Review

Expert Opinion

Bone-marrow-derived mesenchymal stem cell therapy for neurodegenerative diseases

Ofer Sadan, Eldad Melamed & Daniel Offen†
†*Neurosciences Laboratory, Felsenstein Medical Research Center, Rabin Medical Center, Petah Tikva 49100, Israel*

Background: Stem-cell-based therapy is a promising new approach to handling neurodegenerative diseases. One of the most promising cellular sources is bone-marrow-derived mesenchymal stem cells (MSCs) also termed multipotent stromal cells. MSCs represent an autologous source and are abundant and non-tumorigenic. Additionally, MSCs possess the useful characteristics of homing and chemokine secretion.
Objective/methods: Since neurodegenerative diseases have many pathological processes in common, a specific therapeutic agent could potentially ameliorate the symptoms of several distinct neurodegenerative diseases. In this review we demonstrate the wide variety of mechanisms by which MSCs can influence neurodegenerative processes.
Results/conclusions: The mechanisms by which transplanted MSCs influence neurodegenerative diseases can be broadly classified as cellular replacement or paracrine secretion, with the latter subdivided into trophic factor secretion or immunomodulation by cytokines. Emerging research suggests that genetic manipulations before transplantation could enhance the therapeutic potential of MSCs. Such manipulation could turn the cells into a 'Trojan horse', to deliver specific proteins, or promote reprogramming of the MSCs into the neural lineage. Clinical trials testing MSC-based therapies for familial amyotrophic lateral sclerosis and multiple sclerosis are in progress.

Keywords: immunomodulation, mesenchymal stem cells, migration, neurodegenerative diseases, neurotrophic factors, reprogramming

Expert Opin. Biol. Ther. (2009) 9(12):1487-1497

1. Introduction

1.1 Neurological diseases – common pathways

Neurological diseases are characterized by dysfunction associated with loss of neural cells and tissue. The various known disorders can be categorized according to the specific location and cell type involved, for example, the loss of dopaminergic neurons in Parkinson's disease [1], the mechanism involved, for example, a vascular dysfunction in stroke [2], or an autoimmune reaction in multiple sclerosis [3] or in myasthenia gravis [4], temporally, for example, an acute insult as in stroke [2] versus a chronically progressive disorder as in Huntington's disease [5]. Essentially the neurological diseases are differentiated by their phenotype, for example the main motor feature of Parkinson's disease is hypoactivity with rest tremor [1], while in Huntington's disease it is involuntary movements and the condition is considered as a hyperkinetic disorder. Despite gross dissimilarities, many neurological disorders, and virtually all neurodegenerative diseases, display common pathophysiological processes.

Apoptosis, for example, is well documented in amyotrophic lateral sclerosis [6], Huntington's disease [7] and Parkinson's disease [8]. Other processes that similarly occurs in several neurodegenerative diseases are mitochondrial dysfunction [9] and

informa healthcare

10.1517/14712590903321439 © 2009 Informa UK Ltd ISSN 1471-2598

excitotoxicity [10]. For instance, the degeneration of dopaminergic cells in Parkinson's disease involves protein misfolding, oxidative stress, mitochondrial dysfunction and apoptotic death [1] as does the progressive degeneration that occurs in the striatum during Huntington's disease [11]. The overlapping nature of the underlying processes raises the possibility that neurological diseases sharing pathophysiological features could be treated using universal strategies. There are numerous examples of single treatment strategies that have been implemented in several diseases models, such as the anti-apoptotic antibiotic minocycline that demonstrated a beneficial influence on models of amyotrophic lateral sclerosis (ALS) [12], spinal cord injury [13] and Huntington's disease [14]. A second example is the use of stem cells as a treatment strategy, as will be elaborated in this review.

1.2 Stem-cell-based therapies for neurological diseases

Stem-cell-based treatments have the potential to ameliorate the symptoms of various neurodegenerative diseases. One stem-cell-based therapeutic approach is to replace damaged cells. Since in Parkinson's disease there is loss of a specific neuron type at a specific location, namely the dopaminergic neural population in the substantia nigra, many studies have focused on examining whether replacement therapy can be used to treat Parkinson's disease. The replacement cells are either differentiated stem cells [15-17] or post-mitotic fetal grafts [18-20]. The latter have also been used to treat Huntington's disease [21-23] with mixed results. The latest report actually demonstrated an accelerated neurodegeneration in the implanted graft [24].

Another stem-cell-based therapeutic approach is to transplant stem cells into the diseased neural tissue in order to improve the environment, for example through release of neuroprotective factors. Some stem cells produce and secrete various types of trophic factors [25,26]. Alternatively, the gene for specific factor can be introduced into stem cells to ennsure specific expression and secretion [27,28].

A third approach is to use stem cells to induce or enhance neurogenesis. Since discovery of neurogenesis in the human brain [29], much effort has been directed towards finding methods to stimulate or mimic this regenerative process. It was suggested that stem cells have the potential to enrich the neural stem cell niche [25] or to themselves become self-renewing neural progenitors [30,31].

1.3 Which stem cells to use for cell therapy?

Several types of stem cells could serve as sources for cellular therapy. Generally, stem cells are classified according to their developmental origin. Here we will discuss three main types: embryonic stem cells (ESCs), adult stem cells and induced pluripotent stem cells (iPS). ESCs were first isolated from a human donor in 1998 [32]. In developmental terms, these are the earliest stem cells and, considered as totipotent. ESCs, can differentiate into various neuronal cell types, [33,34], astrocytes [35] and oligodendrocytes [36]. The neural phenotypes of these *in vitro*-differentiated ESCs resemble most closely those of the equivalent mature cells *in vivo*. However, using ESCs as a source for stem cell therapy is problematic for three reasons. Firstly, acquiring and manipulating ESCs raises contentious ethical issues. Secondly, even differentiated ESCs can be tumorigenic (leading to formation of teratomas [32]). Finally, since ESCs represent a non-autologous source, their transplantation must be accompanied by immunosuppressive treatments.

Adult stem cells can be derived from virtually any tissue or organ. A dramatic illustration of their potential is the recent creation of functioning prostate tissue from a single adult prostate stem cell [37]. Adult stem cells are also found in the CNS. Neural stem cells have been found in two locations, in the sub-ventricular zone (SVZ) and in the sub-granular zone of the hippocampus [38], the latter group known to be involved in learning and memory. Although a variety of insults, particularly stroke, can trigger SVZ neural stem cells to undergo neurogenesis, their natural regenerative potential is considered limited. Neural stem cells can be induced to fully differentiate into various neural cell types. However the availability of neural stem cells is low, since harvesting them requires dissection from the adult brain. Moreover, lately, it has been shown that they can produce CNS tumors [39].

