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Prodigious therapeutic effects of combining Mesenchymal stem cells with Magnetic Nanoparticles

Mesenchymal stem cells and Magnetic Nanoparticles

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Abstract

Mesenchymal stem cells (MSCs) have gained wide-ranging reputation in the medical research community due to their promising regenerative abilities. MSCs can be isolated from various resources mostly Bone marrow, Adipose tissues and Umbilical cord. Huge advances have been achieved in comprehending the possible mechanisms underlying the therapeutic functions of MSCs. Despite the proven role of MSCs in repairing and healing of many disease modalities, many hurdles hinder the transferring of these cells in the clinical settings. Among the most reported problems encountering MSCs therapy *in Vivo* are the loss of tracking signal post-transplantation, insufficient migration, homing and engraftment post-infusion, and undesirable differentiation at the site of injury. Magnetic Nanoparticles (MNPs) have been used widely for various biomedical applications. MNPs have a metallic core stabilized by an outer coating material and their magnetic properties can be modulated by an external magnetic field. These magnetic properties of MNPs were found to enhance the quality of diagnostic imaging procedures and can be used to create a carrying system for targeted delivery of therapeutic substances mainly drug, genes and stem cells. Several studies highlighted the advantageous outcomes of combining MSCs with MNPs in potentiating their tracking, monitoring, homing, engraftment and differentiation. In this review, we will discuss the role of MNPs in promoting the therapeutic profile of MSCs which may improve the success rate of MSCs transplantation and solve many challenges that delay their clinical applicability.

Key Words: Mesenchymal stem cells (MSCs); Magnetic Nanoparticles (MNPs); Tracking; Homing; Migration; Differentiation

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Core Tip: The regenerative abilities of MSCs have been thoroughly investigated and discussed. Despite the great improvement in understanding the curative mechanisms of MSCs, many challenges are still there which slow down the transferring of these cells in the treatment guidelines. Loss of tracking signal, poor migration and homing to the injury site, and undesirable differentiation are the most reported hurdles that thwart the therapeutic outcomes of MSCs in clinical trials. The new strategy of combining MSCs with MNPs has been proven to boost the success rate of MSCs transplantation. MNPs have been employed as an effective contrast agent for long term tracking and monitoring of injected MSCs. MNPs also increase the migration and homing tendency of MSCs and enhance the committed differentiation of these cells. Future studies should be designed to investigate the long term safety profile of these MNPs and determine the suitable formulation and doses based on the specificity of each disease model and the source of MSCs.

INTRODUCTION

Mesenchymal stem or stromal cells(MSCs) are the mostly investigated stem cells due to their enchanting, wide-range therapeutic and regenerative potential [1]. Since their discovery by Friedenstein in 1970, MSCs have been thoroughly analyzed and characterized to discover the mechanistic explanations for their therapeutic abilities [2]. MSCs are easily reached stem cells and can be isolated from many sources including bone marrow, adipose tissues and umbilical cord [3]. These cells are extensively studied compared to other types of stem cells because they are ethically benign and have low teratogenic tendency [3]. In addition, MSCs have an acceptable safety profile and less likely to cause serious side effects [3]. MSCs beneficial effects have been linked primarily to the ability of MSCs to secrete a cocktail of therapeutically active paracrine factors [4]. These paracrine factors secreted by MSCs can attenuate many pathological processes including apoptosis, necrosis, fibrosis, and inflammation and initiate repairing mechanisms in the damaged organs [4]. MSCs immunomodulatory functions also contribute strongly to their curative potential [5]. Moreover, MSCs can exert actual

regeneration of the injured tissues by adopting the intrinsic machinery and differentiating to many functional cell types such as osteocytes, chondrocytes, adipocytes, and cardiomyocytes-like cells [6]. Endogenous or exogenous MSCs must migrate and home in the damaged tissues in order to gain their therapeutic benefits [3]. After homing in the damaged tissues, MSCs should endure the harsh microenvironment that may present [7]. Despite the numerous studies that highlighted the therapeutic efficiency of MSCs, many serious obstacles encumber the shift of MSCs from bench to bedside and delay their presence in the treatment guidelines [8]. The most reported post-transplantation challenges that researchers bump into when they use MSCs in clinical studies are; 1) The disparities in the differentiation potential between *In vitro* and *In vivo*, 3) The shift in their immunological characteristics and cytokines secretion profile under different stress microenvironments that may exist at the site of injury mainly Hypoxia and inflammation, 3) the poor homing and migratory abilities of administered MSCs which may vary based on the route of injection and microenvironment status, 4) the loss of signal emitted from labelled cells due to the leakage of contrast agent after being injected, leads to difficulties in tracking and monitoring of these cells [5,8,9].

