process associate with neonatal TBI. A key challenge, but equally may be an advantage of drug administration in neonates pertains to the early developmental stage of the neonatal brain, which is more plastic and likely more susceptible to drug treatment allowing robust endogenous neurogenesis and entry of substanes from periphery to the brain due to an immature blood brain barrier. Since neonatal TBI presents with multiple cell death processes, finding a drug with multipronged action may be optimal in sequestering this neurodegeneration. Stem cells may serve as a biologic that may act like a drug that displays such multipronged properties.

3. Cell therapy for neonatal TBI

3.1 Advancing autologous stem cell therapy with UCBCs and BMSCs

Stem cell treatment has become a major area of study when dealing with TBI due to its potential to augment natural repair mechanisms post injury [1]. Stem cell therapy has shown beneficial effects in animal models of HIE because it can replace neurons, protect and promote host cells, and control the immune response [1, 2]. Because neonatal TBI shares some overlapping pathologies with HIE, treatments that show promise in HIE will likely exert similar therapeutic effects in neonatal TBI. Accordingly, there is potential for stem cell therapy to be effective in neonatal TBI based on the treatment's safe and effective profile in HIE. As mentioned earlier, the major stem cell types being investigated for therapeutic use are embryonic, fetal, neonatal, and adult tissues. In regard to TBI, two types of adult stem cells, umbilical cord blood cells (UCBCs) and bone marrow stromal cells (BMSCs), have shown promise in ameliorating TBI symptoms in preclinical trials. Both BMSCs and UCBCs are multipotent stem cells, meaning that they can differentiate into more than one type of cell but do not have the unlimited differentiation capabilities that pluripotent stem cells have. UCBCs are an attractive option for stem cell therapy in part due to the wide variety of cells they contain: most notably hematopoietic stem cells, endothelial progenitor cells, and mesenchymal stem cells (MSC) [16]. In particular, UCB-derived MSC may be an efficient treatment option, as they have been shown to differentiate into neural cell types and promote brain development [2, 16]. UCBCs may help patients afflicted with HIE to recover motor and neurological functions and may cause neurovascular cells to release both stimulatory and neurotrophic factors [2]. Regarding autologous UCBCs, immunosuppressive drugs may not be needed, but the cells are less likely to differentiate into neural cells [2]. Moreover, while immunosuppressive drugs are not required for autologous therapy, there is still a requirement for matching and the possibility of graft-versus-host disease occurring for allogeneic therapy. Accordingly, the use of immunosuppression and the need for donor-recipient major histocomaptibility complex matching will need more in-depth investigation for improving engraftment, and potentially cell differentiation.

UCBCs have shown great therapeutic potential in subjects with TBI, as they have been shown to decrease neuroinflammation and promote endogenous neurogenesis [17]. Similarly, BMSCs have been shown to interact with the host body to enhance the circulation of anti-inflammatory cytokines, decreasing inflammation post-TBI [18]. BMSCs appear to be a desirable treatment for neurological disorders for several reasons: they can pass through the blood brain barrier (BBB) fairly easily and differentiate into neuronal cell types, they can be derived from the individual in need of treatment (meaning they can be autologously transplanted), they have improved neurological deficits in a number of studies involving neonatal animals, and they are easier to obtain and culture than other types of stem cells (including UCBCS) [19–20]. BMSCs have proven successful in chronic stages of TBI in adult Wistar rats; one study found them to promote neurogenesis and differentiate into neurons [21]. More research is needed in order to transfer this data into a clinical setting. Another subdivision of stem cells is their origin: they are often allogeneic, autologous, or xenogeneic. Allogeneic stem cells are derived from different individuals of the same species, autologous stem cells are derived from the same individual using them, and xenogeneic stem

cells are derived from entirely different species. As expected, the host organism's immune response is strongest when using xenogeneic cells and weakest when using autologous cells [22]. Between the three, autologous transplantation does not require immunosuppressants, uses cells that are readily available, and is less ethically controversial [23]. Stem cell use in neonatal cases is appealing due to the high degree of plasticity of developing organs and because the developing immune systems of infants are less likely to reject exogenous stem cell transplantations. Delayed cord clamping is possibly the earliest opportunity for stem cell delivery and has the potential for prophylactic benefits. Delayed cord clamping allows the newborn human to receive an increased volume of hematopoietic cells which could facilitate potential salubrious effects on brain disorders for the newborn as well as in adulthood [24]. Neonatal TBI has several different pathological features than adult TBI, meaning that the conditions of stem cell transplantation may also differ.

