INTRODUCTION TO ALZHEIMER’S DISEASE

Alzheimer’s disease (AD) is a neurodegenerative disorder with insidious onset and slow progression. It is a growing health problem and has a huge impact on individuals and society. Epidemiological study has revealed that the number of AD patients aged 60 and above in China is close to 9.83 million with a 95% confidence interval of 9.39–10.29.1 The incidence of population over 65 years of age is about 1%–3%.2 After the age of 70, the risk of AD doubles every 5 years.3 Clinically, patients may be in the preclinical period without overt symptoms for about 8–10 years.2 Later, they can experience progressive memory decline, aphasia, apraxia, inattention, executive dysfunction, personality changes, and behavioral symptoms. Once AD is diagnosed, the average survival time of patients is about 4.2 years for men and 5.7 years for women.4 The pathological features of AD are manifested by extracellular amyloid beta (Aβ) plaques, hyperphosphorylated tau in intracellular neurofibrillary tangles, neuronal death, synapse loss, and brain atrophy. Many therapies have been tested to improve or at least effectively modify the course of AD. Meaningful data indicate that the transplantation of stem cells can alleviate neuropathology and significantly ameliorate cognitive deficits in animal models with Alzheimer’s disease. Transplanted stem cells have shown their inherent advantages in improving cognitive impairment and memory dysfunction, although certain weaknesses or limitations need to be overcome. This review recapitulates rodent models for AD, the therapeutic efficacy of stem cells, influencing factors, and the underlying mechanisms behind these changes. Stem cell therapy provides perspective and challenges for its clinical application in the future.
death, synapse elimination, and brain atrophy.\textsuperscript{5,6} These characteristics are highlighted through related mechanisms such as oxidative stress, free radical generation, metabolic dysfunction, and the release of inflammatory cytokines (e.g., tumor necrosis factor [TNF]-\textalpha and interleukin [IL]-1\textbeta). Detrimental factors activate cell death pathway and induce synaptic deficit in the hippocampus, leading to cognitive impairment and memory decline. Drug treatment for AD includes acetylcholinesterase inhibitors such as donepezil, galantamine, rivastigmine, and tacrine, N-methyl-d-aspartate (NMDA) receptor antagonist such as memantine, and A\textbeta-directed monoclonal antibody such as aducanumab.\textsuperscript{7,8} Several natural compounds that can decrease amyloid plaques, neurofibrillary tangles, and neuroinflammation have been evaluated in clinical trials as well.\textsuperscript{9,10} So far, no drugs have been demonstrated to prevent or delay the progression of AD. Stem cell therapy as a novel technology has been explored in animal models with AD. Acquirable research results have proved that the transplantation of stem cells can improve memory and learning abilities. The longer life expectancy well reflects the therapeutic effect of transplanted stem cells on different AD-like models.\textsuperscript{11,12} However, the functional role of stem cells varies greatly, and there are some weaknesses or limitations that need to be overcome. The etiology of AD involves multiple risk factors, such as genotype, aging, infection, immunity, toxin intake, environmental pollutants, sociopsychological factors, and so on.\textsuperscript{13–15} Genetically, the E4 allele of apolipoprotein E (APOE) on chromosome 19 is the susceptible locus for late-onset Alzheimer’s disease.\textsuperscript{16} APOE4 homozygotes dramatically increase the risk of AD, 14.5 times higher than APOE3 homozygotes. About 45%-50% of AD patients carry at least one APOE4 allele.\textsuperscript{17–20} There is an interaction between APOE4 expression and herpes simplex virus type 1 in the progression of Alzheimer’s disease.\textsuperscript{21} Other infections are also related to neuroinflammation that leads to A\textbeta_{42} production and tau pathology.\textsuperscript{22–25} Nowadays, sporadic AD is generally considered to be the result of the interaction between genetic susceptibility and environmental factors.\textsuperscript{26} Genetic traits can be modified by environment and lifestyle. Moreover, certain disorders, such as hypothyroidism, cerebrovascular disease, type 2 diabetes mellitus, immune-related disease, viral infection, epilepsy, depression, and schizophrenia, are predisposing factors for the development of AD. Altogether, the development of Alzheimer’s disease is a multifactorial process characterized by a high degree of neuropathological heterogeneity.

2 | OVERVIEW OF STEM CELL THERAPY FOR ALZHEIMER’S DISEASE

Many different compounds, biochemicals, or mediators are used for intervention studies in animal models with Alzheimer’s disease, such as microRNAs, cytokines, chemical inhibitors, and cell-derived exosomes.\textsuperscript{11,27–29} Their therapeutic effects are altered with animal species, delivery approaches, evaluation indicators, and time intervals. A multitude of research data support that the transplantation of stem cells is associated with the improvement of synaptic plasticity and cognitive performance.\textsuperscript{1,30,31} Therapeutic stem cells can transdifferentiate into neuronal lineage, which is a promising approach to stimulate neurogenesis circuitry.

2.1 | Types of stem cells

Based on the tissue source (e.g., embryo, placenta, amniotic fluid, bone marrow, fat, menstrual blood, or dental pulp), stem cells can be roughly classified into three categories: autologous, allogenic, or induced pluripotent stem cells (iPSCs). During a literature search, 75 preclinical studies that contain complete information on stem cell therapy were collected. Further analysis indicated that the common types of stem cells are brain-derived neural stem cells (NSCs), bone marrow-derived mesenchymal stem cells (BM-MSCs), human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs), and embryonic stem cells (ESCs) (Figure 1). Several types of stem cells are described in detail below.

2.1.1 | NSCs

The transplanted NSCs compensate for the loss of neurons and have a direct effect on the recipient tissue (Table 1). Moreover, transplanted NSCs can produce paracrine cytokines to exert indirect effect on neurogenesis. The function of transplanted NSCs can be enhanced through preconditioning. For instance, the transplantation of NSCs that express growth factor promotes neurogenesis and improves cognitive impairment in an AD-like rodent model.\textsuperscript{32} NSCs overexpressing choline acetyltransferase can reverse spatial memory and learning deficits.\textsuperscript{33} The underlying mechanisms are related to the paracrine release of neuroprotective factors, the attenuation of mixed proteinopathy (amyloid and tau), immunomodulation, the inhibition of neuroinflammation, and the promotion of neurogenesis/synaptogenesis.\textsuperscript{11,34} However, the transplanted NSCs can also transdifferentiate into non-neuronal glia, which is an adverse event in its application.\textsuperscript{35}

2.1.2 | BM-MSCs

Bone marrow-derived mesenchymal stem cells have been broadly investigated in the treatment of animal models with Alzheimer’s disease. Because of their accessibility, relative ease of handling, and the wide range of cell types into which they can transdifferentiate, BM-MSCs are now one of the most frequently used stem cell types. The transplanted BM-MSCs can transdifferentiate into neurons, secrete acetylcholine neurotransmitters, and produce neurotrophins such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). Also, the transplanted BM-MSCs inhibit A\textbeta- and tau-related cell death. Meanwhile, the expression of anti-inflammatory cytokines such as IL-10 and IL-4 is upregulated, whereas the levels of pro-inflammatory cytokines such as TNF-\textalpha and IL-1\beta are downregulated. Furthermore, the intravenous administration of BM-MSCs that can
migrate to the hippocampus improves spatial learning, cognitive ability, and memory deficits. Intravenous delivery is a minimally invasive approach that has significant advantages over intracranial injection. Unfortunately, the infiltration of intravenous BM-MSC into multiple organs is still a problem. Another potential issue is that the transplanted BM-MSCs may cause thrombosis during stem cell therapy.

