ABSTRACT: Tendon injuries affect all levels of athletic horses and represent a significant loss to the equine industry. Accumulation of microdamage within the tendon architecture leads to formation of core lesions. Traditional approaches to tendon repair are based on an initial period of rest to limit the inflammatory process followed by a controlled reloading program designed to promote the maturation and linear arrangement of scar tissue within the lesion. However, these treatment protocols are inefficient, resulting in prolonged recovery periods and frequent recurrence. Current alternative therapies include the use of bone marrow-derived mesenchymal stem cells (BMSC) and a population of nucleated cells from adipose containing adipose-derived mesenchymal stem cells (AdMSC). Umbilical cord blood-derived stem cells (UCB) have recently received attention for their increased plasticity in vitro and potential as a therapeutic aid. Both BMSC and AdMSC require expansion in culture before implantation to obtain a pure stem cell population, limiting the time frame for implantation. Collected at parturition, UCB can be cryopreserved for future use. Furthermore, the low immunogenicity of the UCB population allows for allogeneic implantation. Current research indicates that BMSC, AdMSC, and UCB can differentiate into tenocyte-like cells in vitro, increasing expression of scleraxis, tenascin c, and extracellular matrix proteins. When implanted, BMSC and AdMSC engraft into the tendon and improve tendon architecture. However, treatment with these stem cells does not decrease recovery period. Furthermore, the resulting regeneration is not optimal, as the resulting tissue is still inferior to native tendon. Umbilical cord blood-derived stem cells may provide an alternate source of stem cells that promote improved regeneration of tendon tissue. A more naïve cell population, these cells may have a greater rate of engraftment as well as an increased ability to secrete bioactive factors and recruit additional reparative cells. Further work should clarify the role of distinct stem cell sources in the regenerating tendon and the need for a naïve or differentiated cell type for implantation.

Key words: adipose, bone marrow, horse, stem cell, tendon, umbilical cord blood

INTRODUCTION

Tendons are elastic, dynamic structures that connect muscle to bone and function to facilitate movement, absorb shock, and in the case of the digital flexor tendons, support the distal limb. These fibrous structures can be cryopreserved for future use. Furthermore, the low immunogenicity of the UCB population allows for allogeneic implantation. Current research indicates that BMSC, AdMSC, and UCB can differentiate into tenocyte-like cells in vitro, increasing expression of scleraxis, tenascin c, and extracellular matrix proteins. When implanted, BMSC and AdMSC engraft into the tendon and improve tendon architecture. However, treatment with these stem cells does not decrease recovery period. Furthermore, the resulting regeneration is not optimal, as the resulting tissue is still inferior to native tendon. Umbilical cord blood-derived stem cells may provide an alternate source of stem cells that promote improved regeneration of tendon tissue. A more naïve cell population, these cells may have a greater rate of engraftment as well as an increased ability to secrete bioactive factors and recruit additional reparative cells. Further work should clarify the role of distinct stem cell sources in the regenerating tendon and the need for a naïve or differentiated cell type for implantation.

provide tensile strength during normal movement as well as during strenuous exercise. Acute tendon injury typically manifests as a core lesion and is often preceded by chronic degeneration and accumulation of microdamage, characterized by the loss of collagen fiber cross-linking. These injuries result in lameness, which requires substantial recovery time and carry a high risk of reinjury. In the United Kingdom, nearly one-half of all injuries in racehorses are related to failed tendon and ligament function (Pinchbeck et al., 2004). Fetlock support injuries, typically involving the superficial and/or deep digital flexor tendons, are the most common cause of musculoskeletal injury in racing Thoroughbreds (Stover and Murray, 2008). Core lesions in the digital flexor tendons are not unique to elite athletic horse
animals are prone to reinjury due to the formation of scar tissue within the lesion (Goodship et al., 1994). Animals are prone to reinjury due to the formation of fibrocartilage scar tissue (Clegg et al., 2007), which although strong is less elastic and therefore functionally inferior to normal tendon tissue. These changes in the capacity of the tendon to store energy and recoil affect the ability of the tendon to adapt and equally disperse the load, potentially creating microdamage leading to reinjury. Re-injury tends to occur in regions directly adjacent to the core lesion where normal tendon fascicles pull away from unforgiving scar tissue and increase the size of the lesion.

