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MINIREVIEWS

Adult stem cells in neural repair: Current options, limitations and perspectives

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Abstract

Stem cells represent a promising step for the future of regenerative medicine. As they are able to differentiate into any cell type, tissue or organ, these cells are great candidates for treatments against the worst diseases that defy doctors and researchers around the world. Stem cells can be divided into three main groups: (1) embryonic stem cells; (2) fetal stem cells; and (3) adult stem cells. In terms of their capacity for proliferation, stem cells are also classified as totipotent, pluripotent or multipotent. Adult stem cells, also known as somatic cells, are found in various regions of the adult organism, such as bone marrow, skin, eyes, viscera and brain. They can differentiate into unipotent cells of the residing tissue, generally for the purpose of repair. These cells represent an excellent choice in regenerative medicine, every patient can be a donor of adult stem cells to provide a more customized and efficient therapy against various diseases, in other words, they allow the opportunity of autologous transplantation. But in order to start clinical trials and achieve great results, we need to understand how these cells interact with the host tissue, how they can manipulate or be manipulated by the microenvironment where they will be transplanted and for how long they can maintain their multipotent state to provide a full regeneration.

Key words: Stem cells; Stem cell therapy; Adult stem cells; Neural stem cells; Bone marrow stem cells; Mesenchymal stem cells; Olfactory ensheathing cells

Core tip: Adult stem cells are useful tools to treat various diseases, but we must first comprehend how they work to use their capacity at maximum. Ageing, inflammation, other stem cells of the host tissue and the co-transplantation with another stem cells type can change their profile and compromise the regeneration process. Having these barriers in mind, several researchers started to look more closely to adult stem cells. In this review we will show some interesting results from experimental and clinical trials at this group of stem cells.

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INTRODUCTION

Stem cells represent a promising step for the future of regenerative medicine. As they are able to differentiate into any cell type, tissue or organ, these cells are great candidates for treatments against the worst diseases that defy doctors and researchers around the world.

Stem cells can be divided into three main groups: (1) embryonic stem cells, which are cells of the inner layer of the blastocyst and form the three primary germ layers (ectoderm, mesoderm and endoderm); (2) fetal stem cells, which are found in the embryo and form the various organs of the human body; fetal stem cells include neural crest cells, hematopoietic cells, fetal mesenchymal stem cells, fetal neural stem cells and pancreatic islet progenitors; and (3) adult stem cells, which are found in various regions of the adult organism, such as bone marrow, skin, eyes, viscera and brain (adult stem cells are also known as somatic stem cells).

In terms of their capacity for proliferation, stem cells are also classified as totipotent, pluripotent or multipotent. Totipotent stem cells have a high capacity for differentiation and can form a complete individual, but they lack the capacity for self-renewal. Pluripotent cells, on the other hand, are capable of differentiating into any of the 200 or more kinds of cells that make up the human body. Finally, multipotent cells give rise to cells of a specific tissue, *e.g.*, hematopoietic stem cells give rise to blood cells, while neural stem cells give rise to neurons and glia[1,2]. Another group of stem cells that has been extensively studied in recent years includes induced pluripotent stem cells (IPS). IPS cells are adult differentiated cells that return to their pluripotent state by genetic engineering mechanisms. Some researchers believe these cells have great potential, but there have been numerous reports of extensive epigenetic and transcriptome aberrations with these cells, as well as tumor formation[3,4].

ADULT STEM CELLS

Adult stem cells are multipotent cells that can differentiate into unipotent cells of the residing tissue, generally for the purpose of repair. These cells can be obtained from several different regions of the adult organism, they can be used for autologous transplantation and their great advantage resides in the fact that embryos do not have to be destroyed in order for these cells to be obtained[5,6].

Regardless of the cell type chosen, there is a relative degree of difficulty in extracting viable stem cells from their *in vivo* niche. There is approximately one hematopoietic stem cell for every 10000 bone marrow cells, and one mesenchymal stem cell for every 10000-100000 cells[7]. For this reason, researchers use substances that can stimulate the growth of these cell populations as well as facilitate the process by which they are obtained. For example, G-CSF (granulocyte stimulating factor) stimulates the production of $CD34^+$ hematopoietic stem cells that can be extracted by simple puncture of peripheral blood, which is less invasive than bone marrow aspiration. Other substances that enhance the isolation of adult stem cells are currently under investigation[8].