The first adult stem cells ever isolated were hematopoetic stem cells from the bone marrow. Subsequently, in 1968 it was discovered that the bone marrow contains also non-hematopoetic stem cells [40], which were named mesenchymal stem cells or multipotent stromal cells (MSCs). These cells are known to be a reservoir for the bone, fat and cartilage tissues. Three distinct advantages of using MSCs as a source for stem cell therapy are their reportedly low tumorigenic potential, their wide availability and that they represent an autologous source. Moreover, as we will describe below, MSCs can be induced to differentiate into a wider range of cell types, much more than initially suspected.

The third potential source of stem cells for therapy is induced pluripotent cells (iPS). An innovative emerging technology has been developed whereby either mouse- or human-derived mature cells, mainly skin fibroblasts, are induced to become pluripotent cells. The iPS technology employs lentiviral vectors to introduce into the mature cells four genes that together delete epigenetic inhibition of pluripotency. A convincing demonstration of their pluripotent capacity was achieved when the iPS cells were injected into a blastocyst, before implantation, which resulted in chimeric mice [41]. The main advantages of using iPSs as a source for therapy are that they represent an autologous source and exhibit unlimited differentiation potential. However, it was shown that iPSs are similar to ESCs not only in terms of differentiation capacity but also with respect to tumorigenicity. Accordingly, the disadvantage of using iPSs is the concern regarding tumor formation. An additional worry is the use of lentivirus as vectors in the process, vectors that might induced dangerous mutations in the host genome. Recently, safer methods have been suggested in order to induce the four genes for example 'piggyBac' technology [42].

In this review we focus on using MSCs as a source for cellular therapy for neurodegenerative diseases. Of the three

aforementioned stem cells types, MSCs are closest to being approved for clinical use, because of their safety profile and availability. In fact, these cells are already approved for various procedures, namely for supporting transplantation of hematopoetic stem cells and for treating graft-versus-host disease [43,44], and systemic lupus erythematosus [45]. Clinical trials are also in progress for neurological disorders, namely ALS [46] and mutiple sclerosis [47,48].

2. Mesenchymal stem cells – what is so special about them?

2.1 Definition – what are MSCs?

Cells isolated from the mononuclear fraction of the bone marrow, fat tissue [47] or cord blood [48] that display adherence and plasticity are defined as MSCs [40,49,50]. Usually, the stem cell nature of the isolated cells is validated by an *in vitro* test, such as differentiation into osteocyes, adipocytes and chondrocytes. In addition, MSCs express at the membrane specific CD markers that can serve as characteristic features. Typically, MSCs are positive for CD105, CD73 and CD90 and negative for CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-DR. A unique marker for MSCs is still lacking, although Bühring *et al.* have suggested novel specific markers that are in the process of being validated [51]. The location and role of MSCs *in vivo* remains enigmatic. Some MSCs are located in stromal tissue, at least those in bone marrow, and a recent study by Meirelles *et al.* suggests that the MSC niche is in the perivascular space [52]. MSCs were also successfully harvested from other tissues such as umbilical cord blood [53], placenta [54], fat tissue [55] and even from the fallopian tubes [56]. Probably because of their perivascular location, MSCs can be harvested from almost all tissues.

2.2 Do MSCs possess neural predisposition?

There are several studies that have been interpreted as showing that MSCs are predisposed to become neural cell types. This idea challenges the common knowledge that neural cell types are generated only from the ectoderm lineage and bone marrow is considered to come from the mesoderm. If indeed this is the situation, the neuronal differentiation from MSC might be considered to be transdifferentiation. Transdifferentiation potential was first proposed by Kopen *et al.*, when they found after transplantation of MSCs into a rodent brain, cells that migrate and express neural markers [57]. In support of neural predisposition, MSCs were shown to express, at a basal level, neural genes, including Nestin, neuron-specific enolase and β-tubulin III [58,59]. Furthermore, it was demonstrated that MSCs can be induced to differentiate into neural-like cells using protocols similar to those devised for differentiating ESCs. Typically the protocols involve exposure to cytokines, such as EGF, fibroblast growth factor 2 and 8, brain derived growth factor, or chemicals, such as N2 supplement and cyclic AMP [15,60-66]. However, the vast majority of these studies demonstrated the neural phenotype only in culture, which raises the question of whether these differentiated cells will be able to maintain their neuronal identity and to integrate into the lesioned CNS. It is not obvious that cells that were transiently exposed to a defined differentiation cocktail will be able to change to such an extent that it will allow them to become mature neurons. Only a minority of the differentiation protocols were later shown to be effective in animal models [67].

Some groups aimed their transdifferentiation studies towards the oligodendroglial phenotype. One paper that demonstrated a clear *in vitro* differentiation of fetal-blood-derived MSCs into mature oligodendrocytes, and also showed that transplanted cells maintained their phenotype [68]. Oligodendroglial markers were also documented *in vivo* after transplantation into ischemic rats [69]. Schwann cell transdifferentiation was also documented [70].

More recently, MSCs have been induced to become neural-like cells through programming, whereby the expression of certain transcription factors is manipulated. For example, upregulation of LMX1a [71] or downregulation of RE-1 silencing factor [72] results in dopaminergic differentiation, whereas upregulation of neurogenin 1 promotes more generally neuronal differentiation [73].

Nevertheless, it remains debatable whether the observed ability of MSCs to become neural-like cells is reflecting a true predisposition. Montzka *et al.* have claimed that the basal neural gene expression observed in MSCs is variable among individuals and misleading, as it can be misinterpreted as evidence for neural transdifferentiation [59]. Moreover, these 'neuronal' proteins could be playing distinct roles [74]. Furthermore, some morphological changes of MSCs observed in response to differentiation protocols have been shown to be misunderstood; a reduction in cytoplasm size due to cytoskeleton dysregulation has been mistakenly perceived as growth of neurite-like extensions [75-77]. Also, microarray and proteonomic analyses reveal that MSC transdifferentiation is not associated with expected expression changes typical of neural differentiation [75,78]. Finally, and most significantly, none of the MSC transdifferentiation studies demonstrate a fully functional neuronal phenotype, in terms of excitability and reaction to neurotransmitter stimuli. Taken together, these reservations challenge the theory that MSCs are predisposed to become neural-like cells. Alternatively, the mentioned studies and data can be given another interpretation that points to the possibility that the stromal bone marrow cell population contain also cells from other lineages and not only from the mesoderm and therefore it is not possible to prove the transdifferentiation process.