Neonatal brain injuries are especially damaging because they cause disabilities later on in the afflicted individual's life that suggest ongoing damage. Instead of being a static injury, neonatal HIE causes chronic degeneration due to the interruption of developing neurons and neuronal networks [25]. In fact, brain regions connected to and or associated with injured regions often show chronic damage that may cause disabilities throughout the inflicted individual's life [3]. Regarding treatment, therapeutic effects differ between acute and chronic stages. As mentioned above, research points to UCBCs as a potential treatment for acute injury and BMSCs as a potential treatment for chronic injuries. After the initial injury occurs, necrosis and other primary cell death are often visible in the neonatal brain. However, researchers have shown transplanting UCBCs shortly after the initial insult can decrease apoptosis and oxidative stress in the neonatal brain [26]. UCBCs show potential in treating neonatal TBI cases because they can be easily transplanted through autologous means (reducing the possibility of infection or rejection) are readily available, and often have a high proliferative capacity [27]. While the proliferative capacity of stem cells is part of what makes them attractive treatment options, this property can also become tumorigenic if left unregulated [28]. Because neurons and connectivity continues to worsen after the acute-phase, treatment during the acute phase of injury has the potential to better the outcome of individuals afflicted with HIE. Conversely, transplantation of stem cells at chronic stages may be able to improve long term outcomes [3]. Several features of BMSCs point to them being a viable treatment in chronic stages of TBI: they can pass through the BBB, protect injured neurons from cell death, attenuate neuroprotective and neuroregenerative processes and reduce the formation of glial scars [29]. Nonetheless, without any adjunctive treatment, such as BBB permeabilizing agents (i.e., mannitol), stem cells are likely only able to reach the brain under conditions of compromised BBB, such as the pathological condition created by TBI. As researchers continue to uncover information about UCBCs and BMSCs, they remain key contenders for treatment in neonatal cases due to their ease to acquire, widespread benefits, and their potential to be transplanted through autologous means. Accordingly, we focus the subsequent sections to elucidating the therapeutic effects and mechanisms of action of UCBCs and BMSCs.

Many studies have been conducted on the use of cord blood cells in neonates. One study examined the effects of rat UCBCs in neonatal rats with HIE [26]. After induction of HIE in rat pups, the surviving pups were divided into three groups: a control group, a cell-treated

group, and a sham group treated with PBS. 21 days after injury, all three groups underwent a cylinder test and a rotarod test in order to examine behavior and motor abilities of injured rats. Results revealed that rat UCBCs reduced infarct volume and correlated with an improvement in motor functions. The mechanism of action of the UCBCs is not well-known, but many postulate that the cells work by inducing cell proliferation [2]. The efficacy of UCBCs has also been tested in newborn rabbits with cerebral palsy (CP) [2]. After the initial HIE (at 70% gestation), rabbits with mild to severe CP were assigned into one of the three treatment groups. One group received human umbilical cord blood cells (HUCBCs), one received media that transported the HUCBCs, and the third group was given a saline solution. After analyzing the results of phase one, phase two was initiated. In this phase, there were only two groups; one group received 2.5 × 10 cells and the other received a saline solution. Results focused on the following factors typical of CP: tone, posture, movement, righting, and dystonia. After completion of the two phases, researchers found that high dose HUCBCs (5.6 × 10 cells) cured abnormal phenotypes and resulted in improved motor functions while a lower dose (2.5 × 10 cells) improved symptoms but only to a lesser degree. In a clinical setting, one study provided evidence that autologous UCBCs improve the fate of human babies born with HIE [30]. Out of the 52 infants enrolled in the study, 23 were given UCBCs. A one-year survival rate of about 74% lead researchers to the conclusion that UCBCS has the potential to be a treatment option for babies born with HIE. More clinical research is needed before the cells can be used on a large scale, but results have been promising. Regarding the mechanism of action of the UCBCs, the researchers postulate that because few cells entered newborn brains, the effects are likely due to paracrine signaling instead of direct proliferation or integration [2]. The mechanism of action of stem cells is largely unknown. Many researchers, however, believe that stem cells act through paracrine signals, as the survival rate of implanted stem cells is often poor. This poor survival rate suggests the work of paracrine factors because the efficacy of the factors does not require cellular integration [20]. Because HIE is a type of brain injury, researchers have begun to extend such stem cell treatment to broader TBI models [1].