Another issue of concern is the cell senescence related to the expansion time *in vitro*. Cell proliferation is decreased mainly due to telomerase activity, and several researchers have focused on telomerase activation in an attempt to increase and maintain population growth *in vitro*. However, it focusing only on correcting the shortened telomeres is not sufficient, and studies should focus on the role of other factors that participate in telomere maintenance, which may also play an important role in cell differentiation[9].

Senescence of adult organisms has to be considered, given that cell function, potency and replication decrease with time, while mutations may increase. In the case of the nervous system, mutations may result in neuronal loss, abnormal cell function, increased neuronal longevity (resulting in an even greater accumulation of mutations) and decreased regenerative capacity after an injury. These findings have been reported in studies investigating cell proliferation during learning: while young animals showed better performance than older animals, pharmacological stimulation in the older animals led to improved performance, with the newborn neurons integrating into the existent neural circuits[10-12]. Moreover, the aging of stem cell niches may contribute to the aging of stem cells, changing the organism's regulatory microenvironment, which in turn influences the aging process of other cells. To summarize can be quoted the influence of protein p53 expression levels: when expressed at low levels, it contributes to stem cell metabolic maintenance, but when expressed at high levels, it decreases the number of stem cells by inducing cell death, and the role of energetic metabolism and the production of reactive oxygen species that acts directly in stem cell niches[13].

Another important feature of stem cells is their immunomodulatory power, which allows them to "feel" the environment and change their patterns of migration, interaction and survival. When transplanted into the lesion site, some stem cells interact with the proinflammatory environment, migrate to the site of injury and differentiate into the required cell type in order to effect repair. Moreover, some stem cells play an important role in the proliferation and migration of new cells to the site of injury. This helper profile has

been observed in neural stem cells and mesenchymal stem cells. In the case of mesenchymal stem cells, this function can play an important role in changing the macrophage proinflammatory profile into a proregenerating role, once there is no longer an urgent need for a robust immune response[14-16].

Understanding the biology of stem cells and their niches, as well as the mechanisms involved in their multipotent state, are basic criteria to achieve great experimental results and to take the next step towards clinical trials.

MESENCHYMAL STEM CELLS/BONE MARROW STEM CELLS

The bone marrow is the only organ in which two different types of stem cells coexist: the bone marrow stem cell (BMC, also called hematopoietic stem cell) and the mesenchymal stem cell (MSC, also called mesenchymal stromal cell). Bone marrow cells are responsible for generating blood cells, while mesenchymal stromal cells are responsible for supporting hematopoietic progenitors by regulating the niche microenvironment and by facilitating the maturation of blood cells. Mesenchymal cells can also be extracted from adipose tissue, umbilical cord, skin and placenta[17,18].

Experimental studies have shown that MSCs can survive and migrate to the lesion site, prevent astrogliosis and microglial activation, and delay the loss of motoneurons. A comparative study between BMCs and MSCs showed that BMCs are relatively more effective in motor function recovery and have a higher survival rate[18,19]. In clinical trials with BMCs, authors reported motor and sensory improvement, as well as improvement in patients' quality of life, with some being able to sit again and even get dressed with partial assistance[19-23]. MSCs also showed great results when transplanted with T cells, controlling inflammatory activity in order to create the proper microenvironment for cell transplantation[24]. The immunomodulating effect of MSCs has also been reported in other clinical trials and MSCs have been shown to play an important role as immunomodulators and angiogenic agents in drug resistant patients as well as in patients with cerebral palsy, critical limb ischemia and kidney transplants[25-32]. In another study conducted with 40 patients, bone regeneration was achieved when a great number of $CD34^+$ cells were transplanted to the lesion site, 20 patients achieved mature bone regeneration, even in the group that received a low number of cells 4 patients achieved bone regeneration. However, when transplanted together with MSCs, these cells were able to use paracrine and autocrine cross-talk up-regulation to achieve bone regeneration[33].

Despite these positive results, several side effects were reported when MSCs from adipose tissue were administered *via* the cephalic vein, including chest pain and tightness, mild fever, furuncle on the upper thigh, musculoskeletal pain, painful neck and shoulder, increased sputum, upper respiratory infection, urinary incontinence, urinary tract infection, aggravation of spasticity, neuropathic pain, pain exacerbation, headache, low thyroid stimulating hormone and somnolence[34].