Lately, it has been suggested that the so-called neural transdifferentiation of MSCs is in fact a reflection of their developmental ontogeny, for it appears that a sub-population of MSCs originate from the neural crest. Morikawa *et al.* have shown that a specific population of MSCs, those expressing platelet derived growth factor receptor α (PDGFα) and Sca-1 but lacking expression of the hematopoetic marker CD45 and TER119, co-express neural crest markers such as Twist, p75NTR, Snail1, Snail2, Sox9 and Mpz [79]. Also, in *in vivo* experiments Takashima *et al.* have demonstrated that some MSCs are derived from the

neural-crest-origin cells [80]. Moreover, further support for the developmentally neural origin of MSCs is that under specific medium conditions human-derived astrocytes can differentiate into mesenchymal-like cells and more importantly, these cells can then be differentiated into osteocytes and adipocytes [81]. Recently, Phinney has proposed that MSC cultures are not homogeneous, and perhaps one subpopulation is physiologically responsible for receiving signals from the nervous system in the bone marrow, which could explain the basal expression of neural genes and accords with a neural origin for a subpopulation of MSCs [74]. With regards to this theory, the group of Verfaillie claimed to isolate a specific stem cell population from the bone marrow that possess multipotent differentiation capabilities and can remain in an undifferentiated state for over 100 passages. These cells, termed multipotent adult progenitor cells (MAPCs), were shown to differentiate *in vitro* into cell types from the mesoderm, ectoderm and endoderm [82]. When transplanted *in vivo*, MAPCs were shown to reconstitute the hematopoetic niche in irradiated mice [83]. Furthermore, these cells were shown to integrate into the hippocampus in neonatal hypoxic–ischemic rats [84]. Other groups isolated another population termed marrow-isolated adult multilineage inducible (MIAMI) cells, and altogether it seems that the marrow consists of early embryonic-like stem cells [85]. These findings suggest that there are subpopulations in the bone marrow niche that hold better differentiation capabilities than others.

2.3 Do MSCs exert a paracrine effect?

MSCs can produce and secrete a variety of soluble substances, mainly trophic factors [26,86,87]. Two *in vitro* studies have underscored the capacity of MSCs to influence indirectly other cells. Neuronal primary cultures can be protected from NO exposure by pre-treatment with MSCs-conditioned media. Specifically it was shown that essentially brain-derived neurotrophic factor (BDNF) mediates this effect as anti-BDNF antibodies neutralize protection [26]. Also, endothelial progenitors are induced to undergo angiogenesis when co-cultured with MSCs *in vitro*, probably due to MSC secretion of VEGF [88].

Importantly, MSCs have also been shown to affect indirectly other cells *in vivo*. Li *et al.* have reported that in a rat experimental stroke model, peripheral neurotrophin levels are higher after the animals are infused with MSCs [87]. Furthermore, MSCs exhibiting an astrocytic phenotype have been shown to protect the 6-hydroxydopamine-induced striatal lesion model from Parkinson's disease [89]. This astrocytic phenotype accords with MSCs having a neural predisposition, and is associated with expression of astrocytic markers, expression of glutamate uptake machinery [90] and increased secretion of neurotrophic factors [89,91]; the latter feature probably mediating the protection from Parkinson's disease. In a different work, transplantation of human-derived MSCs into the spinal cord of a rodent transgenic model of ALS, improved the animals' motor function and survival of motoneurons and reduced inflammation [92].

In addition, MSCs can regulate immune cells through cytokine secretion. For example, MSCs can inhibit lymphocyte proliferation *in vitro*, even when exposed to allogenic cells [93]. Studies are underway to investigate whether this immunomodulatory effect can be exploited to treat multiple sclerosis (MS), an immune-based disease. Administration of MSCs intravenously or via the ventricles has been shown to reduce the disability of experimental allergic encephalomyelitis (EAE) animal models of MS, by protecting the axons and reducing the proliferation rate of lymphocytes [94]. It was thought that direct administration into the ventricles would be favorable, however a complimentary study found that even intraperitoneal administration is enough to ameliorate MS symptoms, supporting the hypothesis that the effect is paracrine [95]. In summary, MSCs can exert a paracrine effect both *in vitro* and *in vivo*. Therefore, MSCs possess the potential to serve as therapeutic tools to deliver soluble factors and treat assorted neurological disorders.

2.4 Homing – is MSC a 'smart missile'?

MSCs possess migratory or homing capability. Intravenously administered MSCs have been shown to migrate into recipient bone marrow, as well as other tissues such as liver, lung, kidney and thymus in non-human primates [96,97]. Indeed, human-derived MSCs when transplanted into a sheep embryo intrauterinely produce functional (differentiated) cells in various tissues including cartilage, bone, tendon and heart [98], which indicates plasticity and homing. Moreover, MSCs induce immunomodulation, as was shown in this research, since the origin of the transplanted cells was human, which defines it as xenotransplantation. The fact that the innate immune system of the sheep did not attack the cells even though they are from a different species proves that MSCs can suppress the surrounding immune cells. Also, human-derived MSCs when transplanted intracranially into non-human primates can be found widely distributed up to six months after transplantation [99]. Moreover, MSCs have been reported to migrate towards tumors *in vivo*, raising the possibility that they can serve as novel vectors for anti-tumor agents [100,101].

Several studies have shown migration of MSCs towards neural lesions, mainly stroke lesions [102], but also a quinolinic-acid-induced lesion [91] and 6-hydroxydopamine-induced lesion [89,103]. Notably, the migratory routes appear to be along white matter tracks, a behavior expected of astrocytes [104]. The natural tendency of MSCs to migrate towards neural lesions has important clinical implications, as it suggests that transplanted MSCs will not need to be injected directly into lesioned tissue but will locate it themselves. However, it is noteworthy that the neural lesions studied to date probably involve localized immune reactions with high levels of chemokines that attract the MSCs, a situation not usually a feature of human neurodegenerative processes, with the exception of stroke.

2.5 Neurogenesis – can MSCs help create new neurons?

Accumulating data indicates that the brain has repair mechanisms, whereby new neurons and astroglial cells are produced. However, it seems that brain repair is ineffective when faced

with major pathological processes such as stroke and neurodegenerative diseases. It has been proposed that MSCs could aid and stimulate neurogenesis and thus improve brain repair. One promising study transplanted human-derived MSCs into the dentate gyrus of the hippocampus and demonstrated greater numbers of neural stem cells, both new and immature and subsequently, more differentiated neurons and astrocytes. The neurogenic effect was attributed to secretion of neurotrophic factors by the transplanted cells [25]. Moreover, in a stroke model it was shown that transplantation of MSCs not only promotes the proliferation of neural stem cells, but also their survival and differentiation. Similarly, soluble factors secreted by the transplanted MSCs were considered to mediate the neurogenic effect [105], this idea was supported by studies of *in vitro* co-cultures of neural and mesenchymal stem cells [106].

Although it is considered most likely that MSCs enhance neurogenesis indirectly, Alexanian *et al.* have claimed that co-culturing MSCs with neural cells induces neural differentiation of MSCs [107,108]. Future research should delineate the mechanism underlying stimulation of neurogenesis *in vivo* by transplanted MSCs, specifically, the significance of any or all of the following: stimulation of endogenous neural stem cells, local transdifferentiation into neural cells or some sort of fusion with endogenous neural cells.

2.6 Trojan horses – genetic manipulations

As outlined above, MSCs possess naturally many traits that make them a promising and practicable source for stem cell therapy. However, recently the question of whether genetic manipulations before transplantation could enhance the therapeutic potential of MSCs has been investigated. Such manipulation could achieve one of two goals: i) to turn the cells into a 'Trojan horse', for example by introducing a transgene encoding a neurotrophic factor; and ii) to promote programming of the MSCs into the neural lineage, by engineering overexpression of a specific transcription factor.

