

Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Intravenous Mesenchymal Stem Cells (MSC)

Evidence Summary

The immunomodulatory properties of MSC injections benefit a wide range of conditions; however, the heterogeneity between studies makes it difficult to determine an optimal protocol.

Neuroprotective Benefit: MSC injections show consistent benefits in animal models of Alzheimer's disease, but standardization of cell preparations will likely be necessary before clinical use.

Aging and related health concerns: Preclinical data suggests benefits for many indications; osteoarthritis data is still equivocal.

Safety: So far, most evidence suggests that single MSC injections are safe if done in an appropriate setting. Less is known about repeated injections.

What is it?

Mesenchymal stem cells (MSCs) are multipotent stromal cells that were initially isolated from non-hematopoietic bone marrow. They have self-renewal properties and are able to differentiate into cells from the mesodermal lineage including osteoblasts, adipocytes, and chondrocytes. MSCs can be isolated from several tissues including bone marrow, adipose, skin, the umbilical cord, and the placenta. Although they are considered stem cells, their value derives from their non-stem/progenitor properties, especially their immunomodulatory properties ([Ankrum et al, 2014](#)). For instance, they can affect the innate immune system by pushing macrophages or microglia to a more anti-inflammatory phenotype ([Uccelli and de Rosbo 2015](#)). Although often considered “immune privileged”, most allogenic MSCs die within 48 hours and recent evidence suggests that they might elicit a cellular immune response, suggesting that they should be thought of as “immune evasive” (as they survive longer than other cells, such as fibroblasts). Therefore, future work to help MSCs better evade the immune system might make them more effective ([Ankrum et al, 2014](#)).

Neuroprotective Benefit: MSC injections show consistent benefits in animal models of Alzheimer’s disease, but standardization of cell preparations will likely be necessary before clinical use.

Types of evidence:

- 8 pre-clinical studies using different types of MSCs in Alzheimer’s disease mouse models

Human research to suggest protection from cognitive decline or dementia:

None

Human research to suggest benefits to patients with dementia:

None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Alzheimer’s disease:

Intravenously (IV) injected MSCs show some efficacy in multiple mouse models of Alzheimer’s disease, in both prophylactic and treatment paradigms. Cells that have been used include human adipose-derived, placental-derived, umbilical cord-derived, ischemia-tolerant (from Stemmedica), and murine bone marrow-derived MSCs.

A single IV injection of human placental-derived or murine bone marrow (BM)-derived MSCs in aged Alzheimer’s rodents restored cognition to the level of control animals in multiple studies ([Kim et al,](#)



[2013](#); [Yun et al, 2013](#); [Kanamaru et al, 2015](#)). In addition, a single injection was reported to decrease soluble amyloid beta 42 (~28%) amyloid beta plaques (up to ~50%), amyloid precursor protein (APP), gamma secretase activity, BACE1 expression, markers of inflammation (reactive astrocytes, microglia, iNOS levels, Cox2 expression, and pro-inflammatory cytokines IL-1 and TNF α), and cell death in the hippocampus. Increases in markers of anti-inflammatory cytokines (e.g. IL-10), growth factors (e.g. Tgf β), and enzymes that degrade amyloid beta (e.g. insulin degrading enzyme) were also reported ([Kim et al, 2013](#); [Yun et al, 2013](#); [Kanamaru et al, 2015](#); [Harach et al, 2016](#)).

Multiple injections of human umbilical cord-derived, human adipose-derived or ischemia-tolerant MSCs in young and aged Alzheimer's animal models also prevented cognitive deficits (or restored cognition) to the level of control animals, decreased amyloid beta plaques (up to 50%) in the cortex (though mixed results in the hippocampus), decreased APP, and decreased soluble amyloid beta. These effects might have been due to an increase in enzymes that degrades amyloid beta (such as neprilysin – though mixed results were reported), or an increase in anti-inflammatory cytokines (e.g. IL-10) or growth factors (e.g. VEGF) ([Kim et al, 2012](#); [Yang et al, 2013](#); [Harach et al, 2016](#)).