2.1.3 | hUCB-MSCs

The beneficial characteristics of hUCB-MSCs include noninvasive collection, hypo-immunogenicity, superior tropism, high differentiation potentials, and paracrine activity. Therefore, hUCB-MSCs have been emerging as an alternative source for allogeneic MSC-mediated therapy. The therapeutic effects of hUCB-MSCs have been verified in 5 x FAD mice and nontransgenic Sprague-Dawley rats. Moreover, their safety and efficacy have also been evaluated through phase-I/IIa clinical trials (NCT02054208) in patients with Alzheimer’s disease. The secretome of hUCB-MSCs includes multifunctional molecules, such as the inhibitory effect of galectin-3 on aberrant tau phosphorylation, the role of ICAM-1 in the removal of Aβ plaques, and the effect of growth/differentiation factor 15 (GDF-15) on neurogenesis in AD models. hUCB-MSCs may significantly reduce Aβ-dependent AD pathology, as demonstrated by the coculture system of hUCB-MSCs and mouse primary hippocampal neurons. The paracrine thrombospondin-1 (TSP-1) of hUCB-MSCs can rescue neurons from the Aβ peptide-induced loss of synaptic density, thereby improving cognitive function in the AD-like mouse model.

2.1.4 | ESCs

Transplanted mouse ESC-derived neuronal precursor cells can transdifferentiate into cholinergic cell phenotype, improving spatial
memory performance in ibotenic acid-induced AD-like rats. Another study reports that human ESCs can transform into GABAergic and cholinergic neuronal subtypes, leading to improvements in spatial memory and learning ability in mouse model. Although ESC transplantation has shown the ability to improve cognitive function in rodent models, its clinical significance is limited due to the pluripotent uncontrolled cell growth and tumorigenesis. Despite much preclinical research, there are inherent ethical and immunogenic limitations in the use of allogeneic ESC-based therapies.

### 2.1.5 iPSCs

iPSCs are a product of autologous source using up-to-date cell technology. Human iPSCs have been generated from primary fibroblasts that are isolated from patients with familial AD or from healthy individuals. In iPSCs from sporadic AD, APOE4 can be converted to APOE3 to attenuate multiple AD-related pathologies, such as Aβ aggregates and hyperphosphorylated tau. The transplantation of iPSCs has shown long-term survival and efficacy in preclinical studies, including ischemic stroke rodent model and APP transgenic mice. The therapeutic effect of iPSC-derived somatic cells on patients with familial AD is being evaluated through clinical trial NCT00874783. Human iPSC-derived precursors can differentiate into mature cholinergic neurons and form synaptic networks, improving neurological function and ameliorating memory impairment. iPSC-NSCs can reduce pro-inflammatory factors through a neurotrophin-associated bystander effect after their implantation in the ipsilesional hippocampus. However, the benefits of autologous iPSCs are limited by the phenotypic neuropathology of neurons generated from AD patients, including abnormal Aβ level, increased p-tau, decreased neurite length, and susceptibility to inflammatory challenge.

### 2.2 Delivery methods of stem cells

#### 2.2.1 Intravenous

Intravenous administration is a relatively convenient method for stem cell delivery, which can be implemented multiple times through the peripheral vein. However, the transfused stem cells travel in the systemic circulation, and they may infiltrate into different organs, with especially large accumulation in the lungs. Stem cells injected through the tail vein take time to cross the blood-brain barrier and enter the hippocampus for functional activities. Hence, the therapeutic efficiency of the intravenous method needs to be improved.

#### 2.2.2 Intrahippocampal

Intrahippocampal delivery avoids the blood-brain barrier but requires a 3-dimensional positioning device and imaging system. Moreover,

### Table 1 Advantages and limitations of different stem cells in the treatment of AD

| Stem cell types | Advantages | Limitations/weaknesses | References |
|-----------------|------------|------------------------|------------|
| NSCs            | Multipotent; easy adaption in brain; no need for transdifferentiation | Invasive collection; poor survival; tumorigenesis; non-neuronal glia; intrahippocampal or intraventricular stereotactic injection | J. Neurosci. 2012; 32:7926-7940. Exp. Neurol. 2013; 247:73-79. Bioconjugate Chem. 2013; 24:1798-1804. |
| BM-MSCs         | Autologous transplantation; easy handling; multipotent; intravenous application; phase-I/II clinical trials | Low rate of neuronal differentiation; tumorigenesis; thrombosis; poor homing and multiple organ infiltration | Cell Stem Cell. 2008; 2:313-319. Theranostics. 2017 Jan 1;7(1):106-116. Neurology. 2003; 23:169-180. Stem Cells Dev. 2011; 20:1297-1308. |
| hUCB-MSCs       | Noninvasive collection; easy handling; multipotent; phase-I/IIa clinical trials | Ethical and immunogenic issues; tumorigenesis; poor homing; stereotactic brain injection | Alzheimers Dement. 2015 Jul 26;11(2):95-102. Alzheimers Res Ther. 2021 Sep 14;13(1):154. |
| ESCs            | Unlimited self-renewal; pluripotent | Ethical and immunogenic issues; uncontrolled differentiation and teratoma formation; only a few studies in experimental animals | Development. 2004; 131:5515-5525. Am. J. Pathol. 2005; 166:1781-1791. Nat. Biotechnol. 2002; 20:933-6. |
| iPSCs           | Multipotent; autologous; multipotent | Only a few studies in experimental animals; possible pathological phenotype | Hum Mol Genet. 2014 Sep 15;23(R1):R17-26. BMC Genom. 2015; 16:84 Hum. Mol. Genet. 2014; 23:3523-3536. |
| Other (e.g., DPSCs, AD-MSCs, etc.) | Autologous; multipotent | Only a few studies in experimental animals | Cell Stem Cell. 2008; 2:313-319. J. Neurosci. Res. 2013; 91:660-670. Aging. 2013; 34:2408-2420. Cell Biol Int. 2017 Jun;41(6):639-650. |
stereotactic injection is a traumatic operation that reaches the functional area of the hippocampus. Therefore, it is inappropriate to perform multiple injections, which limits its clinical application. In addition, the local pressure can be increased after the stem cells are injected into the hippocampus. This pressure change may generate a physical impact, but its potential influence remains to be determined. In contrast, peripheral vein delivery does not have this type of problem.

