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**Stem cell therapy for Alzheimer's disease**

Liu XY *et al.* Alzheimer's disease

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**Abstract**

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by memory loss and cognitive impairment. It is caused by synaptic failure and excessive accumulation of misfolded proteins. To date, almost all advanced clinical trials on specific AD-related pathways have failed mostly due to a large number of neurons lost in the brain of patients with AD. Also, currently available drug candidates intervene too late. Stem cells have improved characteristics of self-renewal, proliferation, differentiation, and recombination with the advent of stem cell technology and the transformation of these cells into different types of central nervous system neurons and glial cells. Stem cell treatment has been successful in AD animal models. Recent preclinical studies on stem cell therapy for AD have proved to be promising. Cell replacement therapies, such as human embryonic stem cells or induced pluripotent stem cell–derived neural cells, have the potential to treat patients with AD, and human clinical trials are ongoing in this regard. However, many steps still need to be taken before stem cell therapy becomes a clinically feasible treatment for human AD and related diseases. This paper reviews the pathophysiology of AD and the application prospects of related stem cells based on cell type.

**Key words:** Alzheimer's disease; Stem cell; Therapy; Pathogenesis; Animal experiment; Clinical trial

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**Core tip:** Alzheimer’s disease (AD), a progressive neurodegenerative disorder featuring memory loss and cognitive impairment, is caused by synaptic failure and the excessive accumulation of misfolded proteins. Stem cell-based therapies cast a new hope for AD treatment as a replacement or regeneration strategy. The results from recent preclinical studies regarding stem cell-based therapies are promising. Human clinical trials are now underway. However, a number of questions remain to be answered prior to safe and effective clinical translation. This review explores the pathophysiology of AD and summarizes the relevant stem cell research according to cell type. We also briefly summarize related clinical trials. Finally, future perspectives are discussed with regard to their clinical applications.

**INTRODUCTION**

Dementia is a neurodegenerative, debilitating, and fatal disease characterized by progressive cognitive impairment, behavioral disorders, and loss of function in daily life. Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50%-70% of dementia cases worldwide[1]. The 2018 World Alzheimer's Disease Report shows that 50 million people worldwide have dementia. With a new case occurring every 3 s worldwide, AD has rapidly become an epidemic, with the number of cases predicted to be 152 million by 2050[2].

AD has several neuropathological hallmarks, including the deposition of β-amyloid (Aβ) peptides in the extracellular matrix between neurons (known as amyloid plaques), the intracellular formation of neurofibrillary tangles arising from the accumulation of hyperphosphorylated tau protein in neurons, neuronal loss, neuroinflammation, and oxidative stress. Despite advances in understanding the etiology of AD, treating the disease by retaining acetylcholine and reducing glutamate is limited to symptom management[3]. Although cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers combined with some relatively new clinical standards can help diagnose alive patients, the certainty of diagnosis was achieved only by post-mortem autopsy[3]. These criteria highlight that the gold standard for the etiological diagnosis remains the neuropathological assessment. Accordingly, the results of CSF biomarkers for AD may provide explanatory evidence for neurocognitive symptoms and predict the type of evolution, especially when there are no other obvious causes of cognitive impairment. Reducing Aβ levels has been the dominant treatment strategy in development to halt, retard, or even reverse the progression of AD pathology. In fact, currently available treatments include three types of cholinesterase inhibitors, one N-methyl-daspartate receptor antagonist, and one combined drug therapy (memantine plus donepezil) are currently approved for clinical use[4]. However, it is unclear how valuable such a palliative drug-based approach can be.

Therefore, new and effective treatments, such as removing toxic deposits and replacing lost neurons, need to be developed to improve the pathological state of the disease, stimulate neural precursors, prevent nerve death, enhance structural neural plasticity, and so forth. At the same time, it is also necessary to provide a better environment for the remaining cells. Current breakthroughs in preclinical research and clinical trials of stem cells have ignited hope for the treatment of refractory neurodegenerative diseases such as AD. They are considered to be the most suitable choice to provide uniform and unique cells required for cell replacement therapy[5]. This review focuses on the mechanisms of AD pathogenesis and discusses clinical and preclinical findings on the role of stem cells in the treatment of AD.

**RESEARCH PROGRESS IN THE PATHOGENESIS OF AD**

***Genetics of AD pathogenesis***

Studies have shown that two typical misfolded proteins accumulate in the brain of patients with AD. The first is Aβ, which is a pathological cleavage product of amyloid precursor protein (APP). The accumulation of Aβ into plaques and smaller oligomers is one of the pathological features of AD[6]. APP mutations have been confirmed to be associated with hereditary familial AD. Familial AD is an early-onset autosomal dominant genetic disease. The age of onset is less than 65 years, but it only accounts for 2% of all AD cases[7] . Many failed clinical trials targeted this pathway directly or indirectly through small-molecule or antibody therapies to reduce Aβ production or promote Aβ clearance[6,8]. The second misfolded protein in AD is tau, a microtubule-associated protein that aggregates in cells in the form of neurofibrillary tangles. The most closely related pathological feature is AD cognitive decline[9,10]. However, the vast majority (> 98%) of cases of AD, which do not involve mutations in APP processing pathways, are sporadic, and the age of onset is more than 65 years[6]. For this population, the main predictive factor for AD is the genetic risk factor apolipoprotein (APO) E4, in addition to age[6]. APOE4 carriers account for 60%–75% of AD cases. Compared with noncarriers, patients with AD and APOE4 are younger[11].