OLFACTORY ENSHEATHING CELLS

Neurogenesis in the olfactory system continues to take place even in the adult. Stem cells proliferate in the subventricular zone of the forebrain, generating neural progenitors that migrate to the olfactory bulb to create new interneurons. If an injury occurs, these neurons are immediately replaced through a surge in neurogenesis. Olfactory ensheathing cells (OECs) surround the axons of the sensory neurons in the olfactory epithelium and form synapses in the olfactory bulb in the brain. Due to their ability to guide the connections between the peripheral nervous system and the central nervous system, as well as their ability to differentiate into non-olfactory cell types, these cells are excellent candidates for cell transplantation[35]. These multipotent cells have been extensively studied in cases of spinal cord injury, and authors have reported that transplants were safe and patients experienced motor and sensory improvement, as well as recovered bladder function and activity of several muscles below the injury level[36,37]. In an amyotrophic lateral sclerosis (ALS) clinical trial conducted with OECs in China, researchers reported that patients experienced no benefits, two patients had severe side effects and one even died following transplantation[38]. One theory contends that OECs should be transplanted together with neural stem cells in order to potentiate the growth of neural processes. OECs have been shown to stimulate axon regeneration by secreting growth factors, axon guidance molecules and basement membrane components. They also aid in tissue repair by effecting structural remodeling and support, modulating the immune system, enhancing neurotrophic and antigenic stimuli and metabolizing toxic macromolecules. Finally, OECs may be transplanted together with growth factor (*e.g.*, bFGF, or basic fibroblast growth factor) to sustain cell survival and proliferation[39-41].

NEURAL STEM CELLS

Neural stem cells were first described by Altman in 1960 and have the potential to differentiate into any cell type in the central nervous system[42-45]. It is known that adult neurogenesis occurs in two brain regions, the subventricular and subgranular zones of the dentate gyrus, and the spinal cord[45].

Neural stem cells have been used to treat several neurologic conditions such as spinal cord injury, ALS, Parkinson's disease, traumatic brain injury, Huntington'

Table 1 Adult stem cells transplantations: Published clinical trials from the past 4 years

Ref.	Year	No. of patients	Age range	Type of cell grafted	Adjuvant treatments	Follow-up
Dai *et al*[53]	2013	20	22-54 yr	MSCs	-	6 mo
García-Santos *et al*[54]	2013	11	33-61 yr	MSCs	-	12 mo
Tian *et al*[55]	2013	97	21.1-38.2[1] yr	MSCs	-	14 d
Frolov *et al*[56]	2012	20	18-55 yr	HSCs	-	48 mo
Karamouzian *et al*[20]	2012	31	10-50 yr	BMCs	-	33 mo
Martínez *et al*[57]	2012	67	49.2 ± 10.3[1] yr	CD133+	-	12 mo
Mazzini *et al*[28]	2012	19	20-75 yr	MSCs	-	108 mo
Moviglia *et al*[47]	2012	7	33-78 yr	NSCs	T-cell vaccine	12 mo
Prasad *et al*[58]	2012	11	30-70 yr	MNCs	-	52 wk
Brazzini *et al*[59]	2010	53	38-81 yr	BMCs	-	1-18 mo
Karussis *et al*[26]	2010	19	53.0[1] yr	MSCs	-	25 mo
Lee *et al*[60]	2010	16	64.0 ± 11.6[1] yr	MSCs	-	5 yr
Venkataramana *et al*[61]	2010	7	22-62 yr	MSCs	-	12-36 mo

[1]The authors only provide mean values. MSCs: Mesenchymal stem cells; HSCs: Hematopoietic stem cells; BMCs: Bone marrow stem cells; NSCs: Neural stem cells; MNCs: Mononuclear cells from bone marrow.

s disease and several demyelinating diseases. The main issues to consider when using neural stem cells are how the transplanted cells will interact with the host microenvironment, how the local immunological response will interfere with and prevent neurorestoration, and how the transplanted neural stem cells will modulate the microenvironment *via* paracrine and autocrine effects. These mechanisms need to be clarified before moving on to clinical trials. Several investigators have questioned the behavior of transplanted cells and several transplantation strategies have been tested, including co-transplantation with other stem cell types, T cells or neurospheres. Nevertheless, much work needs to be done in order to better comprehend how neural stem cells interact with the host tissue[45-52]. Clinical trials have not shown statistically significant results, Moviglia *et al*[47] transplanted neural stem cells in seven patients with ALS and only in five patients were observed motor improvements. In their combined protocol the local immunological response were controlled by a T-cell vaccination before the transplants of NSCs, but authors agree that the transplantation of neural stem cells is safe and feasible[46-49] (Table 1).

CONCLUSION

Adult stem cell transplantation represents a promising choice of treatment for the field of regenerative medicine, but several aspects must still be clarified before proceeding with clinical trials. More studies are needed to establish how to obtain a large population of adult stem cells and to ensure the safety and viability of the transplants. We must also understand these cells' mechanisms of interaction and how we can use these mechanisms to achieve full regeneration.