2.2.3 | Intracerebroventricular

Intracerebroventricular method is similar to intrahippocampal administration, and also requires 3-dimensional positioning device and imaging system. The physical pressure in the cerebral ventricle is elevated after the injection of stem cells. Accordingly, the physical pressure of cerebral tissue is proportional to the volume of transplanted stem cells and depends on the delivery method. Sometimes, even if the same cell type (i.e., BM-MSCs) is used, the volume of stem cells has to be adjusted due to different delivery procedures. 11

2.2.4 | Intranasal

The intranasal route is a noninvasive and convenient way that can easily and repeatedly deliver drugs, exosomes, and stem cells to the brain. 58,59 This injury-free method shows clinical feasibility and has important advantages over conventional injection or intracranial transplantation. 60 The intranasal delivery of stem cells has been performed in APP/PS1 transgenic mice, and the functional improvement has been verified. 59 Currently, nanotechnology has been combined with the intranasal administration of stem cells, which has exhibited a synergistic effect on the treatment of neurological diseases. 60,61 The therapeutic efficiency of intranasal administration has not yet been proven.

2.3 | The functional mechanism of stem cells

Preclinical studies have shown that there is a complex signal network involved in the improvement of cognitive function following stem cell therapy. Representative signal pathways and potential mechanisms are summarized as follows.

2.3.1 | Neurogenesis/Synaptogenesis

The transplanted stem cells contribute to hippocampal neurogenesis and synaptic plasticity (Figure 2). hUCB-MSCs can be stereotactically injected into the hippocampus of APP/PS1 transgenic mice, which stimulates neurogenesis and synaptic plasticity through paracrine GDF-15. 39 AD-MSCs improve endogenous neurogenesis in both the subgranular and subventricular zones, and reduce cognitive decline in APP/PS1 mice. 62 BM-MSCs are transfused into APP/PS1 mice via the tail vein to promote hippocampal neurogenesis. 11,63 The transplanted stem cells can up-regulate the expression of galectin-3, activate the Wnt signaling pathway, and facilitate the secretion of autocrine and paracrine cytokines such as BDNF and NGF, which are associated with the improvement of cognitive ability. 39,64-66

2.3.2 | Amyloid-β and tau pathologies

The deposition of Aβ aggregates and the formation of neurofibrillary tangles are related to the neuronal death and synaptic loss. The administration of hUCB-MSCs mitigates the hyperphosphorylation of tau and ameliorates memory impairment in mice. Furthermore, the secretion of essential galectin-3 takes part in the removal of aberrant tau tangles by modulating protein-protein interactions. 42 The intrahippocampal transplantation of hAM-MSCs remarkably decreases Aβ deposits and improves memory function in APP/PS1 mice. 67 BM-MSCs not only reduce the production of Aβ peptides in the cortex and hippocampus, but also promote the degradation and transport of Aβ proteins. Moreover, BM-MSCs can attenuate the phosphorylation level of tau protein in the APP/PS1 mice. 11

2.3.3 | Inflammation and immunoregulation

The therapeutic effect of BM-MSCs on APP/PS1 transgenic mice involves immunoregulatory mechanisms, including peripheral monocyte recruitment, microglial M1/M2 polarization, pro-/anti-inflammatory cytokines, neurotrophin-mediated synaptic plasticity, and so on. 68 BM-MSCs can regulate the microenvironmental immune activity by inhibiting the excessive activation of microglia. The expression of pro-inflammatory TNF-α and IL-1β is downregulated, whereas the level of anti-inflammatory IL-10 is upregulated. Moreover, BM-MSCs dramatically reduce the number of astrocytes and microglia. 69,70 Human menstrual blood-derived MSCs are able to reduce the level of several pro-inflammatory cytokines such as IL-1β and TNF-α, which are associated with an altered microglial phenotype in APP/PS1 transgenic mice. 71 Inflammation/immunoregulation is a key axis associated with the improvement of synaptic function and cognitive performance.

2.3.4 | Paracrine and autocrine cytokines

Injected hUCB-MSCs can secrete paracrine GDF-15 in the hippocampus of APP/PS1 transgenic mice, which promotes neurogenesis and synapse formation. 39 Also, hUCB-MSCs produce galectin-3 to reduce the hyperphosphorylation of tau, thereby lessening aberrant tau tangles. 42 BM-MSCs can stimulate the hippocampal angiogenesis through vascular endothelial growth factor (VEGF) expression. 70 Moreover, BM-MSCs regulate the expression of Nrf2, reduce oxidative stress, and decrease neuronal
The upregulation of neurotrophic factors such as BDNF and NGF raises the number of NeuN-positive neurons and boosts neuronal repair.\(^{63,74,75}\)

### 2.3.5 Enhancement of synapse formation

The transplanted BM-MSCs have effects on synapse formation and endogenous neurogenesis. Potential mechanisms involve (i) the generation of neurotrophic factors, with stem cell transplantation improving cognitive performance, which may contribute to the recovery of synaptic connectivity through the release of neurotrophins (i.e., growth-associated protein-43 [GAP-43], BDNF)\(^{73,76}\); and (ii) the proliferation of regulatory T cells. The immunoregulation of the central nervous system depends on the interaction between microglia and T cells. The microglia-mediated proliferation of A\(\beta\)-reactive Th2 cells is linked with the expression of cytokines IL-4 and IL-10, which may counterbalance the toxic level of nitric oxide (NO) induced by the A\(\beta\) protein.\(^{77,78}\) MSCs can stimulate the proliferation of regulatory T cells.\(^{79,80}\) T cells mediate synaptic plasticity by shaping the crosstalk of distinct immune cells or specialized immune networks.

### 2.3.6 Novel balance theory

Stem cell therapy for AD is related to the integrative effect of different mechanisms, such as inflammation, immunoregulation, oxidative stress, apoptosis, autophagy, and angiogenesis (Figure 3).\(^{11}\) These mechanisms alter the regional homeostasis in the hippocampus and mediate functional reconstruction by establishing a new balance.\(^{34}\) The new balance theory involves many advanced subjects, such as stem cell heterogeneity and therapeutic effect, the role of
stem cell–derived extracellular vesicles or exosomes, and synaptic plasticity mediated by the crosstalk between T cells and microglia.

3 | THERAPEUTIC EFFICACY OF STEM CELLS AND ITS INFLUENCING FACTORS

3.1 | The evaluation of therapeutic effect

Stem cells such as NSCs, BM-MSCs, hUCB-MSCs, ESCs, and iPSCs have been investigated in different AD-like animal models. Furthermore, hUCB-MSCs, hPD-MSCs, hBM-MSCs, and hAD-SVF are being tested in different clinical trials. The evaluation of therapeutic efficacy involves (i) behavioral performance tests in animal models, and (ii) biochemical and pathohistological indicators.