At present, efforts are aimed at promoting tendon regeneration and restricting scar formation, thereby reducing recovery time and costs as well as improving prognosis and decreasing the incidence of reinjury. The use of cell-based therapies has gained considerable attention from clinicians and owners based on primarily clinical use that supports the application of these cell populations for promoting tendon regeneration. However, there is a lack of conclusive data regarding specific culture, expansion, and treatment protocols. Although bone marrow-derived mesenchymal stem cells (BMSC) and adipose tissue-derived mesenchymal stem cells (AdMSC) are commonly used because they are easily obtained, umbilical cord blood-derived stem cells (UCB) are currently under investigation to determine if they possess a greater capacity to proliferate, differentiate, and/or promote tendon repair in comparison with other mesenchymal cell (MSC) populations.

**STEM CELL THERAPY**

Regenerative medicine is a growing field that uses naïve, undifferentiated stem cell populations to treat a variety of pathological states, ranging from metabolic and neurological disorders to musculoskeletal defects in humans and animals. The therapeutic potential of stem cells lies not only in their ability to contribute healthy, differentiated cells to a compromised tissue bed but also in their production of beneficial growth promoting factors and chemotactic recruitment of additional reparative cells. The precise in vivo effects of stem cells are as of yet undetermined but are likely dependent on the specific stem cell population, culture, and delivery methods and the tissue to which they are introduced. In the horse, BMSC and AdMSC have received the most attention as therapeutic aids in soft tissue repair.

**Bone Marrow-Derived Mesenchymal Stem Cells**

Isolation of BMSC (or mesenchymal stromal cells) has been occurring in research and medical practice for a number of years. In vivo, these cells support the formation of hematopoietic cells and aid in bone healing following fractures. The BMSC derived from humans, mice, and horses attach to culture plates and exhibit a fibroblast-like morphology when cultured in vitro. They represent a very small portion of the total cell population of the bone marrow; reported numbers vary from 0.001 to 0.01% (Pittenger et al., 1999). Expansion of equine BMSC requires a significant amount of time in culture, often 3 to 6 wk (Smith et al., 2003; Crovace et al., 2010; Caniglia et al., 2012; Godwin et al., 2012).

Mesodermal cell types, such as osteoblasts, chondrocytes, and adipocytes, are most commonly used to identify the capacity of a MSC population to differentiate. Common differentiation protocols can be used to elicit osteogenic, adipogenic, and chondrogenic differentiation of BMSC. Culture in osteogenic induction medium resulted in rapid mineralization and nodule formation as well as runt-related transcription factor 2 (runx2), type I collagen, osteopontin, and osteonectin expression (Pittenger et al., 1999; Meirelles and Nardi, 2003; Tropel et al., 2004; Vidal et al., 2006). Adipogenic differentiation resulted in the accumulation of lipid rich vacuoles and expression of PPARy2 and lipoprotein lipase (Pittenger et al., 1999; Meirelles and Nardi, 2003; Tropel et al., 2004; Vidal et al., 2006). Culture with transforming growth factor (TGF)-β in a micromass resulted in initiation of the chondrogenic program and expression of type II collagen and aggrecan and the formation of a proteoglycan-rich extracellular matrix (Pittenger et al., 1999; Tropel et al., 2004). Attempts to differentiate BMSC into tenocyte-like cells have been moderately successful. Human BMSC treated with growth and differentiation factor-5 result in the upregulation of collagen 1, scleraxis, and tenascin c transcripts (Tan et al., 2012). Equine BMSC isolated from a single horse expressed tenomodulin after 21 d of supplementation with bone morphogenic protein-12 (Violini et al., 2009). Furthermore, human BMSC transduced with a FLAG-tagged scleraxis increased transcription of decorin, tenomodulin, and collagen 1 compared with mock transduced cells (Alberton et al., 2012). Although these BMSC appear to be capable of adopting a tenogenic phenotype in vitro, whether or not these cells do so when implanted into a tendon lesion is, at this time, unknown.
**Adipose-Derived Stem Cells**

A population of stem cells can be liberated from subcutaneous adipose tissue by enzymatic digestion followed by filtration and centrifugation. Adherence to plastic and subsequent expansion produces a relatively homogenous population of AdMSC. Adipose-derived MSC are spindle shaped and morphologically similar to bone marrow-derived stem cells and UCB. Whereas major histocompatibility complex (MHC) class I surface markers are expressed on human and mouse AdMSC, they lack expression of MHC class II antigens (Yanez et al., 2006). Additionally, human AdMSC did not stimulate lymphocyte proliferation and, in fact, inhibited the proliferation of T cells stimulated with peripheral blood mononuclear cells, indicating that the cells would not cause an immune response if used autologously.