Based on the studies cited here, it is possible to affirm that in the near future we will have effective therapies against various diseases that affect and challenge the medical community and the population at large.

REFERENCES

1 **Gage FH**. Mammalian neural stem cells. *Science* 2000; **287**: 1433-1438 [PMID: 10688783 DOI: 10.1126/science.287.5457.1433]

2 **Hosseinkhani M**, Shirazi R, Rajaei F, Mahmoudi M, Mohammadi N, Abbasi M. Engineering of the embryonic and adult stem cell niches. *Iran Red Crescent Med J* 2013; **15**: 83-92 [PMID: 23682319 DOI: 10.5812/ircmj.7541]

3 **Ma H**, Morey R, O'Neil RC, He Y, Daughtry B, Schultz MD, Hariharan M, Nery JR, Castanon R, Sabatini K, Thiagarajan RD, Tachibana M, Kang E, Tippner-Hedges R, Ahmed R, Gutierrez NM, Van Dyken C, Polat A, Sugawara A, Sparman M, Gokhale S, Amato P, Wolf DP, Ecker JR, Laurent LC, Mitalipov S. Abnormalities in human pluripotent cells due to reprogramming mechanisms. *Nature* 2014; **511**: 177-183 [PMID: 25008523 DOI: 10.1038/nature13551]

4 **Nishimori M**, Yakushiji H, Mori M, Miyamoto T, Yaguchi T, Ohno S, Miyake Y, Sakaguchi T, Ueda M, Ohno E. Tumorigenesis in cells derived from induced pluripotent stem cells. *Hum Cell* 2014; **27**: 29-35 [PMID: 24122447 DOI: 10.1007/s13577-013-0078-3]

5 **Bongso A**, Richards M. History and perspective of stem cell research. *Best Pract Res Clin Obstet Gynaecol* 2004; **18**: 827-842 [PMID: 15582541 DOI: 10.1016/j.bpobgyn.2004.09.002]

6 **Larijani B**, Esfahani EN, Amini P, Nikbin B, Alimoghaddam K, Amiri S, Malekzadeh R, Yazdi NM, Ghodsi M, Dowlati Y, Sahraian MA, Ghavamzadeh A. Stem cell therapy in treatment of different diseases. *Acta Med Iran* 2012; **50**: 79-96 [PMID: 22359076]

7 **Spradling A**, Drummond-Barbosa D, Kai T. Stem cells find their niche. *Nature* 2001; **414**: 98-104 [PMID: 11689954 DOI: 10.1038/35102160]

8 **Bonig H**, Becker PS, Schwebig A, Turner M. Biosimilar granulocyte-colony-stimulating factor for healthy donor stem cell mobilization: need we be afraid? *Transfusion* 2014; **55**: 430-439 [PMID: 24965197 DOI: 10.1111/trf.12770]

9 **Zimmermann S**, Glaser S, Ketteler R, Waller CF, Klingmüller U, Martens UM. Effects of telomerase modulation in human hematopoietic progenitor cells. *Stem Cells* 2004; **22**: 741-749 [PMID: 15342938 DOI: 10.1634/stemcells.22-5-741]

10 **Brann JH**, Firestein SJ. A lifetime of neurogenesis in the olfactory system. *Front Neurosci* 2014; **8**: 182 [PMID: 25018692 DOI: 10.3389/fnins.2014.00182]

11 **Mandairon N**, Sultan S, Nouvian M, Sacquet J, Didier A. Involvement of newborn neurons in olfactory associative learning? The operant or non-operant component of the task makes all the difference. *J Neurosci* 2011; **31**: 12455-12460 [PMID: 21880907 DOI: 10.1523/JNEUROSCI.2919-11.2011]

12 **Moreno M**, Richard M, Landrein B, Sacquet J, Didier A, Mandairon N. Alteration of olfactory perceptual learning and its cellular basis in aged mice. *Neurobiol Aging* 2014; **35**: 680-691 [PMID: 24112795 DOI: 10.1016/j.neurobiolaging.2013.08.034]

13 **Signer RA**, Morrison SJ. Mechanisms that regulate stem cell aging and life span. *Cell Stem Cell* 2013; **12**: 152-165 [PMID: 23395443 DOI: 10.1016/j.stem.2013.01.001]