Examples of behavioral performance tests include Morris water maze, Barnes maze, Y-maze, T-maze, zero-maze, 8-arm maze, plus-maze discriminative avoidance task, shuttle box test, step down test, open field test, and dark avoidance. In clinical trials, the disease-related severity of all subjects is evaluated based on symptoms, cognitive function, memory, and quality of life. Biochemical and pathohistological changes of the AβPP/PS/tau triple transgenic model are informative in assessing co-evolving amyloid and tau pathologies, which are related to the pathomechanism of Alzheimer's disease. The pathophysiological changes of Aβ and tau in the human brain occur before the onset of AD symptoms. There are high levels of Aβ42, t-tau, and p-tau in peripheral neurogenic exosomes and cerebrospinal fluid, which is powerful evidence for the diagnosis of AD.

3.2 | Selection of animal models

Many animal models with Alzheimer's disease mimic the pathological characteristics of amyloidosis, such as the injection of Aβ proteins (e.g., Aβ1-42, Aβ1-40, Aβ25-35) and transgenic models. The advantages of the injection method include high success rate, good stability, rapidness, and ability to use different animal species. However, this method inevitably causes mechanical damage to the cerebral tissue during the injection process, resulting in unpredictable injury. By employing genetic modification of APP, PS1, PS2, and APOE4, over-produced Aβ proteins are deposited in the brain to induce cognitive dysfunction. Of note, end-stage amyloid and tau pathologies in 3× transgenic AD mice are similar to those in sporadic AD, but the comprehensive investigation of AβPP/Aβ and tau reveals key differences in biochemical and pathological characterization. Hyperphosphorylated tau is expressed along with AβPP/τ from an early age, whereas abundant extracellular amyloid plaques and paired helical filaments are observed at a late stage. Transgenic models are useful in evaluating Aβ proteopathy, but not models of sporadic AD as they poorly mirror the pathogenesis of the human disease. In addition, AD-like animal models can also be established by other methods, such as intraperitoneal injection of β-galactose, direct injection of scopolamine to impair cholinergic neurons, gamma knife-mediated hippocampal damage, and so forth.

Interestingly, Aβ produced in the liver is able to induce neurodegeneration as well, which is another potential cause of Alzheimer's disease. Therefore, understanding the advantages and limitations of AD-like models will help select a suitable model that better approximates to human sporadic AD. Since very successful results in
animal models may reflect only limited aspects of human AD pathology, the track record of success in AD clinical trials is very poor.\textsuperscript{88,94}

### 3.3 | To optimize stem cell types

Stem cell therapy can improve cognitive deficits as demonstrated by different AD-like animal models.\textsuperscript{11,42} So far, there are no conclusions regarding the comparison of therapeutic efficacy using different stem cells. In fact, every cell type has its weaknesses or limitations. For instance, ESCs and hUCB-MSCs have ethical and immunogenic issues. Autologous NSCs from brain biopsy may front onto unacceptable attitude and technical challenge. Relatively, BM-MSCs seem to have certain advantages, but they are still complicated by various problems, such as heterogeneity, low viability, and poor homing to lesion area. According to available data, the therapeutic efficiency of stem cells is altered due to (i) viability and heterogeneity, (ii) preconditioning, and (iii) gene manipulation.

The passage number of cultured MSCs has a significant impact on the pluripotency. Mouse BM-MSCs can maintain functional morphology and multipotent state in the 4th generation.\textsuperscript{95,96} The expression of CD29, CD44, and CD90 on the membrane of rat BM-MSCs is gradually increased with passage numbers, reaching the peak after 5-6 generations.\textsuperscript{77,98} It is generally believed that the BM-MSCs before 7 passages have high viability and are suitable for stem cell therapy.

The viability of MSCs may be enhanced through preconditioning, genetic modification, and culture system. Stem cells preconditioned with dimethylglycine can enhance the therapeutic efficiency of Aβ-induced animal models.\textsuperscript{73} Other preconditioning methods, such as hypoxia, lipopolysaccharide (LPS), inflammatory cytokines, vitamin E, electromagnetic stimulation, and low-level lasers, can also improve the viability and immunomodulatory effect of stem cells.\textsuperscript{79,99}

Mesenchymal stem cells can be modified through gene manipulation to enhance therapeutic efficiency. When BM-MSCs overexpressing VEGF are transplanted into APP/PS1 mice, the accumulation of amyloid deposits is reduced, which can significantly improve AD cognitive impairment in the middle and late stages of AD in mice.\textsuperscript{70} The transplantation of MSCs expressing antisense-miR-937 lowers the deposition of Aβ proteins, stimulates the secretion of BDNF, and improves behavioral deficits as demonstrated by social recognition test and plus-maze discriminative avoidance task in APP/PS1 mice.\textsuperscript{74}

### 3.4 | To optimize delivery methods

As mentioned above, common methods for stem cell delivery include intravenous, intrahippocampal, intracerebroventricular, and intranasal. Each method has different advantages and weaknesses. Sometimes, the delivery method is a key factor in determining the therapeutic efficacy of transplanted stem cells. For example, it is necessary to repeatedly transplant the stem cells to achieve a satisfactory result. It has been demonstrated that repeated transplantation is more effective than single treatment regimen in the rat model.\textsuperscript{81,100} In the clinical trial NCT03117738, autologous adipose tissue derived MSCs (AdMSCs) will be intravenously transfused 9 times at 2-week intervals. In clinical application, it is impractical for patients to receive multiple injections through the intrahippocampal or intracerebroventricular method.

### 4 | PROSPECTIVE AND CHALLENGE

#### 4.1 | The biosafety of stem cells

The transplanted stem cells can alter their phenotype and function after being implanted in different tissues. Early study has discovered that the transplantation of ESCs can induce teratoma formation in vivo. Moreover, tumorigenesis has been reported from autologous important as its effectiveness. Interestingly, stem cell-derived exosomes (SC-Exos) act as cell-free mediators for the intercellular information exchange.\textsuperscript{79,76,101} The intracerebroventricular injection of SC-Exos can reduce Aβ plaques and tau tangles to improve cognitive function in transgenic APP/PS1 mice.\textsuperscript{101} The therapeutic advantages of stem cells and SC-Exos will be determined through parallel comparative studies in the future.

#### 4.2 | The standardization of stem cell culture

Whatever the tissue origin of stem cells, the specification of passage numbers represents an important parameter before being able to take advantage of stem cells with greater safety. So far, there is no standardized protocol for stem cell culture. For example, some studies have transplanted BM-MSCs at passages 1-2, but other studies have used BM-MSCs at passages 4-6 or passages 7-10.\textsuperscript{63,102} This may explain why therapeutic effects are so inconsistent. In addition to the type of stem cells, therapeutic efficiency is also affected by other factors, such as cell concentration, the species of recipients, and delivery methods. Thus, it is imperative to standardize the protocol for stem cell therapy.