Magnetic Nanoparticles (MNPs) have gained great attention among the medical researchers due to their unique biochemical and physical characteristics, their intrinsic biocompatibility and being biodegradable through normal cellular pathways which make them suitable for wide range of biomedical applications [10]. The intrinsic magnetic field elicited by the MNPs, which can be modulated externally by an applied magnetic field , is the basis for using these MNPs as contrast agents for biomedical imaging [11], biomarkers and biosensors [12], and targeted drug [13], cell and gene delivery [14]. Combining MNPs with stem cells was found to enhance their therapeutic performance and solve many challenges that hamper their regenerative potential and delay their clinical applications [15]. There are many types of MNPs that have been fabricated, but the most non-toxic and non- immunogenic MNPs that have been used with MSCs are Iron oxide nanoparticles such as magnetite (Fe3O4) or its oxidized form

maghemite (γ-Fe2O3) [16–18]. These iron oxides based MNPs can be synthesized with different particles' diameters such as Superparamagnetic iron oxide (SPIO) nanoparticles (50–200 nm diameter) [19] and ultra-small superparamagnetic iron oxide (USPIO) nanoparticles (around 35 nm diameter) [20]and different types of stabilizing non-toxic coating substrates such as dextran, polyethylene glycol (PEG), and Silica [21]. In general, the uptake of MNPs by MSCs is mediated mostly through endocytosis. MNPs usually are engulfed by MSCs to form endosomes, which then transformed into Mature multivesicular endosomes (MVEs). The MVEs then combined with lysosomes and get digested and decomposed into Fe3+. The free iron released into the cytoplasm of MSCs modified many cellular pathways to induce and promote their survival, migration, homing, anti-apoptosis and anti-inflammatory, and differentiation. These magnetized MSCs can be further modulated and guided to enhance their therapeutic outcomes by external magnetic fields. The internalization of MNPs inside MSCs can be also achieved by passive diffusion if their particle size is small and by using MNPs that bind specific cell surface immune marker found on MSCs. The prodigious power of using MNPs with MSCs to potentiate their tracking, migration and homing, differentiation and regenerative abilities will be the focus of this review.

Magnetic Nanoparticles (MNPs) as a contrast agent to track MSCs:

The use of mesenchymal stem cells (MSCs) in the clinical settings requires more accurate tracking methods of MSCs after transplantation to determine their destinations, survival and final differentiated fates [22]. To visualize transplanted MSCs using imaging modalities importantly the computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI), these cells must be labelled with contrast agents [23–26]. The problem with the traditional contrast agents is the high leakage rate which causes the loss of emitted signal after short time course [27]. The contrast features of MNPs and their high safety profile encouraged many researchers to use them for labeling MSCs prior to injection [16]. MSCs labelled with MNPs have less leaking tendency and do not affect their stemness [28], rate of

proliferation and the differentiation potential beside providing higher contrast-to-noise ratio for effective imaging [29,30].