3.2 Harnessing inflammation via stem cell dose, route, and timing of delivery

Because brain insults, including HIE and TBI, cause a more rapid activation of microglia in neonatal cases than in adult cases, an inflammatory response from the immune system often occurs shortly after injury [8–9, 32–34]. While there is likely a narrow therapeutic window following the initial injury, it is postulated that targeting the initial inflammation (with treatments such as stem cells) may reduce the deficits caused by HIE and neonatal TBI [35–36]. Because inflammation often increases the initial damage and causes the injury to spread to neighboring neurons, targeting inflammation may be a key method for reducing the functional deficits associated with TBI [37]. Many factors contribute to the success of stem cell transplantation, including timing, route, and cell dosage. In terms of the timing of the stem cell therapy, injection upon injury (acutely) tends to lessen inflammation and cell death while injection at a later time (chronically) improves long-term function [35, 38–39]. Specifically, acute injuries tend to weaken the blood brain barrier (BBB), providing a narrow therapeutic window for injection of stem cells directly into the central nervous system (CNS) [35]. Acute treatment and injection are imperative for decreasing inflammation as well as ameliorating the secondary cell death cascade. By this attribute, acute injection displays

immediate therapeutic effects as well as lessening the need for potential chronic treatment [3, 40]. There is great potential for using acute and chronic injections in tandem through the use of booster shots to further attenuate the multi-faceted benefit of stem cells on brain injury. Stem cells can be injected directly into the site of injury, but research shows that this is not necessary [3, 41]. In many studies, stem cells transplanted at locations other than the injury prove successful due to the migration of the stem cells to the injured tissue [3]. Additionally, intravascular methods of stem cell delivery may be difficult in CNS disorders with intact BBBs [35]. Stem cells have been injected intravenously, directly into brain regions (i.e. intracerebral), or intra-arterially [28], and each injection route comes with advantages and disadvantages: intravenous injections are not very invasive but may be unable to surpass the BBB, intra-arterial injections is more invasive but has a higher probability of mobilizing cells across the BBB, while intracerebral injections display the highest degree of cell engraftment but are by far the most invasive. The anti-inflammatory effects seen with peripheral injections are likely due to the systemic dispersion of anti-inflammatory molecules that are not able to penetrate intact BBBs [35, 42–43]. However, such peripheral injections may show a greater degree of success in acute stages when the BBB is injured, allowing the anti-inflammatory molecules to more easily reach the CNS [35]. Furthermore, peripheral injections are most efficiently used early after the injury, as they pose less of a threat of damaging recently injured brain regions [35, 42]. With chronic inflammation, injecting stem cells directly into the brain may be most effective when dealing with chronic TBI, as the brain has had some period to heal while at the same time likely presenting with tapered chemoattractants to induce migration of stem cells from periphey [45–46]. Even though the efficacy of these methods differs in regards to the timing of injection, both may be done through autologous means in order to avoid rejection [28, 45]. Finally, cell dosage depends largely on the host's microenvironment. More studies are needed to determine general guidelines for cell dosages, but it is likely that the dosages will remain highly variable due to the varying pathologies that TBI injuries present. While the overarching goal is to use the least amount of cells and obtain the most benefits, certain conditions may require higher dosages. Stem cell transplantations often display low degrees of cell engraftment/survival. It is relatively unknown where the non-grafted stem cells end up, presenting another question for future studies [47]. Because neuroprotection has been observed in experiments with low rates of cell survival, transplanted stem cells may exert neuroprotection through trophic factors. Many of these trophic factors can likely cross intact BBBs, providing evidence that cell engraftment is not necessary for treatments to be effective. Because cell engraftment is not necessarily needed for neuroprotection, less invasive methods or even stem cell-free products will likely be sufficient in improving patient outcomes [48]. Accumulating evidence suggests that beneficial effects associated with stem cell therapy may come from factors or cell components released by the cells upon injection, such as exosomes and microvesicles, altogether advancing the concept of stem cell-free products as alternative sources for transplantation [39]. The advent of such stem cell-free products may allow reduction for the needed cell dose to achieve clinically effective outcomes.