#### 4.3 | Further evaluation of stem cell delivery

Common delivery methods in preclinical studies include stereotactic injection in the brain and intravenous injection in the peripheral vein. Stereotactic injection in the brain is a traumatic procedure, generally a single treatment. Its clinical application and therapeutic effect are thus limited. Multiple injections through peripheral veins can also improve the cognitive ability of AD-like models to a certain extent, but the optimization of this method needs further evaluation. Recently, nasal administration has been utilized to deliver stem cells, which can alleviate the cognitive impairment in AD-like mice.\textsuperscript{58} However, this is a new alternative method whose effectiveness and stability have to be determined by future study.
4.4 The prospects of stem cell therapy

Autologous stem cells are the most-used cell type owing to easy isolation and intravenous transplantation, without immunogenic and ethical issues.\(^{103}\) Still, there are some problems that need to be resolved, such as long-term safety, optimum cell source and delivery procedure, the response of donor cells to the AD-pathogenic microenvironment, and the mechanisms of action (Figure 3). Nevertheless, stem cells have been employed in the treatment of AD-like animal models for decades, and the accumulation of a large amount of research data has laid the foundation for the clinical trial of AD. Predictably, stem cell therapy will become a good candidate for the treatment of AD and other neurological diseases.

5 SUMMARY

Stem cell therapy for AD carries enormous promise, but it remains under development. Now, preclinical studies demonstrate proof of concept and reveal the underlying therapeutic mechanisms. Stem cell therapy has been tested in clinical trials. The accumulation of research data has laid the foundation for the future clinical treatment of AD patients. Perhaps the synergy of different methods can be employed in therapeutic strategy that involves cell modification, gene manipulation, and pharmacological intervention. Regarding the efficacy of stem cell therapy in AD patients, more time will be needed to draw conclusions.

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CONFLICT OF INTEREST

Authors of this review are editorial board members of AMEM, but were excluded from the peer-review process and all editorial decisions related to the publication of this article.

ORCID

Chuan Qin https://orcid.org/0000-0002-6261-1232
Kewei Wang https://orcid.org/0000-0001-5869-2490

REFERENCES

1. Jia L, Du Y, Chu L, et al. Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: a cross-sectional study. Lancet Public Health. 2020;5(12):e661-e671. doi:10.1016/S2468-2667(20)30185-7
2. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer’s disease. Nat Rev Dis Prim. 2015;1:15056. doi:10.1038/nrdp.2015.56
3. Lane CA, Hardy J, Schott JM. Alzheimer’s disease. Eur J Neurol. 2018;25(1):59-70. doi:10.1111/ene.13439
4. Larson EB, Shadlen MF, Wang L, et al. Survival after initial diagnosis of Alzheimer disease. Ann Intern Med. 2004;140(7):501-509. doi:10.7326/0003-4819-140-7-200404060-00008
5. Boche D, Nicoll JAR. Invited Review - Understanding cause and effect in Alzheimer’s pathophysiology: implications for clinical trials. Neuropathol Appl Neurobiol. 2020;46(7):623-640. doi:10.1111/nan.12642
6. Sheppard O, Coleman M. Alzheimer’s disease: etiology, neuropathology and pathogenesis. In: Huang X, ed. Alzheimer’s Disease: Drug Discovery [Internet]. Exon Publications; 2020:1-21. doi:10.36255/exonpublications.alzheimersdisease.2020.ch1
7. Ghai R, Nagarajan K, Arora M, Grover P, Ali N, Kapoor G. Current strategies and novel drug approaches for Alzheimer disease. CNS Neurol Disord Drug Targets. 2020;19(6):867-869. doi:10.2174/1871527319660020717091513
8. Alexander GC, Emerson S, Kesselheim AS. Evaluation of Aducanumab for Alzheimer disease: scientific evidence and regulatory review involving efficacy, safety, and futility. JAMA. 2021;325(17):1717-1718. doi:10.1001/jama.2021.3854
9. Long JM, Holtzman DM. Alzheimer disease: An update on pathology and treatment strategies. Cell. 2019;179(2):312-339. doi:10.1016/j.cell.2019.09.001
10. Yiannopoulou KG, Papageorgiou SG. Current and future treatments in Alzheimer disease: an update. J Central Nervous Syst Dis. 2020;12:1179573520907397. doi:10.1177/1179573520907397
11. Qin C, Lu Y, Wang K, et al. Transplantation of bone marrow mesenchymal stem cells improves cognitive deficits and alleviates neuropathology in animal models of Alzheimer’s disease: a meta-analytic review on potential mechanisms. Transl Neurodegen. 2020;9(1):20. doi:10.1186/s40035-020-00199-x
12. Shin JY, Park HJ, Kim HN, et al. Mesenchymal stem cells enhance autophagy and increase beta-amyloid clearance in Alzheimer disease models. Autophagy. 2014;10(1):32-44. doi:10.4161/auto.26508
13. Tanzi RE, St George-Hyslop PH, Gusella JF. Molecular genetic approaches to Alzheimer’s disease. Trends Neurosci. 1989;12(4):152-158. doi:10.1016/0166-2236(89)90055-6
14. Reitz C, Mayeux R. Alzheimer disease: epidemiology, diagnostic criteria, risk factors and biomarkers. Biochem Pharmacol. 2014;88(4):640-651. doi:10.1016/j.bcp.2013.12.024
15. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. Nat Rev Neurol. 2011;7(3):137-152. doi:10.1038/nrneurol.2011.2
16. Lambert JC, Heath S, Even G, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer’s disease. Nat Genet. 2009;41(10):1094-1099. doi:10.1038/ng.439
17. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer’s disease. Neurology. 1993;43(8):1467-1472. doi:10.1212/wnl.43.8.1467
18. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer disease meta analysis consortium. JAMA. 1997;278(16):1349-1356.
19. Sando SB, Melquist S, Cannon A, et al. APOE epsilon 4 lowers age at onset and is a high risk factor for Alzheimer’s disease; a case control study from central Norway. BMC Neurology. 2008;8:9. doi:10.1186/1471-2377-8-9
20. Rosenberg JB, Kaplitt MG, De BP, et al. AAVrh.10-mediated APOE2 central nervous system gene therapy for APOE4-associated Alzheimer’s disease. Human Gene Ther Clin Dev. 2018;29(1):24-47. doi:10.1089/humc.2017.231
21. Linard M, Letenneur L, Garrigue I, Doize A, Dartigues JF, Helmer C. Interaction between APOE4 and herpes simplex virus type 1 in Alzheimer’s disease. Alzheimer’s Dementia. 2020;16(1):200-208. doi:10.1002/alz.12008
22. Koedel U, Finslerle V, Pfister HW. Lyme neuroborreliosis-epidemiology, diagnosis and management. Nat Rev Neurol. 2015;11(8):446-456. doi:10.1038/nrneurol.2015.121
23. Dominy SS, Lynch C, Ermini F, et al. Porphyromonas gingivalis in Alzheimer’s disease brains: evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv. 2019;5(1):eaau3333. doi:10.1126/sciadv.aau3333