Iron oxide nanoparticles (IONs) are the most commonly used MNPs for labelling and tracking MSCs due to their non-toxic and non-immunogenic features, high spatial resolution and penetration depth, and the non- ionizing radiation characteristics [31].Superparamagnetic iron oxide nanoparticles (SPIONs), ultrasmall iron oxide nanoparticles (USPIO-PAA) [32], glucosamine-modified iron oxide nanoparticles (USPIO-PAA-GlcN) [33], and microgel iron oxide (MGIO) [34] are the most studied MNPs for MSCs labelling and tracking by multiple imaging methods. Using SPIONs for stem cell labeling and tracking is a relatively new application. Recently, ferumoxytol (Feraheme®, AMAG Pharmaceuticals), an ultrasmall SPION used clinically as an MRI contrast agent [35]. Ferumoxytol colloidal particle size is less than 50 nm and can be phagocytized efficiently by the MSCs – which have an inherited phagocytosis property- and can then be imaged and tracked by MRI [35]. FeraTrack™, a dextran coated SPIONs, have a positive surface charge making it cell penetrable through a vesicular endocytosis route [36]. FeraTrack™ has gained utility as a biocompatible MRI contrast agent for cell tracking purposes due to their high safety profile [36]. Mesentier-Louro *et al* used FeraTrack to track bone marrow derived MSCs at site of injury in a rodent model of optical nerve injury [37]. They reported that the after injecting FeraTrack™ labeled MSCs intravitreously, they migrated to the site of optical nerve injury and remained there for up to 18 wk which is suitable to monitor their integration with the host tissues at the site of injury using MRI. The incorporation of cationic compounds such as poly-l-lysine and protamine onto the surface coating of SPIONs can enhance labeling of MSCs by promoting interactions with the negatively charged cell surface [37]. Guldris *et al* studied the contrast characteristics of SPIOs and USPIOs coated with poly (acrylic acid) (PAA), and USPIO-PAA-GlcN as labeling agents for MSCs *in vitro* [33]. A portion of these MNPs was cultured with MSCs for 24 h at a concentration of 100 µg mL–1. In the second group, the conditions were maintained, but polylysine (PLL) was used to promote particle uptake. The study found that in the absence of PLL, SPIO-PAA

showed a very low and non-homogeneous labeling efficiency. USPIO-PAA and USPIO-PAA-GlcN showed little to no internalization by MSCs, while combining USPIO-PAA-GlcN with polylysine enhances their biocompatibility with MSCs and increases the detection sensitivity by MRI in both *in vitro* and *in vivo* experiments [33]. Studies also reported that using an external pulsed magnetic field (PMF) opened channels in the cell membrane and increased the uptake of SPIONs by MSCs which intensified the contrast signal [38,39]. Interestingly, Ngen *et al* developed a dual-contrast agent by combining SPIONs and gadolinium chelate to monitor and track MSCs [40]. This dual contrast agent generates powerful positive contrast and increases the signal gain [40]. Furthermore, this dual-contrast agent was also able to distinguish between dead and live cells at the site of injury. This helps in estimating the percentage of MSCs survival rate, as Gadolinium dependent positive contrast is expunged in the live cells, whereas enhanced contrast level found in dead cells [40].

Microgel iron oxide (MGIO) particles were studied to track human fetal MSCs through using 1.5T MRI [41]. MGIO particles were found to achieve high detection sensitivity with low cellular toxicity through a simple incubation protocol, which makes them useful for cellular tracking using standard MRI scanners [41]. These results were similar to that reported by Maila □nder *et al* using adult bone marrow derived MSCs [42]. The tracking efficacy achieved by MGIO was higher than that achieved with USPIO particles and the larger polystyrene particles [41]. Extracellular vesicles (EVs) are secreted lipid bilayered vesicles containing enzymes, nucleic acids and lipoproteins that are involved in intercellular communication. MSCs can activate various repairing machineries by secreting EVs [43]. SPIONs were also used to facilitate the labelling and imaging of EVs derived from MSCs. Dabrowska *et al* labeled these EVs derived from MSCs using the fluorescent lipophilic stain PKH26 and SPION nanoparticles conjugated with rhodamine (Molday ION Rhodamine B™) which was found to be highly biocompatible with EVs to be imaged using MRI [44]. The prospective use of MNPs in MSCs tracking is highly encouraging. MRI and MNPs are complementary and provide

integrated information, like tracking and monitoring MSCs transplanting and engulfing overtime, and this will provide more information to guide further therapy.

Magnetic Nanoparticles (MNPs) to enhance the homing of transplanted MSCs:

Most of MSCs curative applications require injecting these cells directly to the injured tissues or delivering them intravenously, which requires their migration and homing in the damaged tissues [45,46]. MSCs homing is one of the major challenges in clinical settings because only a small percentage of delivered MSCs reaches the desired injury site and integrates with host tissues, while the majority of the administrated cells are trapped in the draining organs and get washed.