Adipose-derived MSC have been induced to differentiate into osteogenic, adipogenic, chondrogenic, and tenogenic cell types (Gronthos et al., 2001; Katz et al., 2005; Wagner et al., 2005; Guilak et al., 2006; Oedayrissaingh-Varma et al., 2006; Liu et al., 2007; Yoshimura et al., 2007; Mehlhorn et al., 2009; Zhu et al., 2009). Comparison of human AdMSC and BMSC indicates that AdMSC are less efficient at osteogenic differentiation, despite considerable similarity in gene expression throughout the differentiation process (Liu et al., 2007). Adipogenic differentiation was observed following treatment with insulin and 3-isobutyl-1-methylxanthine (IBMX; Gronthos et al., 2001; Katz et al., 2005; Guilak et al., 2006; Oedayrissaingh-Varma et al., 2006; Liu et al., 2007; Yoshimura et al., 2007). Cells formed lipid vacuoles and secreted leptin. Culture in chondrogenic differentiation media containing TGF-β led to the expression of proteoglycans and type II collagen (Guilak et al., 2006; Liu et al., 2007; Yoshimura et al., 2007). However, the AdMSC are again less efficient at chondrogenesis, producing less collagen 2α1 (Col2a1), chondroitin sulfate, and hyaluronan than BMSC, at least in rats (Yoshimura et al., 2007). Canine AdMSC co-cultured with primary tenocytes or cultured in the presence of IGFI and TGF-β increased expression of scleraxis, decorin, tenomodulin, collagen 1, and collagen 3 transcripts (Schneider et al., 2011). Supplementation with growth differentiation factor-5 increased glycosaminoglycan and hydroxyproline content in cultured rat AdMSC as well as increased scleraxis, tenomodulin, collagen 1, and aggrecan mRNA abundances (Park et al., 2010). Work in our laboratory indicates that culture in matrigel may be sufficient to initiate tenogenic differentiation. Equine AdMSC cultured in 30% matrigel increased expression of scleraxis and tenascin c (Reed and Johnson, 2013), possibly due to the presence of a complex, 3-dimensional extracellular matrix that promotes growth of AdMSC in colonies and initiates changes in cell to cell contact.

**Umbilical Cord Blood-Derived Stem Cells**

Umbilical cord blood-derived stem cells are isolated from umbilical cord blood collected at parturition and further purified by centrifugation through a density gradient, such as Ficoll. These cells are adherent in plastic cultureware, exhibit a fibroblast-like appearance, and have the ability to proliferate although they are contact inhibited. Umbilical cord blood-derived stem cells have been successfully isolated from humans, sheep, pigs, dogs, and horses and appear to maintain the same basic characteristics across species (Bieback et al., 2004; Lee et al., 2004b; Fuchs et al., 2005; Zhao et al., 2006; Koch et al., 2007; Kumar et al., 2007; Reed and Johnson, 2008). Although the explicit protein markers of UCB remain elusive, most reports agree that this population is negative for cluster of differentiation molecule (CD) 34, CD45, and MHC class II and only weakly positive for MHC class I (Lee et al., 2004a). The absence of CD34 and CD45 indicates a nonhematopoietic lineage. The minor expression of MHC classes I and II indicate the lack of immunogenicity of this cell type. Additionally, a mixed lymphocyte reaction indicated that human UCB did not stimulate lymphocyte proliferation, consistent with low levels of immunogenicity (Zhao et al., 2006). The presence of octamer-binding transcription factor 4 (Oct-4), NANOG, tumor rejection antigen 1-60 (Tra1-60), tumor rejection antigen 1-81 (Tra1-81), stage-specific embryonic antigen 3 (SSEA-3), and stage specific embryonic antigen 4 (SSEA4) in equine and human UCB indicates a naïve phenotype (Baal et al., 2004; Reed and Johnson, 2008).