4. Caveats and Future Directions

In neonatal TBI, when open wounds or skull fractures are not visible, early diagnosis can often be difficult as symptoms, such as excessive crying of the baby, are not unique to TBI. Similarly, symptoms of brain damage including TBI may not be apparent until the child begins to develop and mature behaviorally and cognitively. A current effective method for diagnosing neonatal TBI acutely is computer tomography (CT) scanning, however, doctors are often hesitant to submit the newborn to CT due to the risks associated with ionizing radiation [49]. As a result of the limited diagnosing ability, stem cell therapy may not feasible as an acute treatment. To make acute stem cell therapy effective, a method of diagnoses must be developed that does not harm the neonate. A possible area of development is in highly sensitive imaging technologies, such as quickbrain MRI, which removes the radiation concern [49–51].

Autologous stem cell transplantation in the neonate requires first harvesting of the cells. The therapeutic window is essential for acute treatment of neonatal TBI and the time associated with stem cell harvesting could prevent the use of stem cells as an acute neonatal TBI treatment. In order for stem cell treatment to be effective, a high concentration of stem cells must be harvested; the limited time frame presents a challenge for harvesting the appropriate amount of stem cells. Besides increasing the harvesting rate of the stem cells a possible alternative is the use of allogenic stem cell transplantation. This could include a system for storing stem cells such as UCBCs for use at a moment’s notice to treat neonatal TBI acutely [52]. Such storage and use of UCBCs does create ethical dilemmas surrounding ownership and consent. The ethical question raised here is does the mother or child maintain ownership of the UCBCs, considering that the child as a fetus is unable to give consent to fetal tissue collection, and therefore collection may present with ethical concerns [53]. Accordingly, more research must be done in the area of harvesting stem cells for autologous treatment. The use of BMSCs does not encounter the same ethical dilemmas as ownership is clear and informed consent is given before donation. The NIH Bone Marrow Stromal Cell Transplantation Center (BMSC TC) was created in 2008 to create an infrastructure for the manufacture of clinical grade human BMSCs and to facilitate the use of ex vivo expanded BMSCs for the treatment of patients in the clinical setting [54].

A key technical issue associated with stem cell transplantation in neonatal TBI is the ability of delayed treatments to reverse the chronic progression of the injury. The afflicted developing brain continues to be affected by the initial injury throughout development, raising the question of how to prevent this disastrous progression [55–56]. Because stem cells have been shown to induce neuroprotection and neuroregeneration, they may show potential in chronic stages of TBI [17, 55, 57]. Stem cell treatments are more effective in neonatal cases when given both three and ten days post injury (in regards to only three days after) [58]. The degree of stem cell interaction with the host may vary depending on the time of injection [58–59].

While certain stem cells (i.e. BMSCs) may be able to reduce inflammation, the mechanism of action for this anti-inflammatory property is unknown. As discussed in the preceding sections, while neuroinflammation after TBI is not fully understood, it is possibly a major

cause of chronic symptoms and disabilities [60]. Suppressing inflammation has been shown to decrease infarct size [60], but whether or not stem cell treatment alone can regulate inflammation enough to reverse and prevent chronic progression of TBI is yet to be determined. The lack of understanding on the anti-inflammatory properties of stem cells presents another issue that needs to be further addressed before approving stem-cell based treatments.

Additionally, most studies to date dealing with stem cells and neonatal brain disorders have focused on acute phases of TBI. However, focusing solely on immediate treatment poses a threat to infants who do not display symptoms of neurological impairment immediately. Unfortunately, there is little information to corroborate the efficacy of stem cell treatment six weeks or longer after neonatal TBI although stem cell transplants have been demonstrated to be effective in chronic stage in other diseases, such as stroke, HIE, and adult TBI. The ability of stem cells like BMSCs to deliver trophic factors may represent an alternative option for treating chronic diseases [61–62]. Because trophic factors are known to help neurons function, stem cells' ability to deliver them may help restore the injured brain long after the initial injury, in conjunction with stem cell-paved biobridges [62–64] and the elusive cell replacement-based regenerative medicine [28, 62–64]. Though the mechanism of action of stem cells is not clearly known, recent studies have posed the possibility of them working through a biobridge: a pathway that allows host neurogenic cells to travel to the site of injury and initiate endogenous repair mechanisms [63]. Stem cell transplantations are considered to be a key component of the formation of biobridges, as they create the biobridge that allows the migration and proliferation of host cells [64]. Biobridge formation shows promise in neuroregeneration in adult models of TBI and stroke, but it is currently unknown if biobridges are successful in chronic diseases characterized with high degrees of cell death [65]. Also, as previously mentioned, the majority of data about biobridges come from adult studies. To apply this concept to neonatal cases, there needs to be both animal and clinical studies examining the existence and efficiency of bio bridges in infants. Another possible mechanism of action of stem cells is cell replacement. Cell replacement has been a topic of interest for years, as many researchers believe that providing new neurons to the injured brain could significantly decrease disabilities following injury [66]. The idea of neuronal replacement has implications in chronic disorders, as studies have found neuronal replacement to occur in brains subjected to chronic conditions [67]. To date, cell replacement has most notably been scarcely demonstrated in adult PD models [68], indicating that more research will be needed to determine whether cell replacement mechanisms are suitable for neonatal TBI cases.