14 **Giusto E**, Donegà M, Cossetti C, Pluchino S. Neuro-immune interactions of neural stem cell transplants: from animal disease models to human trials. *Exp Neurol* 2014; **260**: 19-32 [PMID: 23507035 DOI: 10.1016/j.expneurol.2013.03.009]

15 **Ulivi V**, Tasso R, Cancedda R, Descalzi F. Mesenchymal stem cell paracrine activity is modulated by platelet lysate: induction of an inflammatory response and secretion of factors maintaining macrophages in a proinflammatory phenotype. *Stem Cells Dev* 2014; **23**: 1858-1869 [PMID: 24720766 DOI: 10.1089/scd.2013.0567]

16 **Xing J**, Hou T, Jin H, Luo F, Change Z, Li Z, Xie Z, Xu J. Inflammatory microenvironment changes the secretory profile of mesenchymal stem cells to recruit mesenchymal stem cells. *Cell Physiol Biochem* 2014; **33**: 905-919 [PMID: 24713626 DOI: 10.1159/000358663]

17 **Chen Z**, Wang Y, Shi C. Therapeutic implications of newly identified stem cell populations from the skin dermis. *Cell Transplant* 2014 Jun 26; Epub ahead of print [PMID: 24972091 DOI: 10.3727/096368914X682431]

18 **Pastor D**, Viso-León MC, Jones J, Jaramillo-Merchán J, Toledo-Aral JJ, Moraleda JM, Martínez S. Comparative effects between bone marrow and mesenchymal stem cell transplantation in GDNF expression and motor function recovery in a motorneuron degenerative mouse model. *Stem Cell Rev* 2012; **8**: 445-458 [PMID: 21717132 DOI: 10.1007/s12015-011-9295-x]

19 **Vercelli A**, Mereuta OM, Garbossa D, Muraca G, Mareschi K, Rustichelli D, Ferrero I, Mazzini L, Madon E, Fagioli F. Human mesenchymal stem cell transplantation extends survival, improves motor performance and decreases neuroinflammation in mouse model of amyotrophic lateral sclerosis. *Neurobiol Dis* 2008; **31**: 395-405 [PMID: 18586098 DOI: 10.1016/j.nbd.2008.05.016]

20 **Karamouzian S**, Nematollahi-Mahani SN, Nakhaee N, Eskandary H. Clinical safety and primary efficacy of bone marrow mesenchymal cell transplantation in subacute spinal cord injured patients. *Clin Neurol Neurosurg* 2012; **114**: 935-939 [PMID: 22464434 DOI: 10.1016/j.clineuro.2012.02.003]

21 **Pal R**, Venkataramana NK, Bansal A, Balaraju S, Jan M, Chandra R, Dixit A, Rauthan A, Murgod U, Totey S. Ex vivo-expanded autologous bone marrow-derived mesenchymal stromal cells in human spinal cord injury/paraplegia: a pilot clinical study. *Cytotherapy* 2009; **11**: 897-911 [PMID: 19903102 DOI: 10.3109/14653240903253857]

22 **Saito F**, Nakatani T, Iwase M, Maeda Y, Hirakawa A, Murao Y, Suzuki Y, Onodera R, Fukushima M, Ide C. Spinal cord injury treatment with intrathecal autologous bone marrow stromal cell transplantation: the first clinical trial case report. *J Trauma* 2008; **64**: 53-59 [PMID: 18188099 DOI: 10.1097/TA.0b013e31815b847d]

23 **Saito F**, Nakatani T, Iwase M, Maeda Y, Murao Y, Suzuki Y, Fukushima M, Ide C. Administration of cultured autologous bone marrow stromal cells into cerebrospinal fluid in spinal injury patients: a pilot study. *Restor Neurol Neurosci* 2012; **30**: 127-136 [PMID: 22232031 DOI: 10.3233/RNN-2011-0629]

24 **Moviglia GA**, Fernandez Viña R, Brizuela JA, Saslavsky J, Vrsalovic F, Varela G, Bastos F, Farina P, Etchegaray G, Barbieri M, Martinez G, Picasso F, Schmidt Y, Brizuela P, Gaeta CA, Costanzo H, Moviglia Brandolino MT, Merino S, Pes ME, Veloso MJ, Rugilo C, Tamer I, Shuster GS. Combined protocol of cell therapy for chronic spinal cord injury. Report on the electrical and functional recovery of two patients. *Cytotherapy* 2006; **8**: 202-209 [PMID: 16793729 DOI: 10.1080/14653240600736048]