Two promising studies highlight the therapeutic potential of exploiting MSCs as Trojan horses. Firstly, BDNF-overexpressing MSCs transplanted into a stroke animal model reduce behavioral deficits, infarct size and the number of apoptotic cells [109]. A similar therapeutic effect is observed when glial-cell-derived neurotrophic factor (GDNF)-overexpressing cells are used, but not when the cells overexpress ciliary neurotrophic factor or NT-3 [110]. Secondly, GDNF-overexpressing human MSCs have been shown to ameliorate disease progression in a rat model of familial ALS when transplanted into the muscles [111]. The cells continue to secrete GDNF *in vivo*, reduce the number of denervated end-plates in the muscle and rescue spinal motor neurons.

Recently, researchers investigating stem-cell-based therapies for neurological diseases have realized the potential of programming MSCs to express more robustly a neural phenotype. This approach was drawn from the aforementioned work with iPSs [41] and was encouraged by the observation that neurons derived from iPSs ameliorate Parkinson's disease symptoms in a rat model of Parkinson's disease [112]. MSCs have been programmed into the neural lineage by knocking out RE1 silencing factor (REST, also known as neuronal restrictive silencing factor, NRSF) [113] and these transgenic MSCs have been shown to exhibit characteristics of dopaminergic cells, in terms of dopamine production and more importantly, electrophysiologically [72]. In addition, MSCs have been programmed to become neural cells by engineering overexpression of neurogenin 1; the transgenic cells express voltage-gated channels characteristic of neurons. Importantly, neurogenin 1-overexpressing cells were found to integrate into ischemic brain tissue and ameliorate motor function in a rat stroke model [73]. Most recently, overexpression of the transcription factor LMX1a has been shown to program MSCs to become functional dopaminergic cells [71].

3. Safety

The main safety concern when considering stem-cell-based therapy is the possibility of cancerous growth. ESCs and iPSs have the undesirable potential to induce teratomas *in vivo* and are therefore considered less safe than MSCs. Most significantly, over the last few decades many bone-marrow transplantations have been performed without cancerous complications, supporting the premise that MSCs, a subpopulation of the bone marrow, do not create tumors *in vivo*.

One caveat has been raised recently concerning the safety of using MSCs for cellular therapy. A sub-population of cells that are attracted by chemokines and support epithelial tumor growth and progression have been characterized as bone-marrow-derived MSCs, termed carcinoma-associated fibroblasts (CAFs) [114-116]. It has been shown that systemically administered MSCs possess a distinct tropism to tumors *in vivo* [117,118]. Recent studies have demonstrated that MSC that are cultured for a very long period can exhibit some neoplastic transformation towards what seems to be cancer stem cells, either spontaneously [119] or in immortalized MSCs by expression telomerase reverse transcriptase [120]. However, the vast majority of the papers reviewed here did not use cells after such a long cultivation *ex vivo*. It appears unlikely that MSCs are involved in the initiation of the epithelial tumor [121], and therefore MSC-based treatments can be considered safe.

4. Conclusions

Neurodegenerative diseases exhibit overlapping pathophysiological processes. Stem-cell-based treatments have the potential to ameliorate the symptoms of various neurodegenerative diseases. MSCs are a promising autologous source for stem cell therapy primarily due to their safety and abundance. Additionally, MSCs possess the useful characteristics of homing and chemokine secretion. Moreover, emerging transgenic technologies should enable MSCs to serve as 'Trojan horses', carrying neurotrophic factors to certain tissues, and to serve better as neural-like cells, after being programmed robustly into the neural lineage (**Figure 1**). Indeed clinical trials testing

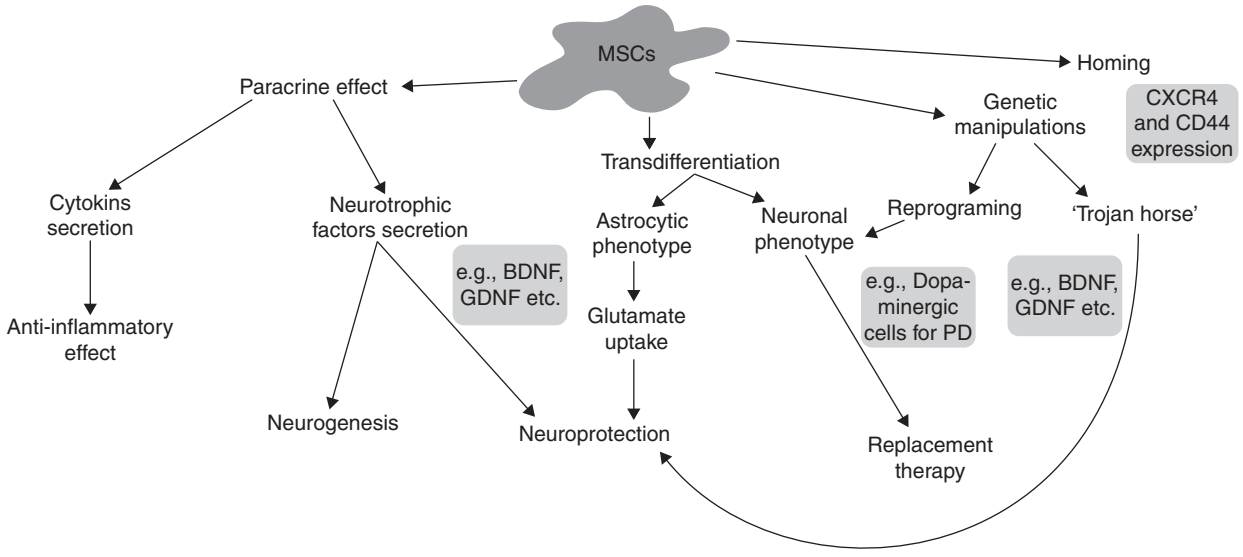

Figure 1. Mechanisms of mesenchymal stem cell (MSC)-based treatment. MSCs transplantation can influence the treated tissue in two main ways, the less established manner is transdifferentiation, and the more accepted manner is the paracrine effect.
Adapted from [28].

MSC based therapies for ALS and multiple sclerosis are in progress [46,122]. Recently, a Phase I clinical trial conducted on ALS patients demonstrated that intrathecal transplantation is not toxic or tumorogenic for up to 44 months [123,124].

5. Expert opinion

Neurodegenerative diseases share underlying pathophysiological processes and therefore have the potential to respond to common therapies. Accordingly, over the years almost every drug developed for one disease has later been tested for the others. A relatively new therapy for neurological diseases undergoing testing is based on stem cells, in particular MSCs. Stem cells unlike conventional molecule-based drugs are considered 'dirty drugs'. This is because molecule-based drugs are developed with specific rationale and mechanisms in mind whereas stem cells can influence the treated tissue by various mechanisms and cannot be controlled after transplantation. The only way to control their mechanism of action, at least partially, is to induce a genetic change prior to transplantation, for example, to engineer overexpression of a trophic factor or transcription factor.