24. Blanc F, Philipp N, Cretin B, et al. Lyme neuroborreliosis and dementia. J Alzheimers Dis. 2014;41(4):1087-1093. doi:10.3233/JAD-130446

25. Pia D, Alonso R, Rabano A, Rodal I, Carrasco L. Different brain regions are infected with fungi in Alzheimer’s disease. Sci Rep. 2015;5:15015. doi:10.1038/srep15015

26. Nebel RA, Aggarwal NT, Barnes LL, et al. Understanding the impact of sex and gender in Alzheimer’s disease: a call to action. Alzheimers Dementia. 2018;14(9):1171-1183. doi:j.alzj.2018.04.008

27. Huang HJ, Chen SL, Huang HY, et al. Chronic low dose of AM404 ameliorates the cognitive impairment and pathological features in hyperglycemic 3xTg-AD mice. Psychopharmacology. 2019;236(2):763-773. doi:10.1007/s00213-018-5108-0

28. Teter B, Morihara T, Lim GP, et al. Curcumin restores innate immune Alzheimer’s disease risk gene expression to ameliorate Alzheimer pathogenesis. Neurobiol Dis. 2019;127:432-448. doi:10.1016/j.nbd.2019.02.015

29. Cui GH, Wu J, Mou FF, et al. Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorate cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses in APP/PS1 mice. FASEB J. 2018;32(2):654-668. doi:10.1096/fj.201706040R

30. Bae JS, Han HS, Youn DH, et al. Bone marrow-derived mesenchymal stem cells promote neuronal networks with functional synaptic transmission after transplantation into mice with neurodegeneration. Stem Cells. 2007;25(5):1307-1316. doi:10.1634/stemcells.2006-0561

31. Shen Z, Li X, Bao X, Wang R. Microglia-targeted stem cell therapies for Alzheimer disease: a preclinical data review. J Neurosci Res. 2017;95(12):2420-2429. doi:10.1002/jnr.24060

32. Blorton-Jones M, Kitazawa M, Martinez-Coria H, et al. Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. Proc Natl Acad Sci USA. 2009;106(32):13594-13599. doi:10.1073/pnas.090142010

33. Park D, Yang YH, Bae DK, et al. Improvement of cognitive function and physical activity of aging mice by human neural stem cells over-expressing choline acetyltransferase. Neurobiol Aging. 2013;34(11):2639-2646. doi:10.1016/j.neurobiolaging.2013.04.026

34. Qin C, Li Y, Wang K. Novel balance mechanism participates in stem cell therapy to alleviate neuropathology and cognitive impairment in animal models with Alzheimer’s disease. Cells. 2021;10(10):2757. doi:10.3390/Cells10102757

35. Xuan AG, Luo M, Ji WD, Long DH. Effects of engrafted neural stem cells in Alzheimer’s disease rats. Neurosci Lett. 2009;450(2):167-171. doi:10.1016/j.neulet.2008.12.001

36. Liao L, Shi B, Chang H, et al. Heparin improves BMSC cell therapy: anticoagulant treatment by heparin improves the safety and therapeutic effect of bone marrow-derived mesenchymal stem cell cytotherapy. Theranostics. 2017;7(1):106-116. doi:10.7150/thno.16911

37. Kim DH, Lim H, Lee D, et al. Thrombospondin-1 secreted by human umbilical cord blood-derived mesenchymal stem cells rescues neurons from synaptic dysfunction in Alzheimer’s disease model. Sci Rep. 2018;8(1):354. doi:10.1038/s41598-017-18542-0

38. Lee M, Jeong SY, Ha J, et al. Low immunogenicity of allogeneic human umbilical cord blood- derived mesenchymal stem cells in vitro and in vivo. Biochem Biophys Res Comm. 2014;446(4):983-989. doi:10.1016/j.bbrc.2014.03.051

39. Kim DH, Lee D, Chang EH, et al. GDF-15 secreted from human umbilical cord blood mesenchymal stem cells delivered through the cerebrospinal fluid promotes hippocampal neurogenesis and synaptic activity in an Alzheimer’s disease model. Stem Cells Dev. 2015;24(20):2378-2390. doi:10.1089/scd.2014.0487

40. Ehrhart J, Darlington D, Kuzmin-Nichols N, et al. Biodistribution of infused human umbilical cord blood cells in Alzheimer’s disease-like murine model. Cell Transplant. 2016;25(1):195-199. doi:10.3727/09636915X689604

41. Kim JY, Kim DH, Kim JH, et al. Soluble intracellular adhesion molecule-1 secreted by human umbilical cord blood-derived mesenchymal stem cell reduces amyloid-beta plaques. Cell Death Differ. 2012;19(4):680-691. doi:10.1038/cdd.2011.140

42. Lim H, Lee D, Choi WK, Choi SJ, Oh W, Kim DH. Galectin-3 secreted by human umbilical cord blood-derived mesenchymal stem cells reduces aberrant tau phosphorylation in an Alzheimer disease model. Stem Cells Int. 2020;2020:8878412. doi:10.1155/2020/8878412

43. Moghadam FH, Alaei H, Karbalaei T, Tanhaei S, Nasr Esfahani MH, Baharvand H. Transplantation of primed or unprimed mouse embryonic stem cell-derived neural precursor cells improves cognitive function in Alzheimerian rats. Differentiation. 2009;78(2-3):59-68. doi:10.1016/j.diff.2009.06.005

44. Bissonnette CJ, Lyass L, Bhattacharyya BJ, Belmadani A, Miller RJ, Kessler JA. The controlled generation of functional basal forebrain cholinergic neurons from human embryonic stem cells. Stem Cells. 2011;29(5):802-811. doi:10.1002/stem.626

45. Liu Y, Weick JP, Liu H, et al. Medial gangliocytic eminence-like cells derived from human embryonic stem cells correct learning and memory deficits. Nat Biotechnol. 2013;31(5):440-447. doi:10.1038/nbt.2565

46. Acharya MM, Christie LA, Lan ML, et al. Rescue of radiation-induced cognitive impairment through cranial transplantation of human embryonic stem cells. Proc Natl Acad Sci USA. 2009;106(45):19150-19155. doi:10.1073/pnas.0909293106

47. Fong CY, Gauthaman K, Bongo A. Teratomas from pluripotent stem cells: a clinical hurdle. J Cell Biochem. 2010;111(4):769-781. doi:10.1002/jcb.22775

48. Duncan T, Valenzuela M. Alzheimer’s disease, dementia, and stem cell therapy. Stem Cell Res Ther. 2017;8(1):111. doi:10.1186/s13287-017-0567-5