Recently, MNPs have been used to improve the homing percentage of transplanted MSCs at the site of injury [47]. Among all nanoparticles, SPIONs are the most extensively used nanomaterials to increase MSCs homing tendency without affecting their viability, proliferation and differentiation [29,30]. MSCs labeled with SPIONs exhibit enhanced homing due to magnetic attraction [48]. Several research groups have investigated the homing and tracking of MSCs after being labelled with SPIONs. Meng *et al* used SPIONs and GFP reporter gene to create a double labelling of Wharton's Jelly human umbilical cord-derived MSCs (WJ-MSCs) [49]. These cells were injected to a nude mouse with cutaneous tissue injury. In this work, they used 25 µg/mL of SPION, and they divided the nude mice into three groups: the first group treated with WJ-MSCs only, the second group treated with GFP/SPIONs-positive WJ-MSCs, and the third group treated with SPIONs/GFP-positive WJ-MSCs and exposed to an external magnetic field (0.5T) [49]. In all three groups, MSCs were injected subcutaneously. The results showed a remarkable increase the migration abilities of GFP/SPIONs-labeled WJ-MSCs *in vivo* without changing their inherited characteristics. The employment of a non-invasive external magnetic field provides a rapid guided homing of WJ-MSCs to the targeted injury site. Yun *et al* used 15 µg/mL Rhodamine B (IRBs), which was added to SPIONs to label MSCs that were injected to mouse model of wounded olfactory bulb. The Rhodamine B/SPIONs-labelled MSCs showed an improved homing by upregulating various homing factors mainly CXCR4 and CXCR4-SDF-1 [49]. Yun *et al* also used a

magnetic field of 0.32 T to direct the Rhodamine B/SPIONs-labelled MSCs rapidly to the site of injury. Based on many studies, SPIONs enhance the MSCs homing by stimulating the expression of chemokine receptors mainly CXCR4-SDF-1α signaling [46].

A recent study by Braniste *et al* in which they created a semiconductor nanoparticle by combining nanometer scale GaN thin layers with a sacrificial zinc ferrite core ($ZnFe_2O_4$) [50]. Braniste *et al* incubated MSCs with (10 mg/mL) semiconductor nanoparticles and applied a remote magnetic field to control the direction of their movement. They found that these semiconductor nanoparticles were effectual to redistribute and rearrange MSCs according to the remote magnetic field intensity, thus enhanced the long term tracking and monitoring of the injected cells *In vivo* [50].

Silva *et al* fabricated gold and maghemite nanoparticles that were functionalized with 2,3-dimercaptosuccinic acid (DMSA) (Au-DMSA and γ-Fe_2O_3-DMSA) [51]. These nanoparticles were incubated with human mesenchymal stem cells and these labelled MSCs were inoculated through intranasal route and tracked using standard computed microtomography. Despite the high biocompatibility of these nanoparticles with MSCs, γ-Fe_2O_3-DMSA and Au-DMSA based contrast was not strong enough for tracking MSCs *in vivo* by standard computed microtomography [51]. An innovative iron-doped hydroxyapatite nanoparticles (FeHA NPs) were prepared by Panseri *et al* and were found to be superior to SPIONs in improving the survival of MSCs due to rapid degradation and lower resulting intracellular iron content [52]. The unique magnetic properties of FeHA NPs make them a suitable carrier for delivering MSCs to the injury site and other therapeutically active products such as drugs, growth factors, and miRNA [52].

Moayeri *et al* used a poly-L-lysine hydrobromide coated superparamagnetic iron oxide nanoparticles (SPIONs) to label adipose-derived stem cells (ADSC- SPION/PLL) [53]. These labeled ADSCs were injected in the medial forebrain bundle in a rat model of Parkinson Disease (PD), and simultaneously an external magnetic field were placed on the top of rat skull for 2 wk [53]. The results of this study showed a significant improvement in the migration and homing of these labeled ADSCs in the damaged sites

of substantia nigra [53]. These abovementioned studies provided strong evidence about the importance of these non-toxic and biocompatible MNPs in potentiating the homing percentage of transplanted MSCs which may improve the successful rate of MSCs transplantation in different disease models.

Magnetic Nanoparticles (MNPs) to improve the migration abilities of transplanted MSCs:

Migration and subsequent engraftment following the infusion of MSCs are essential to enkindle the regenerative power of MSCs. The desultory, undirected movement of MSCs and poor accumulation at the injured site can hinder their therapeutic abilities. It has been found that MNPs can improve the migratory features of MSCs and directed them to the target site [54]. Dextran-coated iron oxide nanoparticles have been reported by Chung *et al* to boost MSCs migration and the subsequent trans-differentiation into dopaminergic like neurons in a mouse model of Parkinson's disease [55].