Currently, the only treatment that has been approved for neonatal brain injuries (especially HIE), is hypothermia. Hypothermia treatments often involve cooling the infant's body to 32–35 degrees celsius for 12–72 hours. This treatment requires immediate action (it's almost always used six hours or less after injury) and while it does decrease the risk of death and disability, the rate of survival is less than 60% [55]. Again, as we noted above, since HIE shares some pathologic similarities with neonatal TBI, the use of hypothermia may have some benefit in neonatal TBI. Indeed, hypothermia may benefit severe adult TBI cases, but more research is needed to translate these findings to neonatal cases [69]. In particular, adult mice exposed to hypothermia treatment improved cognitive functions by increasing neuronal

plasticity [70]. This finding may have implications in neonatal cases of TBI, as the neonatal brain is known to innately have a higher degree of plasticity than the adult brain [71]. Because of the limited therapeutic window of hypothermia treatment, another method is needed to improve the outcomes of neonatal TBI cases. Stem cell treatment can be delivered up to weeks after insult, making them a good candidate for hypothermia combination treatments. BMSCs, in particular, have been tested in brain injury models in combination with hypothermia. BMSCs are readily available (they can be obtained from neonatal tissues such as the placenta and umbilical cord), can survive in the host body up to weeks after transplantation, and have the potential to induce neuroprotection and neuroregeneration [72]. The differences between hypothermia treatment, stem cell treatment, and a combination of the two have been recently examined. Hypothermia alone reduced acute effects (such as primary cell death), but did little to help with long term damage [73]. Conversely, BMSC treatment was shown to increase long term prognosis [73]. The combination of the two treatments showed even more long term benefits than BMSC only treatment, suggesting that future studies are warranted to reveal the full potential of stem cell and hypothermia combination therapies when treating neonatal brain injuries [73]. One possible reason for the success displayed by the combination of hypothermia and BMSC injections is the enhanced neuroprotection displayed in the host brain. Hypothermia treatments have been shown to protect the brain against damage caused by HIE while BMSCs are believed to secrete neurotrophic factors that help with neurorestoration [74]. While combination therapies are strong candidates for treating neonatal brain injuries, more research is needed before the treatment can be used on a widespread basis.

5. Conclusions

TBI is a leading cause of neurological disabilities and one of the major causes of death in it infants. Despite the debilitating symptoms displayed by young patients suffering from these disorders, there are few treatment options available. Given the robust neuroplasticity inherent in the immature brain, neonatal TBI presents as an appealing therapeutic target for regenerative medicine. Whereas positive results in the laboratory have shown encouraging beneficial effects of stem cell therapy in adult TBI, more research is warranted to translating the potential of this cell-based regenerative medicine in neonatal TBI. At this time, the proof-of-concept of stem cell therapy in neonatal TBI is limited to adult animal models of TBI. It is also important to note that most available data come from animal studies, thus additional research and caution must be exercised in translating these results into the clinical setting. A key aspect of adult TBI is the inflammatory response that follows injury characterized by an increase in pro-inflammatory cytokines and microglial activation. In neonates, however, a downregulation of pro-inflammatory cytokines has been observed directly following injury. To this end, stem cells may serve as a promising option for enhancing and recapitulating the innate neonatal neuroprotective and neuroregenerative response. Optimizing stem cell therapy for neonatal TBI may need to be assessed in relation to the safety and efficacy of hypothermia, which is the current treatment for neonatal brain injury. While there are many types of stem cells, two promising sources are UCBCs and BMSCs due to their ease of acquisition and their robust therapeutic effects without adverse (e.g., tumorigenic) reactions. In particular, UCBCs and BMSCs may target inflammation,