As discussed in this review MSC-based therapies can alleviate neurological disease symptoms through various mechanisms. In general the mechanisms can be classified as either cellular replacement or paracrine secretion, with the latter subdivided into trophic factor secretion and immunomodulation by cytokines. Currently, replacement is less applicable clinically to diseases of the CNS, as fully transdifferentiated MSCs that exhibit neuronal phenotypes, such as electrophysiological behavior, have not yet been generated. This notwithstanding, several studies have shown that neural-like MSCs can integrate into neural tissue and sustain their phenotype. However, it remains likely that the therapeutic effect of such neural-like MSCs in animal models is due to cytokine secretion.

Analyzing how transplanted MSCs influence neurodegenerative diseases is challenging, as it is difficult to determine whether the disease is affecting MSC behavior or the MSCs are secreting proteins that affect disease progression. Moreover, it is possible that MSCs react to extrinsic signals and change phenotype accordingly and/or that there are non-identical sub-populations of MSCs, one of which becomes dominant depending on the context. Also, in light of such complexity, it is more than likely that experimental analyses are plagued by research-based bias, whereby the mechanism is examined and proved according to the research hypothesis. These mechanistic issues aside, the data described in this review underscore the therapeutic potential of MSC-based treatments for neurodegenerative diseases, treatments that will hopefully soon become available for clinical use.

When trying to foresee the future of MSC-based treatment, it seems that the clinical applications in the fields of immunology will increase rapidly. Pre-clinical and small clinical trials have already shown the efficacy of MSC in treating diseases such as graft-versus-host disease, systemic lupus erythematotous, autoimmune arthritis and others. It is probably a matter of time until a standard protocol can be developed to include MSCs as another line of therapy for many non-neurological indications. Accordingly, the first clinical application of MSCs in the neurological ward will probably be for treating multiple sclerosis, and after establishing clear and safe protocol other treatment-refractory diseases will follow.

On the research bench, it appears that three main directions will be developed: the first is the establishment of MSC-based treatment as is, without genetic manipulations; the second is to genetically modify the transplanted MSC so these cells will be safe vectors as compared with viral vectors; and the third direction, which currently is not in the main scope of research, is to establish pharmacological-based treatments that will recruit MSCs to the blood stream and allow them to migrate to the diseased tissue (e.g., administrating such a drug hours after a stroke to reduce lesion size).

MSCs are a surprising source for the treatment and understanding of neurological diseases. These cells are a striking example for the need to not to stay captured under known dogmas such as the clear separation between the three germ lines and limited plasticity of adult stem cells. When trying to analyze the current trend of research, MSCs are taking a growing portion of stem-cell-based therapy, and will probably become a standard method of care within several years.

Declaration of interest

The authors state no conflict of interest and have received no payment for the preparation of this manuscript.

Bibliography

1. Lees AJ, Hardy J, Revesz T. Parkinson's disease. Lancet 2009;373:2055-66
2. Edlow JA, Newman-Toker DE, Savitz SI. Diagnosis and initial management of cerebellar infarction. Lancet Neur 2008;7:951-64
3. Steinman L. The gray aspects of white matter disease in multiple sclerosis. PNAS 2009;106:8083-4
4. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neur 2009;8:475-90
5. Stack EC, Matson WR, Ferrante RJ. Evidence of oxidant damage in Huntington's disease: translational strategies using antioxidants. Mitochondria and oxidative stress in neurodegenerative disorders. Ann N Y Acad Sci 2008;1147:79-92
6. Li M, Ona VO, Guégan C, et al. Functional role of caspase-1 and caspase-3 in an ALS transgenic mouse model. Science 2000;288:335-9
7. Thomas LB, Gates DJ, Richfield EK, et al. DNA end labeling (TUNEL) in Huntington's disease and other neuropathological conditions. Exp Neurol 1995;133:265-72
8. Lev N, Melamed E, Offen D. Apoptosis and Parkinson's disease. Prog Neuropsychopharm Bio Psych 2003;27:245-50
9. Knott AB, Bossy-Wetzel E. Impairing the mitochondrial fission and fusion balance: a new mechanism of neurodegeneration. Mitochondria and oxidative stress in neurodegenerative disorders. Ann N Y Acad Sci 2008;1147:283-92
10. Vosler PS, Brennan CS, Chen J. Calpain-mediated signaling mechanisms in neuronal injury and neurodegeneration. Mol Neurobiol 2008;38:78-100
11. Roze E, Saudou F, Caboche J. Pathophysiology of Huntington's disease: from Huntingt in functions to potential treatments. Curr Opin Neurol 2008;21:497-503
12. Zhu S, Stavrovskaya IG, Drozda M, et al. Minocycline inhibits cytochrome *c* release and delays progression of amyotrophic lateral sclerosis in mice. Nature 2002;417:74-8
13. Festoff BW, Ameenuddin S, Arnold PM, et al. Minocycline neuroprotects, reduces microgliosis, and inhibits caspase protease expression early after spinal cord injury. J Neurochem 2006;97:1314-26
14. Chen M, Ona VO, Li M, et al. Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. Nat Med 2000;6:797-801
15. Barzilay R, Kan I, Ben-Zur T, et al. Induction of human mesenchymal stem cells into dopamine-producing cells with different differentiation protocols. Stem Cells Dev 2008;17:547-54
16. Lee SH, Lumelsky N, Studer L, et al. Efficient generation of midbrain and hindbrain neurons from mouse embryonic stem cells. Nat Biotech 2000;18:675-9
17. Perrier AL, Tabar V, Barberi T, et al. Derivation of midbrain dopamine neurons from human embryonic stem cells. PNAS 2004;101:12543-8
18. Kordower JH, Chu Y, Hauser RA, et al. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat Med 2008;14:504-6
19. Li JY, Englund E, Holton JL, et al. Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. Nat Med 2008;14:501-3
20. Mendez I, Vinuela A, Astradsson A, et al. Dopamine neurons implanted into people with Parkinson's disease survive without pathology for 14 years. Nat Med 2008;14:507-9
21. Bachoud-Levi AC, Gaura V, Brugieres P, et al. Effect of fetal neural transplants in patients with Huntington's disease 6 years after surgery: a long-term follow-up study. Lancet Neur 2006;5:303-9
22. Furtado S, Sossi V, Hauser RA, et al. Positron emission tomography after fetal transplantation in Huntington's disease. Ann Neurol 2005;58:331-7
23. Keene CD, Sonnen JA, Swanson PD, et al. Neural transplantation in Huntington disease: long-term grafts in two patients. Neurology 2007;68:2093-8
24. Cicchetti F, Saporta S, Hauser RA, et al. Neural transplants in patients with Huntington's disease undergo disease-like neuronal degeneration. PNAS 2009;106:12483-8
25. Munoz JR, Stoutenger BR, Robinson AP, et al. Human stem/progenitor cells from bone marrow promote neurogenesis of endogenous neural stem cells in the hippocampus of mice. PNAS 2005;102:18171-6
26. Wilkins A, Kemp K, Ginty M, et al. Human bone marrow-derived mesenchymal stem cells secrete brain-derived neurotrophic factor which promotes neuronal survival in vitro. Stem Cell Res 2009;3:63-70
27. Rooney GE, McMahon SS, Ritter T, et al. Neurotrophic factor-expressing mesenchymal stem cells survive transplantation into the contused spinal cord without differentiating into neural

cells. Tis Eng Part A 2009; published online 31 March 2009, doi:10.1089/ten.tea.2009.0045.