In an effort to determine the plasticity of UBC in relation to other stem cell populations, in vitro differentiation protocols have been performed. Umbilical cord blood-derived stem cells have been successfully differentiated into cells from all 3 germ layers; however, differentiation into osteoblasts, chondrocytes, and adipocytes is most commonly used to measure plasticity of MSC. Maturation of UCB into bone and cartilage is routinely achieved. Both human and equine UCB have been differentiated into cells capable of producing calcium deposits stained by von Kossa and Alizarin Red (Kogler et al., 2004; Koch et al., 2007; Reed and Johnson, 2008). Transcription of osteopontin, osteocalcin, osteonectin, Runx2, and type I collagen has been reported in these cells (Kogler et al., 2004; Koch et al., 2007; Reed and Johnson, 2008). Culture of human UCB in media containing dexamethasone and bone morphogenic protein-2 resulted in morphological changes from spindle shaped cells to cuboidal cells in 20 d coupled with increased alkaline phosphatase and type I collagen expression (Hildebrandt et al., 2009). However, it has been noted by some researchers that UCB that differentiate into osteoblasts do not take on the cuboidal
appearance typical of bone marrow-derived osteoblasts (Goodwin et al., 2001).

Chondrogenesis is commonly achieved by culture in a 3-dimensional micromass environment in the presence of TGF-β. Chondrogenic masses derived from human and equine UCB react positively with alcian blue and safranin O, indicating the presence of glycosaminoglycans typical of cartilage (Kogler et al., 2004; Koch et al., 2007; Reed and Johnson, 2008). Further analysis of these cells reveals transcription of cartilage paired-class homeobox protein 1 (cart-1), Col2a1, SRY (sex determining region) box-9 (Sox9), and chondroadherin (Kogler et al., 2004; Koch et al., 2007; Reed and Johnson, 2008). Ovine UCB from blood collected at 80 to 120 d of gestation formed tissue reminiscent of hyaline cartilage when placed on a construct of biodegradable polyglycolic acid polymer treated with poly-L-lactic acid solution and coated with collagen. After 12 wk in a bioreactor in permissive medium, marked chondrogenic differentiation was apparent, presenting characteristics of hyaline cartilage and staining positively for safranin O and toluidine blue. Type II collagen was primarily expressed with little type I collagen present and no type X collagen (Fuchs et al., 2005).

It has been noted that UCB present much less obvious adipogenic differentiation than do BMSC or AdMSC (Wagner et al., 2005; Rebelatto et al., 2008). When treated with insulin and the phosphodiesterase inhibitor, 3-isobutyl-1-methyl-xanthine, UCB obtained lipid vacuoles identified by Oil Red O (Kogler et al., 2004; Koch et al., 2007; Godwin et al., 2012). Bieback et al. (2004) could not obtain adipocytes after culture of human UCB in induction medium containing dexamethasone, IBMX, insulin, indomethacin, and fetal calf serum. No lipid vacuoles were formed in UCB despite the appearance of lipid vacuoles in BMSC treated in a parallel culture. However, continuous culture in induction medium for 5 wk did result in some adipogenic differentiation. Similarly, only sporadic fat cells containing limited amounts of lipid droplets were evident in equine UCB cell cultures after 21 d in adipocyte induction media (Reed and Johnson, 2008). Lee et al. (2004b) achieved adipogenic differentiation but only after the addition of rabbit serum to the induction medium. Kern et al. (2006) reported a failure of human UCB to induce differentiation into adipocytes, even following 5 wk of culture.

The ability of UCB to differentiate into tenocytes has only recently received attention. Work from our laboratory indicates that when equine UCB are cultured in 30% matrigel, scleraxis transcripts are increased (Reed and Johnson, 2013). This increase is inhibited by supplementation with fibroblast growth factor-2. No increase in tenasin c transcripts occurred, regardless of substrata or fibroblast growth factor supplementa-

tion, indicating a less differentiated phenotype when compared with equine AdMSC cultured under identical conditions. Cells cultured in matrigel formed compact colonies with filopodia extending into the surrounding matrix. The 3-dimensional environment, changes in cell to cell contact or the interaction with extracellular matrix components of the matrigel (i.e., entactin, laminin, and collagen IV) may be responsible for the upregulation of the tenocyto genes.