25 **Gupta PK**, Chullikana A, Parakh R, Desai S, Das A, Gottipamula S, Krishnamurthy S, Anthony N, Pherwani A, Majumdar AS. A double blind randomized placebo controlled phase I/II study assessing the safety and efficacy of allogeneic bone marrow derived mesenchymal stem cell in critical limb ischemia. *J Transl Med* 2013; **11**: 143 [PMID: 23758736 DOI: 10.1186/1479-5876-11-143]

26 **Karussis D**, Karageorgiou C, Vaknin-Dembinsky A, Gowda-Kurkalli B, Gomori JM, Kassis I, Bulte JW, Petrou P, Ben-Hur T, Abramsky O, Slavin S. Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. *Arch Neurol* 2010; **67**: 1187-1194 [PMID: 20937945 DOI: 10.1001/archneurol.2010.248]

27 **Mazzini L**, Ferrero I, Luparello V, Rustichelli D, Gunetti M, Mareschi K, Testa L, Stecco A, Tarletti R, Miglioretti M, Fava E, Nasuelli N, Cisari C, Massara M, Vercelli R, Oggioni GD, Carriero A, Cantello R, Monaco F, Fagioli F. Mesenchymal stem cell transplantation in amyotrophic lateral sclerosis: A Phase I clinical trial. *Exp Neurol* 2010; **223**: 229-237 [PMID: 19682989 DOI: 10.1016/j.expneurol.2009.08.007]

28 **Mazzini L**, Mareschi K, Ferrero I, Miglioretti M, Stecco A, Servo S, Carriero A, Monaco F, Fagioli F. Mesenchymal stromal cell transplantation in amyotrophic lateral sclerosis: a long-term safety study. *Cytotherapy* 2012; **14**: 56-60 [PMID: 21954839 DOI: 10.3109/14653249.2011.613929]

29 **Mazzini L**, Mareschi K, Ferrero I, Vassallo E, Oliveri G, Nasuelli N, Oggioni GD, Testa L, Fagioli F. Stem cell treatment in Amyotrophic Lateral Sclerosis. *J Neurol Sci* 2008; **265**: 78-83 [PMID: 17582439 DOI: 10.1016/j.jns.2007.05.016]

30 **Perico N**, Casiraghi F, Gotti E, Introna M, Todeschini M, Cavinato RA, Capelli C, Rambaldi A, Cassis P, Rizzo P, Cortinovis M, Noris M, Remuzzi G. Mesenchymal stromal cells and kidney transplantation: pretransplant infusion protects from graft dysfunction while fostering immunoregulation. *Transpl Int* 2013; **26**: 867-878 [PMID: 23738760 DOI: 10.1111/tri.12132]

31 **Skrahin A**, Ahmed RK, Ferrara G, Rane L, Poiret T, Isaikina Y, Skrahina A, Zumla A, Maeurer MJ. Autologous mesenchymal stromal cell infusion as adjunct treatment in patients with multidrug and extensively drug-resistant tuberculosis: an open-label phase 1 safety trial. *Lancet Respir Med* 2014; **2**: 108-122 [PMID: 24503266 DOI: 10.1016/S2213-2600(13)70234-0]

32 **Wang X**, Cheng H, Hua R, Yang J, Dai G, Zhang Z, Wang R, Qin C, An Y. Effects of bone marrow mesenchymal stromal cells on gross motor function measure scores of children with cerebral palsy: a preliminary clinical study. *Cytotherapy* 2013; **15**: 1549-1562 [PMID: 24100132 DOI: 10.1016/j.jcyt.2013.06.001]

33 **Marx RE**, Harrell DB. Translational research: The CD34+ cell is crucial for large-volume bone regeneration from the milieu of bone marrow progenitor cells in craniomandibular reconstruction. *Int J Oral Maxillofac Implants* 2014; **29**: e201-e209 [PMID: 24683583 DOI: 10.11607/jomi.te56]

34 **Ra JC**, Shin IS, Kim SH, Kang SK, Kang BC, Lee HY, Kim YJ, Jo JY, Yoon EJ, Choi HJ, Kwon E. Safety of intravenous infusion of human adipose tissue-derived mesenchymal stem cells in animals and humans. *Stem Cells Dev* 2011; **20**: 1297-1308 [PMID: 21303266 DOI: 10.1089/scd.2010.0466]

35 **Mackay-Sim A**, St John JA. Olfactory ensheathing cells from the nose: clinical application in human spinal cord injuries. *Exp Neurol* 2011; **229**: 174-180 [PMID: 20832402 DOI: 10.1016/j.expneurol.2010.08.025]