28. Suzuki M, McHugh J, Tork C, et al. Direct muscle delivery of GDNF with human mesenchymal stem cells improves motor neuron survival and function in a rat model of familial ALS. Mol Ther 2008;16:2002-10
29. Eriksson PS, Perfilieva E, Bjork-Eriksson T, et al. Neurogenesis in the adult human hippocampus. Nat Med 1998;4:1313-7
30. Madhavan L, Daley BF, Paumier KL, et al. Transplantation of subventricular zone neural precursors induces an endogenous precursor cell response in a rat model of Parkinson's disease. J Comp Neurol 2009;515:102-15
31. Guzman R, De Los Angeles A, Cheshier S, et al. Intracarotid injection of fluorescence activated cell-sorted CD49d-positive neural stem cells improves targeted cell delivery and behavior after stroke in a mouse stroke model. Stroke 2008;39:1300-6
32. Thomson JA, Itskovitz-Eldor J, Shapiro SS, et al. Embryonic stem cell lines derived from human blastocysts. Science 1998;282:1145-7
33. Yan YP, Yang DL, Zarnowska ED, et al. Directed differentiation of dopaminergic neuronal subtypes from human embryonic stem cells. Stem Cells 2005;23:781-90
34. Shin S, Dalton S, Stice SL. Human motor neuron differentiation from human embryonic stem cells. Stem Cells Dev 2005;14:266-9
35. Lee DS, Yu K, Rho JY, et al. Cyclopamine treatment of human embryonic stem cells followed by culture in human astrocyte medium promotes differentiation into nestin- and GFAP-expressing astrocytic lineage. Life Sci 2006;80:154-9
36. Kang SM, Cho MS, Seo H, et al. Efficient induction of oligodendrocytes from human embryonic stem cells. Stem Cells 2007;25:419-24
37. Leong KG, Wang BE, Johnson L, et al. Generation of a prostate from a single adult stem cell. Nature 2008;456:804-8
38. Zhao CM, Deng W, Gage FH. Mechanisms and functional implications of adult neurogenesis. Cell 2008;132:645-60
39. Amariglio N, Hirshberg A, Scheithauer BW, et al. Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. Plos Medicine 2009;6:221-31
40. Friedens AJ, Petrakov KV, Kuroleso AI, et al. Heterotopic transplants of bone marrow – analysis of precursor cells for osteogenic and hematopoietic tissues. Transplantation 1968;6:230–47
41. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007;131:861-72
42. Woltjen K, Michael IP, Mohseni P, et al. piggyBac transposition reprograms fibroblasts to induced pluripotent stem cells. Nature 2009;458:766-70
43. Fang BJ, Li N, Song YP, et al. Cotransplantation of haploidentical mesenchymal stem cells to enhance engraftment of hematopoietic stem cells and to reduce the risk of graft failure in two children with severe aplastic anemia. Ped Trans 2009;13:499-502
44. Le Blanc K, Frassoni F, Ball L, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet 2008;371:1579-86
45. Sun L, Akiyama K, Zhang H, et al. Mesenchymal stem cell transplantation reverses multiorgan dysfunction in systemic lupus erythematosus mice and humans. Stem Cells 2009;27:1421-32
46. Mazzini L, Mareschi K, Ferrero I, et al. Stem cell treatment in amyotrophic lateral sclerosis. J Neurol Sci 2008;265:78-83
47. Riordan N, Ichim T, Min WP, et al. Non-expanded adipose stromal vascular fraction cell therapy for multiple sclerosis. J Trans Med 2009;7:29: published online 24 April 2009, doi:10.1186/1479-5876-7-29.
48. Liang J, Zhang H, Hua B, et al. Allogeneic mesenchymal stem cells transplantation in treatment of multiple sclerosis. Mult Scler 2009;15:644-6
49. Friedens AJ, Chailakh RK, Latsinik NV, et al. Stromal cells responsible for transferring microenvironment of hematopoietic tissues – cloning in vitro and retransplantation in vivo. Transplantation 1974;17:331-40
50. Horwitz EM, Blanc KL, Dominici M, et al. Clarification of the nomenclature for MSC: the international society for cellular therapy position statement. Cytotherapy 2005;7:393-5
51. Bühring HJ, Battula VL, Treml S, et al. Novel markers for the prospective isolation of human MSC. Hem Stem Cells VI 2007;1106:262-71
52. Meirelles LD, Caplan AI, Nardi NB. In search of the in vivo identity of mesenchymal stem cells. Stem Cells 2008;26:2287-99
53. Delalat B, Pourfathollah AA, Soleimani M, et al. Isolation and ex vivo expansion of human umbilical cord blood-derived CD34+ stem cells and their cotransplantation with or without mesenchymal stem cells. Hematology 2009;14:125-32
54. Yoo YA, Kang MH, Kim BS, et al. Sustained co-cultivation with human placenta-derived MSCs enhances ALK5/Smad3 signaling in human breast epithelial cells, leading to EMT and differentiation. Differentiation 2009;77:450-61
55. Lund P, Pilgaard L, Duroux M, et al. Effect of growth media and serum replacements on the proliferation and differentiation of adipose-derived stem cells. Cytotherapy 2009;11:189-97
56. Jazedje T, Perin P, Czeresnia C, et al. Human fallopian tube: a new source of multipotent adult mesenchymal stem cells discarded in surgical procedures. J Trans Med 2009;7:46: published online 18 June 2009, doi:10.1186/1479-5876-7-46.
57. Kopen GC, Prockop DJ, Phinney DG. Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. PNAS 1999;96:10711-6
58. Blondheim NR, Levy YS, Ben-Zur T, et al. Human mesenchymal stem cells express neural genes, suggesting a neural predisposition. Stem Cells Dev 2006;15:141-64
59. Montzka K, Lassonczyk N, Tschoke B, et al. Neural differentiation potential of human bone marrow-derived mesenchymal stromal cells: misleading marker gene expression. BMC Neurosci 2009;10:16: published online 3 March 2009, doi:10.1186/1471-2202-10-16.
60. Kan I, Ben-Zur T, Barhum Y, et al. Dopaminergic differentiation of human mesenchymal stem cells - utilization of bioassay for tyrosine hydroxylase expression. Neurosci Lett 2007;419:28-33