One unresolved controversy is whether IV-injected MSCs cross the blood brain barrier. Most accumulate in peripheral tissues (such as the liver, heart, and lungs). Three studies reported the presence of MSCs in the brain of Alzheimer's mice soon after a single IV injection (identified by a fluorescent marker or staining for human-specific proteins). However, they were gone around 1 week later ([Kim et al, 2012](#); [Yang et al, 2013](#); [Harach et al, 2016](#)) and another study reported that no MSC were present at 1, 4, or 7 days after injection ([Park et al, 2016](#)). The reasons for these differences, or whether cells even need to get into the brain, are still unclear.

Stroke:

Types of evidence:

- One meta-analysis of preclinical studies
- One meta-analysis of clinical trials

In a meta-analysis of 46 pre-clinical animal stroke studies, 44 reported significant improvements with MSC injections. Most were IV. The meta-analysis reported effect sizes such as 0.93 (95%CI 0.62-1.24) for infarct volume reduction to 1.78 (95%CI 1.43-2.12) for improvement in the modified Neurological Severity Score (mNSS). There was significant publication bias, studies with a smaller effect size were underreported, but after adjusting for these asymmetries, the effect sizes remained large. In addition,



the effect sizes correlated with the study quality (i.e. higher quality studies had greater effect sizes) ([Vu et al, 2014](#)).

However, a meta-analysis of 7 clinical trials with 288 patients reported that MSC injections did not reduce risk of mortality (RR 0.59, 95%CI 0.29-1.19) or significantly improve scores on the NIH Stroke Scale. In most studies, autologous bone marrow MSCs were injected IV or through a peripheral catheter. The authors concluded that there was no significant difference between stem cell and cell-free treatments ([Wang et al, 2016](#)). Despite the lack of statistical significance, almost all studies show some benefit. Future trials will need to standardize cell preparations and treatment protocols to determine the real benefit of MSC injections for stroke.

APOE4 interactions:

Unknown.

Aging and related health concerns: Preclinical data suggests benefits for many indications; osteoarthritis data is still equivocal.

Below is a subset of studies related to aging and health related concerns. As of November 2016, there were nearly 230 MSC clinical trials ongoing for immune-related diseases, such as inflammatory airway disease, irritable bowel disease, rheumatoid arthritis, solid organ transplant, host vs graft disease, and others ([Wang et al, 2016](#)).

Lifespan:

Types of evidence:

- 3 preclinical animal studies

BM-derived, adipose-derived, and amniotic-derived MSCs extended lifespan in several rodent models. Irradiated mice injected with BM-MSCs from young mice lived 100 days longer than those injected with BM-MSCs from old mice ([Shen et al, 2011](#)). In a mouse model of premature osteoporosis (and accelerated aging – median lifespan 39 days), three injections of amniotic-derived MSCs extended the median lifespan to 92 days ([Xie et al, 2015](#)). Injected animals were larger, had less cell death in the thymus and kidney, and greater bone volume. Finally, monthly injections of amniotic-derived and adipose-derived MSCs into 10 month old mice increased lifespan by 23.4% and 31.3%, respectively ([Kim et al, 2015](#)). In addition, injected animals had improved cognition and motor functions.



Atherosclerosis:

Types of evidence:

- 0 human studies
- 7 preclinical animal studies

Bone marrow (BM) and skin (S)-derived MSCs reduced and stabilized atherosclerotic plaques in animal models (mouse ApoE knockout and Ldlr^{-/-} fed a high fat diet (HFD) atherosclerosis models and rabbit vulnerable plaque models).

In a prophylactic paradigm, [Froderman et al \(2015\)](#) intravenously injected BM-MSCs three times into an atherosclerosis mouse model prior to feeding a HFD. Eight weeks after the final MSC injection they reported a 33% reduction in plaque size (with no change in plaque composition), a decrease in the number of effector T cells and monocytes, a 77% decrease in a cytokine that attracts monocytes and T-cells to the site of inflammation (CCL2), and decreases in other pro-inflammatory cytokines (e.g. INF γ and TNF α) and increases in anti-inflammatory cytokines (e.g. IL-10) compared to non-injected mice. In the lesion site, the macrophage and T cell number decreased.