thereby retarding or even halting the progression of the injury. While more research is needed before autologous stem cell therapy can become a clinical treatment option for neonatal brain injuries, it remains a potent approach because of its ability to decrease neuroinflammation and promote neuroprotection and neuroregeneration. Stem cell treatments alone may not completely block all cell death cascades of neonatal TBI, but using them in combination with other established therapies, such as hypothermia, may sequester secondary cell death mechanisms at multiple levels, thus improving the therapeutic outcomes.

6. Expert Opinion: Further Research is Necessary to Develop Treatment Options for Neonatal TBI

Neonatal brain injuries (specifically TBI and HIE) often cause death or severe disabilities throughout inflicted individuals' lives. The severity of these conditions calls for novel treatment options, as the only current option is hypothermia (which has severe limitations and is not always successful). Currently, neonatal TBI is a significant unmet disorder due to the limited amount of treatment options. Autologous stem cell therapy is a potential treatment option due to its ability to initiate neuroprotection and then neuroregeneration [2]. In particular, UCBCs and BMSCs present as efficacious and safe transplantable cells for treating neonatal brain injuries. Both types of stem cells have shown varying degrees of success in animal models of neonatal brain injury, providing evidence that they may also be effective in clinical settings.

A caveat in treating neonatal TBI involves the difficulties in diagnosing neonatal TBI, suggesting that research in this area is needed to identify the target patient candidates for stem cell therapy. Additionally, we discussed that uncertainties remain on the safety and efficacy outcomes of stem cell therapy in both adult and neonatal TBI, raising valid ethical concerns for rapid translation of this emerging therapy from bench to bedside. At this time, stem cell therapy is still an experimental treatment for many neurological disorders, including neonatal TBI, thus stem cell treatments in clinical application should be approached with extreme caution and careful assessment of preclinical studies.

Although several pathological mechanisms accompany neonatal TBI, neuroinflammation stands as a critical cell death pathway that exacerbates the disease progression, which interestingly can equally serve as a target for treatment. While acute inflammation is an innate response to external and internal injuries, sustained inflammation has been shown to cause neurodegeneration [17, 37, 74]. Because secondary cell death is closely associated with inflammation, harnessing the anti-inflammatory properties of stem cells may propel this regenerative property into a therapy for neonatal TBI. Stem cell treatments alone or in combination with other treatment options, such as hypothermia, may be able to slow down or stop the secondary cell death associated with neonatal TBI.

Much progress has been made in the field of stem cell research, but additional studies (both animal and clinical) are needed before treatment can proceed in the clinic. A major caveat in stem cell based treatments is the uncertainty regarding how these cells work. Molecular and cellular mechanisms such as biobridge formation, cell-replacement, regulation via trophic

factors, and more have all been suggested but there has yet to be concrete evidence elucidating the cells mode of action. This degree of uncertainty comes with dangers in clinical settings, as it is difficult to create a standard protocol for treatment without knowing the exact effects and mechanisms of the stem cells. Autologous stem cell therapy, which clearly avoids many stem cell graft rejection complications (76–80), has the potential to treat neonatal TBI through mechanisms that dampen the inflammatory response and subsequently minimizing the deleterious effects of the secondary cell death cascades accompanying the disease progression.

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*articles of interest

**articles of high interest

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Article highlights box

- Neonatal traumatic brain injury is a debilitating disorder that has limited therapeutic options
- Inflammation is a major pathological manifestation of the injured neonatal brain
- Regenerative medicine via stem cell therapy offers a novel treatment for the injured neonatal brain
- Autologous stem cell transplantation can sequester neuroinflammation, thereby reducing the secondary cell death damage associated with neonatal traumatic brain injury
- Translation of stem cell therapy from the laboratory to the clinic will need to consider optimal cell dose, timing, and route of cell delivery
- Enhanced therapeutic outcomes of cell therapy will likely be complemented by combination treatments, such as with hypothermia, altogether targeting the neuroinflammation-plagued neonatal traumatic brain injury