49. Raska J, Hribkova H, Klimova H, et al. Generation of six human iPSC lines from patients with a familial Alzheimer’s disease (n = 3) and sex- and age-matched healthy controls (n = 3). Stem Cell Research. 2021;53:102379. doi:10.1016/j.scr.2021.102379

50. Lin YT, Seo J, Gao F, et al. APOE4 causes widespread molecular and cellular alterations associated with Alzheimer’s disease phenotypes in human iPSC-derived brain cell types. Neuron. 2018;98(6):1141-1154 e7. doi:10.1016/j.neuron.2018.05.008

51. Cavalli E, Battaglia G, Basile MS, et al. Exploratory analysis of iPSCs-derived neuronal cells as predictors of diagnosis and treatment of Alzheimer disease. Brain Sci. 2020;10(3):166. doi:10.3390/brainsci10030166

52. Fujiwara N, Shimizu J, Takai K, et al. Restoration of spatial memory dysfunction of human APP transgenic mice by transplantation of neuronal precursors derived from human iPSC cells. Neurosci Lett. 2013;557(Pt B):129-134.

53. Eckert A, Huang L, Gonzalez R, Kim HS, Hamblin MH, Lee JP. Bystander effect fuels human induced pluripotent stem cell-derived neural stem cells to quickly attenuate early stage neurological deficits after stroke. Stem Cells Transl Med. 2015;4(7):841-851. doi:10.5966/sctm.2014-0184

54. Pang ZP, Yang N, Vierbuchen T, et al. Induction of human neuronal cells by defined transcription factors. Nature. 2011;476(7359):220-223. doi:10.1038/nature10202

55. Balez R, Steiner N, Engel M, et al. Neuroprotective effects of apigenin against inflammation, neuronal excitability and apoptosis in an induced pluripotent stem cell model of Alzheimer’s disease. Sci Rep. 2016;6:31450. doi:10.1038/srep31450
56. Hossini AM, Megges M, Prgjone A, et al. Induced pluripotent stem cell-derived neuronal cells from a sporadic Alzheimer’s disease donor as a model for investigating AD-associated gene regulatory networks. BMC Genom. 2015;16:84. doi:10.1186/s12864-015-1262-5

57. Muratore CR, Rice HC, Srikanth P, et al. The familial Alzheimer’s disease APPV717I mutation alters APP processing and Tau expression in iPSC-derived neurons. Hum Mol Genet. 2014;23(13):3523-3536. doi:10.1093/hmg/ddu064

58. Santamaria G, Brandi E, Vitolò P, et al. Intranasal delivery of mesenchymal stem cell-secretome repairs the brain of Alzheimer’s mice. Cell Death Differ. 2021;28(1):203-218. doi:10.1038/s41418-020-0592-2

59. Danielyan L, Beer-Hammer S, Stolzing A, et al. Intranasal delivery of bone marrow-derived mesenchymal stem cells, macrophages, and microglia to the brain in mouse models of Alzheimer’s and Parkinson’s disease. Cell Transplant. 2014;23(Suppl 1):S123-S139. doi:10.3727/096368914X684970

60. Dali P, Shende P. Advances in stem cell therapy for brain diseases via the intranasal route. Curr Pharm Biotechnol. 2021;22(11):1466-1481. doi:10.2174/1389201021666201218130947

61. Donega V, Nijboer CH, van Velthoven CT, et al. Assessment of therapeutic potential of human embryonic derived neural stem cells improves cell survival and functional recovery after transplantation in hypoxic-ischemic stroke. Cell Transplant. 2015;24(12):2449-2461. doi:10.3727/096368914X679354

62. Rosso SB, Inestrosa NC. WNT signaling in neuronal maturation and synaptogenesis. Front Cell Neurosci. 2013;7:103. doi:10.3389/fncel.2013.00103

63. Jiao H, Shi K, Zhang W, et al. Therapeutic potential of human amniotic membrane-derived mesenchymal stem cells in APP transgenic mice. Oncol Lett. 2016;12(3):1877-1883. doi:10.3892/ol.2016.4857

64. Qin C, Li Y, Wang K. Functional mechanism of bone marrow-derived mesenchymal stem cells in the treatment of animal models with Alzheimer’s disease: inhibition of neuroinflammation. J Inflamm Res. 2021;14:4761-4775. doi:10.2147/JIR.S327538

65. Lee JK, Jin HK, Bae JS. Bone marrow-derived mesenchymal stem cells attenuate amyloid beta-induced memory impairment and apotosis by inhibiting neuronal cell death. Curr Alzheimer Res. 2010;7(6):540-548. doi:10.2174/156720510792231739

66. García KO, Ornellas FL, Martin PK, et al. Therapeutic effects of the transplantation of VEGF overexpressing bone marrow mesenchymal stem cells in the hippocampus of murine model of Alzheimer’s disease. Front Aging Neurosci. 2014;6:30. doi:10.3389/fnagi.2014.00030

67. Zhao Y, Chen X, Wu Y, Wang Y, Li Y, Xiang C. Transplantation of human menstrual blood-derived mesenchymal stem cells alleviates Alzheimer’s disease-like pathology in APP/PS1 transgenic mice. Front Mol Neurosci. 2018;11:140. doi:10.3389/fnmol.2018.00140

68. Safar MM, Arab HH, Rizk SM, El-Maraghy SA. Bone marrow-derived endothelial progenitor cells protect against scopolamine-induced Alzheimer-like pathological aberrations. Mol Neurobiol. 2016;53(3):1403-1418. doi:10.1007/s12035-014-9051-8

69. Esmaeizade B, Artimani T, Amiril, et al. Dimethylaminoxy glycine preconditioning enhances protective effects of bone marrow-derived mesenchymal stem cells in Aβ-induced Alzheimer disease. Physiol Behav. 2019;265-272. doi:10.1016/j.physbeh.2018.11.034

70. Liu Z, Wang C, Wang X, Xu S. Therapeutic effects of transplantation of As-MiR-937-expressing mesenchymal stem cells in murine model of Alzheimer’s disease. Cell Physiol Biochem. 2015;37(1):321-330. doi:10.1159/000430356

71. Li LY, Li JT, Wu QY, et al. Transplantation of NGF-gene-modified bone marrow stromal cells into a rat model of Alzheimer’s disease. J Mol Neurosci. 2008;34(2):157-163. doi:10.1007/s10735-007-9022-x

72. Cui J, Cui C, Cui Y, et al. Bone marrow mesenchymal stem cell transplantation increases GAP-43 expression via ERK1/2 and PI3K/Akt pathways in intracerebral hemorrhage. Cell Physiol Biochem. 2017;42(1):137-144. doi:10.1159/000477122