61. Khoo MLM, Shen BJ, Tao HL, et al. Long-term serial passage and neuronal differentiation capability of human bone marrow mesenchymal stem cells. Stem Cells Dev 2008;17:883-96

62. Levy YS, Merims D, Panet H, et al. Induction of neuron-specific enolase promoter and neuronal markers in differentiated mouse bone marrow stromal cells. J Mol Neurosci 2003;21:121-32

63. Mareschi K, Novara M, Rustichelli D, et al. Neural differentiation of human mesenchymal stem cells: evidence for expression of neural markers and eag K+ channel types. Exp Hem 2006;34:1563-72

64. Sanchez-Ramos J, Song S, Cardozo-Pelaez F, et al. Adult bone marrow stromal cells differentiate into neural cells in vitro. Exp Neurol 2000;164:247-56

65. Trzaska KA, Kuzhikandathil EV, Rameshwar P. Specification of a Dopaminergic phenotype from adult human mesenchymal stem cells. Stem Cells 2007;25:2797-808

66. Woodbury D, Schwarz EJ, Prockop DJ, et al. Adult rat and human bone marrow stromal cells differentiate into neurons. J Neurosci Res 2000;61:364-70

67. Levy YS, Bahat-Stroomza M, Barzilay R, et al. Regenerative effect of neural-induced human mesenchymal stromal cells in rat models of Parkinson's disease. Cytotherapy 2008;10:340-52

68. Kennea NL, Waddington SN, Chan J, et al. Differentiation of human fetal mesenchymal stem cells into cells with an oligodendrocyte phenotype. Cell Cycle 2009;8:1069-79

69. Zhao LR, Duan WM, Reyes M, et al. Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats. Exp Neurol 2002;174:11-20

70. Keilhoff G, Goihl A, Langnese K, et al. Transdifferentiation of mesenchymal stem cells into Schwann cell-like myelinating cells. Eur J Cell Biol 2006;85:11-24

71. Barzilay R, Ben-Zur T, Bulvik S, et al. Lentiviral delivery of LMX1a enhances dopaminergic phenotype in differentiated human bone marrow mesenchymal stem cells. Stem Cells Dev 2009;18:591-601

72. Trzaska KA, Reddy BY, Munoz JL, et al. Loss of RE-1 silencing factor in mesenchymal stem cell-derived dopamine progenitors induces functional maturity. Mol Cell Neurosci 2008;39:285-90

73. Kim SS, Yoo SW, Park TS, et al. Neural induction with Neurogenin1 increases the therapeutic effects of mesenchymal stem cells in the ischemic brain. Stem Cells 2008;26:2217-28

74. Phinney DG. Biochemical heterogeneity of mesenchymal stem cell populations – clues to their therapeutic efficacy. Cell Cycle 2007;6:2884-9

75. Bertani N, Malatesta P, Volpi G, et al. Neurogenic potential of human mesenchymal stem cells revisited: analysis by immunostaining, time-lapse video and microarray. J Cell Sci 2005;118:3925-36

76. Lu P, Blesch A, Tuszynski MH. Induction of bone marrow stromal cells to neurons: Differentiation, transdifferentiation, or artifact? J Neurosci Res 2004;77:174-191

77. Neuhuber B, Gallo G, Howard L, et al. Reevaluation of in vitro differentiation protocols for bone marrow stromal cells: disruption of actin cytoskeleton induces rapid morphological changes and mimics neuronal phenotype. J Neurosci Res 2004;77:192-204

78. Choi CB, Cho YK, Bhanu Prakash KV, et al. Analysis of neuron-like differentiation of human bone marrow mesenchymal stem cells. Biochem Biophys Res Comm 2006;350:138-46

79. Morikawa S, Mabuchi Y, Niibe K, et al. Development of mesenchymal stem cells partially originate from the neural crest. Biochem Biophys Res Comm 2009;379:1114-9

80. Takashima Y, Era T, Nakao K, et al. Neuroepithelial cells supply an initial transient wave of MSC differentiation. Cell 2007;129:1377-88

81. Rieske P, Augelli BJ, Stawski R, et al. A population of human brain cells expressing phenotypic markers of more than one lineage can be induced in vitro to differentiate into mesenchymal cells. Exp Cell Res 2009;315:462-73

82. Jiang Y, Jahagirdar BN, Reinhardt RL, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature 2002;418:41-9

83. Serafini M, Dylla SJ, Oki M, et al. Hematopoietic reconstitution by multipotent adult progenitor cells: precursors to long-term hematopoietic stem cells. J Exp Med 2007;204:129-39

84. Yasuhara T, Hara K, Maki M, et al. Intravenous grafts recapitulate the neurorestoration afforded by intracerebrally delivered multipotent adult progenitor cells in neonatal hypoxic-ischemic rats. J Cereb Blood Flow Metab 2008;28:1804-10

85. Ratajczak MZ, Zuba-Surma EK, Machalinski B, et al. Very small embryonic-like (VSEL) stem cells: purification from adult organs, characterization, and biological significance. Stem Cell Rev 2008;4:89-99

86. Tremain N, Korkko J, Ibberson D, et al. MicroSAGE analysis of 2,353 expressed genes in a single cell-derived colony of undifferentiated human mesenchymal stem cells reveals mRNAs of multiple cell lineages. Stem Cells 2001;19:408-18

87. Li Y, Chen J, Chen XG, et al. Human marrow stromal cell therapy for stroke in rat: neurotrophins and functional recovery. Neurology 2002;59:514-23

88. Duffy GP, Ahsan T, O'Brien T, et al. Bone marrow derived mesenchymal stem cells promote angiogenic processes in a time and dose dependent manner in vitro. Tis Eng Part A 2009;15:2459-70

89. Sadan O, Bahat-Stromza M, Barhum Y, et al. Protective effects of neurotrophic factors secreting cells in a 6-OHDA rat model of Parkinson disease. Stem Cells Dev 2009: published online 25, February, 2009 doi: 10.1089/scd.2008.0411.