36 **Rao Y**, Zhu W, Liu H, Jia C, Zhao Q, Wang Y. Clinical application of olfactory ensheathing cells in the treatment of spinal cord injury. *J Int Med Res* 2013; **41**: 473-481 [PMID: 23569013 DOI: 10.1177/0300060513476426]

37 **Tabakow P**, Jarmundowicz W, Czapiga B, Fortuna W, Miedzybrodzki R, Czyz M, Huber J, Szarek D, Okurowski S, Szewczyk P, Gorski A, Raisman G. Transplantation of autologous olfactory ensheathing cells in complete human spinal cord injury. *Cell Transplant* 2013; **22**: 1591-1612 [PMID: 24007776 DOI: 10.3727/096368912X663532]

38 **Piepers S**, van den Berg LH. No benefits from experimental treatment with olfactory ensheathing cells in patients with ALS. *Amyotroph Lateral Scler* 2010; **11**: 328-330 [PMID: 20433414 DOI: 10.3109/17482961003663555]

39 **Pellitteri R**, Catania MV, Bonaccorso CM, Ranno E, Dell'Albani

P, Zaccheo D. Viability of olfactory ensheathing cells after hypoxia and serum deprivation: Implication for therapeutic transplantation. *J Neurosci Res* 2014; **92**: 1757-1766 [PMID: 24975631 DOI: 10.1002/jnr.23442]

40 **Roet KC**, Verhaagen J. Understanding the neural repair-promoting properties of olfactory ensheathing cells. *Exp Neurol* 2014; **261C**: 594-609 [PMID: 24842489 DOI: 10.1016/j.expneurol.2014.05.007]

41 **Sethi R**, Redmond A, Lavik E. Olfactory Ensheathing Cells Promote Differentiation of Neural Stem Cells and Robust Neurite Extension. *Stem Cell Rev* 2014; **10**: 772-785 [PMID: 24996386 DOI: 10.1007/s12015-014-9539-7]

42 **Altman J**, Das GD. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *J Comp Neurol* 1965; **124**: 319-335 [PMID: 5861717 DOI: 10.1002/cne.901240303]

43 **Altman J**, Das GD. Post-natal origin of microneurones in the rat brain. *Nature* 1965; **207**: 953-956 [PMID: 5886931 DOI: 10.1038/207953a0]

44 **Andressen C**. Neural stem cells: from neurobiology to clinical applications. *Curr Pharm Biotechnol* 2013; **14**: 20-28 [PMID: 23092257 DOI: 10.2174/1389201011314010005]

45 **Batista CE**, Mariano ED, Marie SK, Teixeira MJ, Morgalla M, Tatagiba M, Li J, Lepski G. Stem cells in neurology--current perspectives. *Arq Neuropsiquiatr* 2014; **72**: 457-465 [PMID: 24964114 DOI: 10.1590/0004-282X20140045]

46 **Glass JD**, Boulis NM, Johe K, Rutkove SB, Federici T, Polak M, Kelly C, Feldman EL. Lumbar intraspinal injection of neural stem cells in patients with amyotrophic lateral sclerosis: results of a phase I trial in 12 patients. *Stem Cells* 2012; **30**: 1144-1151 [PMID: 22415942 DOI: 10.1002/stem.1079]

47 **Moviglia GA**, Moviglia-Brandolino MT, Varela GS, Albanese G, Piccone S, Echegaray G, Martinez G, Blasseti N, Farias J, Farina P, Perusso A, Gaeta CA. Feasibility, safety, and preliminary proof of principles of autologous neural stem cell treatment combined with T-cell vaccination for ALS patients. *Cell Transplant* 2012; **21** Suppl 1: S57-S63 [PMID: 22507681 DOI: 10.3727/096368912X633770]

48 **Pluchino S**, Zanotti L, Rossi B, Brambilla E, Ottoboni L, Salani G, Martinello M, Cattalini A, Bergami A, Furlan R, Comi G, Constantin G, Martino G. Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. *Nature* 2005; **436**: 266-271 [PMID: 16015332 DOI: 10.1038/nature03889]

49 **Riley J**, Federici T, Polak M, Kelly C, Glass J, Raore B, Taub J, Kesner V, Feldman EL, Boulis NM. Intraspinal stem cell transplantation in amyotrophic lateral sclerosis: a phase I safety trial, technical note, and lumbar safety outcomes. *Neurosurgery* 2012; **71**: 405-416; discussion 416 [PMID: 22565043 DOI: 10.1227/NEU.0b013e31825ca05f]