**STEM CELLS IN TENDON INJURY**

Use of any stem cell population as a therapeutic aid in the regenerating tendon requires careful consideration of a number of factors, including the use of a delivery agent or matrix, co-delivery of growth factors, timing of the implantation, and number of cells implanted. Whereas granulation tissue and the enclosed nature of core lesions may provide an appropriate scaffold, delivery agents, such as platelet rich plasma, serum, bone marrow supernatant, matrigel, fibrin glue, or synthetic polymers, may improve stem cell retention at the site of the injury. Furthermore, different matrices may provide topographical and mechanical cues to the cells, directing differentiation to specific mature cell types. Growth factors delivered with the stem cells may provide direction to the cells but may also stimulate native stem or other reparative cell populations. Timing of the implantation should be carefully considered as well. Cells may be injected into the lesion during the inflammatory or regenerative phase of repair. Certainly one might hypothesize that earlier implantation would offer greater benefits to the healing tendon by reducing inflammation, recruiting native stem cells, and promoting production of collagen and other extracellular matrix proteins. However, different stem cell populations are likely to promote tissue regeneration by unique mechanisms and therefore one administration protocol might not be applicable to all stem cell types. Furthermore, ideal cell numbers for implantation must be identified and are likely dependent on the relative size of the lesion and type of cell implanted, precluding extrapolation from other stem cell populations. To date, few dose–response studies have been completed. The remainder of this review will focus on the use of BMSC and AdMSC in tendon injuries and the potential for UCB as a therapeutic aid.

Bone marrow-derived stem cells have been used to treat equine tendon lesions with some success. Several reports indicate improved results using equine BMSC injections compared with traditional treatment programs (Smith et al., 2003; Crovace et al., 2007, 2010; Pacini et al., 2007; Guest et al., 2008; Godwin et al., 2012). No negative immune response was reported using autologous or allogeneic equine BMSC injections into
core superficial digital flexor tendon lesions (Smith et al., 2003; Pacini et al., 2007; Guest et al., 2008). Labeled equine BMSC integrated into tendon, assuming tenocyte-like morphology (Guest et al., 2008); however, a low efficiency (0.001%) of engraftment was reported. Equine embryonic stem cells exhibited greater levels of engraftment, indicating a more naïve cell may promote engraftment (Guest et al., 2010). Furthermore, fetal-derived equine embryonic-like stem cells engrafted into collagenase-induced tendon lesions and improved tendon architecture after 8 wk (Watts et al., 2011). Twenty days after implantation of human BMSC into a patellar tendon defect in rats, treated tendons exhibited spindle shaped cells among collagen fibers aligned in parallel (Hankemeier et al., 2007). These data indicate that BMSC can indeed engraft into damaged tendon tissue at appropriate locations.

The benefit of implanted BMSC in tendon repair appears to occur via increased collagen production and improved organization of collagen fibers. Autologous equine BMSC transplanted into collagenase-induced superficial digital flexor tendon lesions decreased the lesion size as a percentage of total tendon cross-sectional area, improved collagen fiber orientation, and expressed greater levels of collagen 1 protein (Crovace et al., 2007, 2010). One month following injection, greater tendon density was apparent in horses injected with BMSC compared with uninjected control horses and after 6 mo, and tendons appeared almost completely repaired (Pacini et al., 2007). In rabbits, biomechanical properties, including stiffness, maximum force, and maximum stress, were all improved in tendons receiving a gel sponge seeded with autologous rabbit BMSC (Juncosa-Melvin et al., 2006). In a patellar tendon defect, rabbit BMSC seeded collagen composite implants strengthened tendons over natural repair (Awad et al., 2003). However, 28% of these grafts showed formation of ectopic bone. Bone-free tendons exhibited improved biomechanics, with increased maximum force, stiffness, and strain energy after 26 wk of recovery. Values reported for cell seeded grafts were intermediate to naturally repaired tissue and normal, healthy tissue indicating an improvement but not return to completely native state. The improvement in biomechanical properties was also reported by Young et al. (1998), who implanted autologous rabbit BMSC into a gap defect model in the gastrocnemius tendon of the rabbit. Treated repairs were stiffer and withstood more force and energy than control repairs but were still weaker than normal tissue. The area of the treated repair declined at a significantly faster rate than control repairs. Horses treated with autologous equine BMSC for tendon repair returned to racing with no further reinjury more than 2 yr after diagnosis (Pacini et al., 2007). Control horses from the same study showed fibrosis during the healing process and all were reinjured within 12 mo after the initial diagnosis. Furthermore, in a study of National Hunt and flat race horses treated with autologous equine BMSC, only 27% of horses were reinjured in the 2 yr following the initial injury, significantly less than the 56% of horses reported for the conservative treatment of controlled exercise and hyaluronan or polysulfated glycosaminoglycans (Dyson, 2004; Godwin et al., 2012). The presented studies indicate that although BMSC can improve tendon architecture, the regenerated tendon is still inferior to native tissue indicating that implantation protocols can be further optimized. Furthermore, no decrease in recovery time has been noted with use of BMSC.