In other studies, when mice were first fed a HFD to induce atherosclerotic plaque formation and then injected with BM- or S-MSCs (single or multiple injections), the MSCs traveled to the atherosclerotic plaques and the plaques were reduced up to 30%-40% ([Wang et al, 2014](#); [Li et al, 2015](#); [Song et al, 2012](#); [Lin et al, 2015](#)). (One study reported that a single injection of MSCs reduced plaque burden 7 days later but not 28 days later [Lin et al, 2015](#)). Interestingly, this does not seem to be due to a change in blood lipids ([Li et al, 2015](#); [Song et al, 2012](#)). Rather it might be due to an increase in regulatory T cells, an increase in anti-inflammatory cytokines and growth factors (e.g. IL-10, Tgf β), and a decrease in inflammatory cytokines, growth factors, and transcription factors (e.g. hs-CRP, INF γ , TNF α , NFkB) ([Wang et al, 2014](#); [Li et al, 2015](#)).

Two studies reported stabilization of vulnerable plaques in rabbit animal models. Rabbits were fed HFD then atherosclerotic plaques were briefly exposed to liquid nitrogen to make them vulnerable. Their plaques have a massive lipid core and thin fibrous cap. However, rabbits with MSC transplants had plaques with smaller lipid cores and thicker fibrous caps. In addition, MSCs improved plaque composition by increasing the number of smooth muscle cells and decreasing collagen fibers. Transplantation also decreased pro-inflammatory factors (e.g. NFkB, MMP-1, MMP-2, and MMP-9) and the number of apoptotic cells ([Wang et al, 2015](#); [Fang et al, 2013](#)).



In summary, MSC injections appear to be very promising in reducing and preventing atherosclerotic lesions. However, the heterogeneity between animal models, cell types, and treatment paradigms makes it difficult to determine an optimal treatment paradigm.

Osteoarthritis:

Types of evidence:

- 4 meta-analyses of clinical trials
- 1 systematic review of clinical trials
- 1 review article

Osteoarthritis (OA) is characterized the breakdown of the collagen matrix between joints and the inability of chondrocytes to compensate for this damage. Since the first published report in 2002, the use of MSC injections for OA has grown in popularity. However, the heterogeneity between studies and the fact that most published reports are single-arm trials makes it difficult to determine whether MSC treatments for OA are effective.

Four meta-analyses on the use of intra-articular injections of MSCs for the treatment of knee osteoarthritis report conflicting results. In a meta-analysis of 18 studies, [Cui et al \(2016\)](#) reported that MSC intra-articular injections were beneficial for knee OA. However, when only RCTs were examined, the benefits were no longer significant. In a meta-analysis of 7 RCTs, [Xia et al \(2015\)](#) reported a significant improvement in physical function but not pain. When two low-quality studies were excluded, the decrease in pain reached significance. In a meta-analysis of 11 studies that looked at four different functional/pain rating scales, [Xu et al \(2015\)](#) reported improvements in some outcomes but not in others. They concluded there was no advantage of stem cell therapy compared with other treatments. A fourth meta-analysis of 17 studies comparing cell-based cartilage treatments vs. cell-free treatments reported a significant benefit with cell-based treatments; however, the study did not separate out RCTs from non-RCT ([Deng et al, 2016](#))

A systematic review from [Filardo et al \(2016\)](#) and a review article from [Afizah and Hui \(2016\)](#), help identify correlations from these discrepant results. First, MSC injections in the clinic appear to be safe (up to 2-year follow-up for most studies), with only minor discomfort and swelling. Second, most studies report some kind of benefit (reflected by clinical improvement, MRI and macroscopic findings) regardless of cell source, indication, or administration method. However, publication bias cannot be excluded. Third, the patient populations that tend to benefit most are younger and have a lower BMI,



smaller lesion size for focal lesions, and are at earlier stages of OA. Fourth, bone marrow-derived MSCs tend to be a better source than adipose-derived MSCs; however, there has never been a head-to-head clinical trial, so this is inconclusive. Fifth, higher doses of MSC injections tend to be more beneficial (although the upper limit is not clear).