Li *et al* also examined the *in vitro* migration of rat bone marrow-derived MSCs to an injury site in the presence or absence of polydopamine (PDA)-capped Fe3O4 (Fe3O4@PDA) superparticles [31]. The results showed a significant difference in the number of migrated cells between control MSCs and MSCs labeled with these superparticles [31]. Iron oxide nanoparticles were also found to increase the number of MSCs in the S-phase, their proliferation index, migration ability and secretion of vascular endothelial growth factor (VEGF) [45]. This suggests that labeling with iron oxide nanoparticles increased MSCs migration, while the cell cycle progression was unaffected. It was also demonstrated that labeling MSCs with Fe3O4@polydopamine nanoparticles (Fe3O4@PDA NPs) increase their migration towards laser burn injury sites in a living rat model, as well as their expression of CXCR4 [45]. The latter could explain the increased migration ability of labeled MSCs. Indeed, previous studies had showed that the migration process is heavily dependent on the interaction between SDF-1α and CXCR4, and the internalization of magnetic iron oxide nanoparticles elevates CXCR4 Levels in MSCs [56,57]. Furthermore, SPIONs have been found to activate

the hepatocyte growth factor/tyrosine-protein kinase Met (HGF/c-Met) pathway in MSCs to regulate their migratory and engraftment properties [58].

Magnetic Nanoparticles (MNPs) to potentiate the Differentiation and Survival of transplanted MSCs:

The superparamagnetic properties of MNPs are not only suitable for improving the homing and migration properties of MSCs, studies found that MNPs can potentiate the MSCs survival and differentiation [59,60]. Several studies demonstrated a substantial enhancement of MSCs differentiation when these cells are combined with magnetic iron oxide nanoparticles, magnetic field and a specialized differentiation medium. MNPs improve the engraftment of MSCs at the injury site which is an essential step to adopt the cellular and molecular machinery required to initiate the differentiation to committed cell type [61–64]. MNPs can be also used to enhance the quality of MSCs cryopreservation and survival after thawing these cells [65]. Naseroleslami *et al* transplanted a SPIONs-labelled amniotic membrane-derived mesenchymal stem cells (hAMSCs) in a rat model of isoproterenol (ISO)-induced myocardial injury [66]. They reported that SPIONs- labeled hAMSCs produce a remarkable activation of cardiac repair machinery in the presence of magnetic field through suppressing NF-κB/MAPK dependent inflammation [66]. Zhang *et al* reconstructed a Fe3O4 MNPs by adding graphene oxide (GO) to generate Fe3O4@GO magnetic nanocomposites (MNCs) that were loaded with bone morphogenetic protein-2 (BMP2) [67]. This Fe3O4@GO MNCs were able to mitigate the cell damage caused by oxidative stress and through delivering BMP2, they also improved the osteogenic differentiation abilities of MSCs [67]. Wang *et al* created a magnetic lanthanum-doped HA/CS scaffolds (MLaHA/CS) [68]. They found after placing the MLaHA/CS scaffolds into rats with calvarial defects, it significantly enhances the recruitment of endogenous MSCs and facilitated regeneration of new bone matrix [68]. The dose of internalized MNPs found to have a great influence on the preferential differentiation of MSCs. When less than 10 pgFe/cell was used, the differentiation of MSCs into chondrocytes, adipocytes or osteocytes using citrate-coated maghemite nanoparticles was similar to that of control unlabeled cells [69]. On the other