50 **Zhu J**, Wu X, Zhang HL. Adult neural stem cell therapy: expansion in vitro, tracking in vivo and clinical transplantation. *Curr Drug Targets* 2005; **6**: 97-110 [PMID: 15720217 DOI: 10.2174/1389450053345055]

51 **Zhu J**, Zhou L, XingWu F. Tracking neural stem cells in patients with brain trauma. *N Engl J Med* 2006; **355**: 2376-2378 [PMID: 17135597 DOI: 10.1056/NEJMc055304]

52 **Zhu W**, Mao Y, Zhou LF. Reduction of neural and vascular damage by transplantation of VEGF-secreting neural stem cells after cerebral ischemia. *Acta Neurochir Suppl* 2005; **95**: 393-397 [PMID: 16463888 DOI: 10.1007/3-211-32318-X_80]

53 **Dai G**, Liu X, Zhang Z, Yang Z, Dai Y, Xu R. Transplantation of autologous bone marrow mesenchymal stem cells in the treatment of complete and chronic cervical spinal cord injury. *Brain Res* 2013; **1533**: 73-79 [PMID: 23948102 DOI: 10.1016/j.brainres.2013.08.016]

54 **García Santos JM**, Blanquer M, Torres del Río S, Iniesta F, Espuch JG, Pérez-Espejo MÁ, Martínez S, Moraleda JM. Acute and chronic MRI changes in the spine and spinal cord after surgical stem cell grafting in patients with definite amyotrophic lateral sclerosis: post-infusion injuries are unrelated with clinical impairment. *Magn Reson Imaging* 2013; **31**: 1298-1308 [PMID: 23810205 DOI: 10.1016/j.mri.2013.05.006]

55 **Tian C**, Wang X, Wang X, Wang L, Wang X, Wu S, Wan Z. Autologous bone marrow mesenchymal stem cell therapy in the subacute stage of traumatic brain injury by lumbar puncture. *Exp Clin Transplant* 2013; **11**: 176-181 [PMID: 22891928 DOI: 10.6002/ect.2012.0053]

56 **Frolov AA**, Bryukhovetskiy AS. Effects of hematopoietic autologous stem cell transplantation to the chronically injured human spinal cord evaluated by motor and somatosensory evoked potentials methods. *Cell Transplant* 2012; **21** Suppl 1: S49-S55 [PMID: 22507680 DOI: 10.3727/096368912X633761]

57 **Martínez HR**, Molina-Lopez JF, González-Garza MT, Moreno-Cuevas JE, Caro-Osorio E, Gil-Valadez A, Gutierrez-Jimenez E, Zazueta-Fierro OE, Meza JA, Couret-Alcaraz P, Hernandez-Torre M. Stem cell transplantation in amyotrophic lateral sclerosis patients: methodological approach, safety, and feasibility. *Cell Transplant* 2012; **21**: 1899-1907 [PMID: 23356668 DOI: 10.3727/096368911X582769]

58 **Prasad K**, Mohanty S, Bhatia R, Srivastava MV, Garg A, Srivastava A, Goyal V, Tripathi M, Kumar A, Bal C, Vij A, Mishra NK. Autologous intravenous bone marrow mononuclear cell therapy for patients with subacute ischaemic stroke: a pilot study. *Indian J Med Res* 2012; **136**: 221-228 [PMID: 22960888]

59 **Brazzini A**, Cantella R, De la Cruz A, Yupanqui J, León C, Jorquiera T, Brazzini M, Ortega M, Saenz LN. Intraarterial autologous implantation of adult stem cells for patients with Parkinson disease. *J Vasc Interv Radiol* 2010; **21**: 443-451 [PMID: 20346882 DOI: 10.1016/j.jvir.2010.01.008]

60 **Lee JS**, Hong JM, Moon GJ, Lee PH, Ahn YH, Bang OY. A long-term follow-up study of intravenous autologous mesenchymal stem cell transplantation in patients with ischemic stroke. *Stem Cells* 2010; **28**: 1099-1106 [PMID: 20506226 DOI: 10.1002/stem.430]

61 **Venkataramana NK**, Kumar SK, Balaraju S, Radhakrishnan RC, Bansal A, Dixit A, Rao DK, Das M, Jan M, Gupta PK, Totey SM. Open-labeled study of unilateral autologous bone-marrow-derived mesenchymal stem cell transplantation in Parkinson's disease. *Transl Res* 2010; **155**: 62-70 [PMID: 20129486 DOI: 10.1016/j.trsl.2009.07.006]

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