Adipose-derived MSC and adipose-derived mononuclear cells also have been investigated as an alternate source of cells for tendon repair. Adipose-derived nucleated cells improved collagen fiber linearity, uniformity, and crimp patterns and overall tendon architecture when implanted into collagenase-induced lesions but resulted in no differences in the rate or quality of repair after 6 wk of recovery (Nixon et al., 2008). The implanted population contained AdMSC as well as fibroblasts and other nucleated cells. No adverse reaction was apparent following implantation. Of 16 horses with tendon lesions treated with equine AdMSC and platelet rich plasma, 14 returned to work and remained active over the 2-yr follow-up period (Del Bue et al., 2008). One horse receiving AdMSC and platelet rich plasma could not return to work due to chronic tendonitis. In a rabbit deep digital flexor tendon injury model, intratendinous injection of allogeneic adipose stromal vascular fraction cells improved yield loads as well as energy absorption compared with controls, indicating improved tendon function (Behfar et al., 2012).

Currently, there are no reports of UCB use in tendon repair; however, based on in vitro data, these cells may be capable of improving tendon regeneration following injury. The ability of UCB to express scleraxis indicates that these cells can differentiate into naïve tenocytes. Further differentiation may require an in vivo environment that provides exposure to temporally and quantitatively appropriate bioactive factors but also to the mechanical stresses induced by movement of the tendon. Umbilical cord blood-derived stem cells may also exhibit improved engraftment compared with AdMSC and BMSC, as the more naïve embryonic stem cell population showed better rates of engraftment compared with adult stem cell populations (Guest et al., 2010).

**SUMMARY AND CONCLUSIONS**

Stem cells certainly hold great promise for the treatment of tendon and other soft tissue injuries in the horse.
However, the current lack of empirical data on the requirements of the regenerating tendon and the actions of implanted stem cell populations limit our ability to make informed decisions regarding the optimal tissue source and dosage of stem cells, delivery agent, inclusion of growth factors, and timing of implantation. Future work should determine if naïve cells remain in the regenerating tendon as stem cells, if they differentiate into tenocytes and produce collagen and other extra cellular matrix proteins, or some combination thereof. Additionally, the secretion and role of chemotactic and other bioactive or immunomodulatory factors should be examined.

Although the discussion of the wide variety of scaffold available for use during implantation is beyond the scope of this review, critical evaluation of possible substrata and matrices should be considered. It is clear that culture conditions, including substrata, affect gene expression and lineage decisions and that this differs among stem cell populations. The delivery agent used to implant stem cells may help retain cells at the site of the injury but also may provide instructural signals that direct differentiation. As such, the choice the delivery agent should be carefully considered, recognizing that the effect of each agent may differ among stem cell populations.

Although BMSC have received the most attention and are thus the best characterized, isolation of these cells requires significant time (i.e., 3 to 6 wk) in culture. This lag time prevents earlier use of these cells, which may prove to be suboptimal. In the horse, current use of AdMSC is coupled with other nucleated cells isolated from the fat pad. Importantly, the stem cell population in this fraction is quite low (i.e., <5% in humans); therefore, the benefits derived from this treatment may be due to other factors in addition to the stem cells (Jurgens et al., 2008). Umbilical cord blood-derived stem cells have no lag time in culture as they are isolated and cultured at birth. These cells are capable of differentiation into immature tenocytes and have low immunogenicity, making them an ideal candidate for allogeneic implantation. Controlled studies are needed to further characterize both MSC and UCB and, more importantly, to document their actions in vivo. This knowledge will be directive in determining the best implantation practices, including time of implantation following injury, requirement of specific scaffolds, and inclusion of growth factors or other trophic factors with the implanted cells.

LITERATURE CITED


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