hand, when higher dose of 30 to 60 pgFe/cell was used, the chondrogenesis was significantly turned off while the adipogenesis and osteogenesis were turned on. Intriguingly, the source of MSCs may also govern their response to certain MNPs [70]. Labusca *et al* showed some discrepancies in the response of adipose- derived MSCs (ADSCs) and Wharton jelly MSCs to uncoated magnetic nanoparticles, with average size of 20 nm [71]. When external magnetic field was applied, the chondrogenic differentiation was more pronounced in the ADSCs cell culture but not in Wharton jelly MSCs cell culture [71]. The possible explanation for these findings was the presence of an active senescent protective mechanism in Wharton- jelly MSCs. Fan and co-authors studied the differences in intracellular iron content, labeling efficiency, cell viability, and Adipogenic and osteogenic differentiation potentials between adipose-derived mesenchymal stem cells (AD-MSCs) and bone marrow derived mesenchymal stem cells (BM-MSCs) after labelling them with superparamagnetic iron oxide nanoparticles (SPIOs). They found that SPIO-labeled AD-MSCs and SPIO-labelled BM-MSCs were similar in their labeling efficiency, intracellular iron level, survival, proliferation, differentiation potentials, and MRI imaging [72]. Since the presence of an external magnetic field can dictate the differentiation fate of MSCs, the same group of investigators, Labusca *et al*, also studied the effect of duration, intensity and frequency of magnetic field on the differentiation abilities of ADSCs labeled with MNPs [73]. These scientists revealed that using an intermittent low intensity magnetic field (0.5 MT) for short time (2 days) triggered their differentiation to adipocytes, while applying intermittent high intensity magnetic field (21.6 MT) for short time (2 days) or continuous low intensity magnetic field (0.5 MT) for longer time (7 days) activated the osteogenic machinery [73]. Wang *et al* injected SPION-labeled ADSCs in a rat model of stress urinary incontinence (SUI). These magnetically labeled MSCs found to have a high survival rate post-transplantation and efficiently enhanced the repairing process of the non-functional sphincter [74]. In the similar context, Xu *et al* showed that umbilical cord-derived MSCs (UC-MSCs) labelled with SPIONs can tolerate the inflammatory microenvironment in mouse model of sepsis by enhancing their immunomodulatory

abilities and the expression of Heme oxygenase 1 (HO-1) and TNF receptor-associated factor (TRAF1) [75]. These findings highlighted the advantageous outcomes of incorporating MNPs with MSCs therapy which may ultimately potentiate the success rate of MSCs transplantation and increase the chance to shift these cells toward bedside. Future studies should be designed to extensively investigate the long-term efficacy and safety of these MNPs labeled MSCs, and in parallel clinical trials must be conducted to reveal the translational possibilities of these MNPs–labeled MSCs. Table 1 summarizes the different studies that used MNPs to improve the transplantation characteristics of MSCs. Combining Nanotechnology with Mesenchymal stem cells opens new avenues to enhance their therapeutic outcomes and long-term regenerative abilities. The incorporation of MNPs with MSCs has been extensively investigated and it revealed great chances to increase their survival , promote their homing and retention at the site of injury, improve their tolerance to stress microenvironments and enhance their integration with host tissues and trigger their differentiation. The use of MNPs with MSCs still in need for further investigation to answer many concerns surrounding their combination. Some of these concerns are related to assessing the safety profile of MNPs on the long-run, determining the optimal non-toxic dose that can be added to MSCs based on the type of pathology and the ultimate target to be achieved, finding the best coating substrate to be used with MNPs without affecting their therapeutic functions, exploring the possibility of combining more than one MNPs for synergistic effects, finding the exact molecular mechanisms that are exerted by MNPs to alter the cellular pathways in MSCs, and studying the impact of the internal microenvironment which varies based on and the type of disease in influencing the uptake of MNPs by MSCs and their ultimate response. A Schematic summary depicted the role of MNPs in improving the transplantation and biological characteristics of MSCs can be found in Figure 1

CONCLUSION

The regenerative abilities of MSCs have been thoroughly investigated and discussed. Despite the great improvement in understanding the curative mechanisms of MSCs, many challenges are still there which slow down the transferring of these cells in the treatment guidelines. Loss of tracking signal, poor migration and homing to the injury site, and undesirable differentiation are the most reported hurdles that thwart the therapeutic outcomes of MSCs in clinical trials. The new strategy of combining MSCs with MNPs has been proven to boost the success rate of MSCs transplantation. MNPs have been employed as an effective contrast agent for long term tracking and monitoring of injected MSCs. MNPs also increase the migration and homing tendency of MSCs and enhance the committed differentiation of these cells. Future studies should be designed to investigate the long term safety profile of these MNPs and determine the suitable formulation and doses based on the specificity of each disease model and the source of MSCs.

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