In conclusion, because of the high heterogeneity between clinical trials, and the fact that most have been single-arm studies, the optimal treatment regimen of MSC injection for OA is still unclear. However, MSC injections for OA appear to be very safe.

Peripheral Neuropathy:

Types of evidence:

- Four preclinical animal studies

In rat/mouse models of diabetic peripheral neuropathy, BM-MSCs, iPSC-derived MSCs, or cryopreserved dental pulp MSCs injected locally into the diabetic animal hind limb improved motor/sensory nerve conduction velocity, vascularization, myelin levels, and nerve number on the animal's foot pad ([Han et al, 2016](#); [Himeno et al, 2013](#); [Hata et al, 2015](#)). [Waterman et al \(2012\)](#) developed an MSC line optimized to be anti-inflammatory (MSC2). After an intraperitoneal injection with these cells, animals had a lower thermal sensitivity than non-diabetic or diabetic mice injected with regular MSCs. Anti-inflammatory cytokines, such as IL-10, were higher in MSC2 injected animals than MSC animals while pro-inflammatory cytokines, such as IL-1 α , IL-1 β , and IL-6, were lower. These cells are being commercially developed by [Commence Bio](#) (currently in pre-clinical development for a number of inflammatory indications).

Safety: So far, most evidence suggests that MSC injections are safe if done in an appropriate setting. Less is known about repeated injections.

Types of evidence:

- 1 meta-analysis

There are many clinics that purport to give stem cell treatments for conditions other than osteoarthritis. Many of these are unregulated, and adverse events sometimes happen that cannot be reversed (see this recent [blog post](#) from stem cell scientist Paul Knoepfler).

In a meta-analysis of 36 studies (8 RCTs), [Lalu et al \(2012\)](#) reported no significant difference in the RCTs for acute infusional toxicity (OR 2.12 95%CI 0.55-8.77), cardiac arrhythmias (OR 0.33 95%CI 0.10-1.04), cardiac adverse events (OR 1.05 95%CI 0.39-2.81), or death (OR 0.60 95%CI 0.28-1.25). In addition, there were no significant increases in gastrointestinal or renal adverse events, pulmonary events, neurological adverse events, infection related events, or tumors. Although MSC injections appear to be relatively safe, MSCs quickly die or are eliminated (per pre-clinical studies), and the safety of repeated injections is less well-known.

Sources and dosing:

In clinical trials for stroke, investigators have intravenously injected 5×10^7 - 1×10^8 of autologous bone marrow-derived MSCs ([Wang et al, 2016](#)). Companies such as Longeveron and Stemmedica are currently conducting clinical trials and injecting up to 100 million and 1.5 million of their proprietary stem cells, respectively. Autologous stem cell collected from the body must be expanded in culture, and the appropriate dosing and cell preparations for MSC injections depends on the cell type and the indication it is being used for. Unfortunately, the field is still very heterogeneous, and clinical trials are still in early stages.

Research underway:

There are currently 247 [ongoing studies](#) using mesenchymal stem cells on [clinicaltrials.gov](#). Five studies are registered for Alzheimer's disease, with three of them currently recruiting ([NCT02833792](#) (Stemmedica Cell Technologies), [NCT02600130](#) (Longeveron), [NCT02054208](#) (Medipost Co)), while two are not yet recruiting ([NCT02899091](#) (CHABiotech), [NCT02672306](#) (South China Research Center for Stem Cell and Regenerative Medicine)).

Search terms:

Pubmed, Google:

All IV publications from Wang et al, 2015 systematic review for Alzheimer's disease

Pubmed:

- mesenchymal stem cell intravenous alzheimer
- mesenchymal stem cell atherosclerosis
- mesenchymal stem cell osteoarthritis (w/ and w/out systematic review/meta analysis)
- mesenchymal stem cell peripheral neuropathy
- mesenchymal stem cell safety (meta-analysis; systematic review)

- mesenchymal stem cell anti-aging
- mesenchymal stem cell longevity

Google:

- Mesenchymal longevity/anti-aging

Clinicaltrials.gov:

- Mesenchymal stem cell (by indication: Alzheimer's disease; atherosclerosis)

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit [Cognitive Vitality's Rating page](#).