90. de Hemptinne I, Vermeiren C, Maloteaux JM, et al. Induction of glial glutamate transporters in adult mesenchymal stem cells. J Neuroch 2004;91:155-66

91. Sadan O, Shemesh N, Barzilay R, et al. Migration of neurotrophic factors-secreting mesenchymal stem cells toward a quinolinic acid lesion as viewed by magnetic resonance imaging. Stem Cells 2008;26:2542-51

92. Vercelli A, Mereuta OM, Garbossa D, et al. 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

93. Barzilay R, Sadan O, Melamed E, et al. Comparative characterization of bone marrow derived mesenchymal stem cells from four different rat strains. Cytotherapy 2009;11:435-42

94. Kassis I, Grigoriadis N, Gowda-Kurkalli B, et al. Neuroprotection and immunomodulation with mesenchymal stem cells in chronic experimental autoimmune encephalomyelitis. Arch Neurol 2008;65:753-61

95. Gordon D, Pavlovska G, Glover CP, et al. Human mesenchymal stem cells abrogate experimental allergic encephalomyelitis after intraperitoneal injection, and with sparse CNS infiltration. Neurosci Lett 2008;448:71-3

96. Devine SM, Bartholomew AM, Mahmud N, et al. Mesenchymal stem cells are capable of homing to the bone marrow of non-human primates following systemic infusion. Exp Hem 2001;29:244-55

97. Devine SM, Cobbs C, Jennings M, et al. Mesenchymal stem cells distribute to a wide range of tissues following systemic infusion into nonhuman primates. Blood 2003;101:2999-3001

98. Liechty KW, MacKenzie TC, Shaaban AF, et al. Human mesenchymal stem cells engraft and demonstrate site-specific differentiation after in utero transplantation in sheep. Nat Med 2000;6:1282-6

99. Isakova IA, Baker K, DuTreil M, et al. Age- and dose-related effects on MSC engraftment levels and anatomical distribution in the central nervous systems of nonhuman primates: identification of novel MSC subpopulations that respond to guidance cues in brain. Stem Cells 2007;25:3261-70

100. Loebinger MR, Eddaoudi A, Davies D, et al. Mesenchymal stem cell delivery of TRAIL can eliminate metastatic cancer. Cancer Res 2009;69:4134-42

101. You M, Kim W, Shim W, et al. Cytosine deaminase-producing human mesenchymal stem cells mediate an antitumor effect in a mouse xenograft model. J Gastroent Hep 2009;24:1393-400

102. Chen JR, Cheng GY, Sheu CC, et al. Transplanted bone marrow stromal cells migrate, differentiate and improve motor function in rats with experimentally induced cerebral stroke. J Anat 2008;213:249-58

103. Hellmann MA, Panet H, Barhum Y, et al. Increased survival and migration of engrafted mesenchymal bone marrow stem cells in 6-hydroxydopamine-lesioned rodents. Neurosci Lett 2006;395:124-8

104. Azizi SA, Stokes D, Augelli BJ, et al. Engraftment and migration of human bone marrow stromal cells implanted in the brains of albino rats similarities to astrocyte grafts. PNAS 1998;95:3908-13

105. Yoo SW, Kim SS, Lee SY, et al. Mesenchymal stem cells promote proliferation of endogenous neural stem cells and survival of newborn cells in a rat stroke model. Exp Mol Med 2008;40:387-97

106. Croft AP, Przyborski SA. Mesenchymal stem cells expressing neural antigens instruct a neurogenic cell fate on neural stem cells. Exp Neurol 2009;216:329-41

107. Alexanian AR, Maiman DJ, Kurpad SN, et al. In vitro and in vivo characterization of neurally modified mesenchymal stem cells induced by epigenetic modifiers and neural stem cell environment. Stem Cells Dev 2008;17:1123-30

108. Alexanian AR. Neural stem cells induce bone-marrow-derived mesenchymal stem cells to generate neural stem-like cells via juxtacrine and paracrine interactions. Exp Cell Res 2005;310:383-91

109. Kurozumi K, Nakamura K, Tamiya T, et al. BDNF gene-modified mesenchymal stem cells promote functional recovery and reduce infarct size in the rat middle cerebral artery occlusion model. Mol Ther 2004;9:189-97

110. Kurozumi K, Nakamura K, Tamiya T, et al. Mesenchymal stem cells that produce neurotrophic factors reduce ischemic damage in the rat middle cerebral artery occlusion model. Mol Ther 2005;11:96-104

111. Suzuki M, McHugh J, Tork C, et al. Direct muscle delivery of GDNF with human mesenchymal stem cells improves motor neuron survival and function in a rat model of familial ALS. Mol Ther 2008;16:2002-10

112. Wernig M, Zhao JP, Pruszak J, et al. Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease. PNAS 2008;105:5856-61

113. Yang YX, Li YH, Lv Y, et al. NRSF silencing induces neuronal differentiation of human mesenchymal stem cells. Exp Cell Res 2008;314:2257-65

114. Santamaria-Martinez A, Barquinero J, Barbosa-Desongles A, et al. Identification of multipotent mesenchymal stromal cells in the reactive stroma of a prostate cancer xenograft by side population analysis. Exp Cell Res 2009;315(17):3004-13

115. Spaeth EL, Dembinski JL, Sasser AK, et al. Mesenchymal stem cell transition to tumor-associated fibroblasts contributes to fibrovascular network expansion and tumor progression. PLoS ONE 2009;4:e4992: published online 7 April 2009 doi:10.1371/journal.pone.0004992.

116. Sasportas LS, Kasmieh R, Wakimoto H, et al. Assessment of therapeutic efficacy and fate of engineered human mesenchymal stem cells for cancer therapy. PNAS 2009;106:4822-7

117. Wang H, Cao F, De A, et al. Trafficking mesenchymal stem cell engraftment and differentiation in tumor-bearing mice by bioluminescence imaging. Stem Cells 2009;27:1548-58

118. Kidd S, Spaeth E, Dembinski JL, et al. Direct Evidence of Mesenchymal Stem Cell Tropism for Tumor and Wounding Microenvironments Using In Vivo Bioluminescence Imaging. Stem Cells 2009: published online 30 Jul 2009, doi: 10.1002/stem.187

119. Rubio D, Garcia-Castro J, Martin MC, et al. Spontaneous human adult stem cell transformation. Cancer Res 2005;65:3035-9

120. Serakinci N, Guldberg P, Burns JS, et al. Adult human mesenchymal stem cell as a target for neoplastic transformation. Oncogene 2004;23:5095-8

121. Tolar J, Nauta AJ, Osborn MJ, et al. Sarcoma derived from cultured mesenchymal stem cells. Stem Cells 2007;25:371-9

122. Slavin S, Kurkalli BGS, Karussis D. The potential use of adult stem cells for the treatment of multiple

sclerosis and other neurodegenerative disorders. Clin Neurol Neurosurg 2008;110:943-6

123. Mazzini L, Ferrero I, Luparello V, et al. Mesenchymal stem cell transplantation in amyotrophic lateral sclerosis: a phase I clinical trial. Exp Neur 2009: published online 13 August 2009, doi: 10.1016/j.expneurol.2009.08.007

124. Mazzini L, Vercelli A, Ferrero I, et al. Stem cells in amyotrophic lateral sclerosis: state of the art. Exp Opin Biol Ther 2009;9(10):1245-58

Affiliation

Ofer Sadan[1] MD, Eldad Melamed[1,2] MD & Daniel Offen[†1] PhD
[1†]Neurosciences Laboratory, Felsenstein Medical Research Center, Rabin Medical Center, Petah Tikva 49100, Israel
Tel: +972 3 937 6130;
Fax: +972 3 937 6130;
E-mail: doffen@post.tau.ac.il
[2]The Norma and Alan Aufzien Chair for Research of Parkinson's Disease,
Tel Aviv University,
Sackler School of Medicine,
Tel Aviv, Israel