73. Regmi S, Pathak S, Kim JO, Yong CS, Jeong JH. Mesenchymal stem cell therapy for the treatment of inflammatory diseases: challenges, opportunities, and future perspectives. Eur J Cell Biol. 2019;98(5-8):151041. doi:10.1016/j.ejcb.2019.04.002

74. Zarif H, Hosseiny S, Paquet A, et al. CD4+(+) T cells have a permissive effect on enriched environment-induced hippocampus synaptic plasticity. Front Synaptic Neurosci. 2018;10:14. doi:10.3389/fnsyn.2018.00014

75. Kamamaru T, Kamimura N, Yokota T, et al. Intravenous transplantation of bone marrow-derived mononuclear cells prevents memory impairment in transgenic mouse models of Alzheimer’s disease. Brain Res. 2015;1605:49-58. doi:10.1016/j.brainres.2015.02.011

76. Hunter JM, Bowers WJ, Maarouf CL, et al. Biochemical and morphological characterization of the AβPP/PS/TAU triple transgenic mouse model and its relevance to sporadic Alzheimer’s disease. J Alzheimers Dis. 2011;27(2):361-376. doi:10.3233/JAD-2011-110608

77. Chen Z, Liu C, Zhang J, Rehlin N, Xing Y, Li Y. Cerebrospinal fluid Abeta42, t-tau, and p-tau levels in the differential diagnosis of idiopathic normal-pressure hydrocephalus: a systematic review and meta-analysis. Fluids Barriers CNS. 2017;14(1):13. doi:10.1186/s12987-017-0062-5

78. Jia L, Qiu J, Zhang H, et al. Concordance between the assessment of Abeta 42, T-tau, and P-T181- tau in peripheral blood neuronal-derived exosomes and cerebrospinal fluid. Alzheimers Dementia. 2019;15(8):1071-1080. doi:10.1016/j.jalz.2019.05.002

79. McLarnon JG, Ryu JK. Relevance of Abeta1-42 intrahippocampal injection as an animal model of inflamed Alzheimer’s disease brain. Curr Alzheimer Res. 2008;5(5):475-480. doi:10.2174/156720508785908874

80. Lin N, Xiong LL, Zhang RP, et al. Injection of Abeta1-42 into hippocampus-induced cognitive lesion associated with neuronal apoptosis and multiple gene expressions in the tree shrew. Apoptosis. 2016;21(5):621-640. doi:10.1007/s10495-016-1227-4

81. Wang K, Sun W, Zhang L, et al. Oleic acid ameliorates Aβ25-35 injection-induced memory deficit in Alzheimer’s disease model rats by maintaining synaptic plasticity. CNS Neurol Disord Drug Targets. 2018;17(5):389-399. doi:10.2174/1871527317666810525113109

82. Drummond E, Wisniewski T. Alzheimer’s disease: experimental models and reality. Acta Neuropathol. 2017;133(2):155-175. doi:10.1007/s00401-016-1662-x
89. Mandour DA, Bendary MA, Alsemeh AE. Histological and immunohistochemical alterations of hippocampus and prefrontal cortex in a rat model of Alzheimer-like disease with a preferential role of the flavonoid "hesperidin". J Mol Histol. 2021;52(5):1043-1065. doi:10.1007/s10735-021-09998-6

90. Nimgampalle M, Kuna Y. Anti-Alzheimer properties of probiotic, Lactobacillus plantarum MTCC 1325 in Alzheimer's disease induced albino rats. J Clin Diagn Res. 2017;11(8):KC01-KC05. doi:10.7860/JCDR/2017/26106.10428

91. Liscak R, Vladyka V, Novotny J Jr, et al. Leksell gamma knife lesioning of the rat hippocampus: the relationship between radiation dose and functional and structural damage. J Neurosurg. 2002;97(5 Suppl):666-673. doi:10.3171/jns.2002.97.supplement

92. Jirak D, Namestkova K, Herynek V, et al. Lesion evolution after gamma knife irradiation observed by magnetic resonance imaging. Int J Radiat Biol. 2007;83(4):237-244. doi:10.1080/09553000601169792

93. Lam V, Takechi R, Hackett MJ, et al. Synthesis of human amyloid restricted to liver results in an Alzheimer disease-like neurodegenerative phenotype. PLoS Biol. 2021;19(9):e3001358. doi:10.1371/journal.pbio.3001358

94. Wisniewski T, Boutajangout A. Immunotherapeutic approaches for Alzheimer's disease in transgenic mouse models. Brain Struct Funct. 2010;214(2–3):201-218. doi:10.1007/s00429-009-0236-2

95. Choi MR, Kim HY, Park JY, et al. Selection of optimal passage of bone marrow-derived mesenchymal stem cells for stem cell therapy in patients with amyotrophic lateral sclerosis. Neurosci Lett. 2010;472(2):94-98. doi:10.1016/j.neulet.2010.01.054

96. Boregowda SV, Krishnappa V, Chambers JW, et al. Atmospheric oxygen inhibits growth and differentiation of marrow-derived mouse mesenchymal stem cells via a p53-dependent mechanism: implications for long-term culture expansion. Stem Cells. 2012;30(5):975-987. doi:10.1002/stem.1069

97. Li C, Wei G, Gu Q, et al. Donor age and cell passage affect osteogenic ability of rat bone marrow mesenchymal stem cells. Cell Biochem Biophys. 2015;72(2):543-549. doi:10.1007/s12013-014-0500-9

98. Semedo P, Palasio CG, Oliveira CD, et al. Early modulation of inflammation by mesenchymal stem cell after acute kidney injury. Int Immunopharmacol. 2009;9(6):677-682. doi:10.1016/j.intimp.2008.12.008

99. Hu C, Li L. Preconditioning influences mesenchymal stem cell properties in vitro and in vivo. J Cell Mol Med. 2018;22(3):1428-1442. doi:10.1111/jcmm.13492

100. Kamiya F, Ueda M, Nito C, et al. Effect of repeated allogeneic bone marrow mononuclear cell transplantation on brain injury following transient focal cerebral ischemia in rats. Life Sci. 2014;95(1):22-28. doi:10.1016/j.lfs.2013.12.016

101. Nakano M, Kubota K, Kobayashi E, et al. Bone marrow-derived mesenchymal stem cells improve cognitive impairment in an Alzheimer's disease model by increasing the expression of microRNA-146a in hippocampus. Sci Rep. 2020;10(1):10772. doi:10.1038/s41598-020-67460-1

102. Han L, Zhou Y, Zhang R, et al. MicroRNA Let-7f-5p promotes bone marrow mesenchymal stem cells survival by targeting caspase-3 in Alzheimer disease model. Front Neurosci. 2018;12:333. doi:10.3389/fnins.2018.00333

103. Vasic V, Barth K, Schmidt MHH. Neurodegeneration and neuroregeneration-Alzheimer's disease and stem cell therapy. Int J Mol Sci. 2019;20(17):4272. doi:10.3390/ijms20174272

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