***Tau protein and AD pathogenesis***

In AD neurons, the protein kinase/protein phosphatase phosphorylation system is imbalanced, resulting in abnormal and overphosphorylated tau protein. The human tau protein is encoded by a single gene containing 16 exons on chromosome 17[12], which is expressed in the brain as six isomers that contain amino acid sequences at the carboxyl and amino ends, where the carboxyl end is repeated. The sequence is a microtubule-binding region, and the tau protein can enhance the stability of microtubules in axons[13,14]. Mitogen-activated protein kinases include the extracellular signal-related kinases, which are activated by multiple stimuli including growth factors, c-Jun N-terminal kinases, and p38 mitogen-activated protein kinases. These kinases cause neuronal tau protein phosphorylation and are closely related to AD disease progression[15]. The tau protein in AD is overphosphorylated and accumulates in cells in the form of double-helix filaments, straight filaments, and tangled skeletons. This hallmark damage is directly related to the degree of dementia[16]. Abnormal tau protein is found in hereditary Parkinson-like frontotemporal dementia related to chromosome 17; it leads to neurodegenerative diseases and dementia[17]. The composition of abnormally hyperphosphorylated tau protein can be used to measure p-tau protein levels in the cerebrospinal fluid[18]. Decreased phosphatase activity, especially reduced protein phosphatase-2A activity, plays a key regulatory role in abnormal hyperphosphorylation of tau protein[19]. PET brain imaging technology shows that the accumulation of tau protein more directly predicts future neurodegenerative changes in patients with AD. The progress of tau pathology and brain atrophy in different regions may reflect a phase shift. Local elevation in tau levels precedes atrophy[20]. Tau may be one of the targets for the early clinical treatment of AD[21].

***β-amyloid protein and AD pathogenesis***

The Aβ is an important hypothesis for the pathogenesis of AD. The relationship between APP and Aβ explains the pathogenesis of the lesion. APP is first cleaved at beta-secretase (BACE) 1 site by β-secretase to produce soluble amylase precursor protein and released outside the cell. Then, C99 remaining in the cell is cleaved by γ-secretase to produce Aβ polypeptide and APP intracellular domain. Aβ peptides, mainly Aβ1–40 and Aβ1–42, are released outside the cell, while APP intracellular domain remains inside the cell[22]. Neuronal damage or death is caused by the accumulation of toxic Aβ in the brain, which causes senile plaques in cells. Aβ1-40 in the brain has the highest content of Aβ, but Aβ1-42 is more likely to form fibers and oligomers. The highly toxic Aβ1-42 oligomers are an important cause of AD[23]. The accumulation of Aβ in the brain and subsequent plaque formation are pathological features of AD[24]. The impaired ability of the central nervous system to export Aβ to the periphery through the barrier is considered to be the cause of Aβ accumulation in AD and eventual plaque formation[25]. Studies have shown that the expression levels of blood–brain barrier endothelial cell receptors change with age and the development of AD. The expression level of efflux receptors decreases, and the expression level of influx receptors increases[26]. Changes and dysfunctions increase the accumulation of Aβ, and neuronal synaptic rupture and apoptosis occur[27].

However, the central conclusion that either accumulation of tau protein or of Aβ protein is the cause of AD, at very least, is premature. The recent failure of clinical trials based on the immunotherapeutic approach against Aβ protein questioned the validity of the “amyloid cascade hypothesis” as the molecular machinery causing the disease. However, important suggestions come from the critical analysis of such flop. Although synapse dysfunction is a key early event and accurate correlate of AD progression, Aβ plaque deposition can occur without synapse loss[28]. Conversely, synapse and dendritic tree loss can occur in areas where there is no Aβ deposition, although synapse loss does usually appear exacerbated near Aβ plaques[29]. Furthermore, synaptic gene dysregulation in early AD can occur independently of alterations in the expression of APP and regulators of APP metabolism[30]. Thus, the timing of an Aβ- or tau-targeted intervention has proven critical for clinical response since once Aβ-induced synaptic dysfunction and extensive neurodegeneration occur, they can no longer be reversed by simply reducing brain amyloid burden[31]. This paradigm has shifted clinical trials from late clinical AD dementia to the early, asymptomatic stages of the disease[32].

In fact, Aβ or tau may be a player in a more complex view of disease and, further, its role may even be variable. We conclude that it is essential to expand our view of pathogenesis beyond Aβ and tau pathology. Current drug design strategies are based on ‘‘one drug-one target’’ paradigm[33], which until now failed to provide effective treatments against AD, due to the multifactorial nature of the disease[34,35]. Reducing Aβ or tau levels has been the dominant treatment strategy in development to halt, retard, or even reverse the progression of AD pathology. However, they are experiencing difficulties in clinical trials[36] as the effects appear independent from symptomatic improvement[37].

The revolutionary discovery of stem cells has cast a new hope for the development of disease-modifying treatments for AD, in terms of their potency in the replenishment of lost cells *via* differentiating towards specific lineages, stimulating *in situ* neurogenesis, and delivering the therapeutic agents to the brain. Indeed, researchers have effectively treated AD in transgenic mouse models in more than 50 different ways[38]. A recently completed open-label phase I clinical trial evaluated the safety and tolerability of intracranially injected allogeneic human umbilical cord blood-derived mesenchymal stem cells (MSCs) (Trial identifier: NCT01297218, NCT01696591)[39]. Alternatively, due to the complex nature of AD pathophysiology, a multimodal approach may be required, incorporating pharmacological targeting of pathology, stimulation of endogenous neurogenesis and synaptogenesis, as well as exogenous neuroreplacement.

**STEM CELL CLASSIFICATION**

In recent years, embryonic stem cells (ESCs), MSCs, brain-derived neural stem cells (NSCs), and induced pluripotent stem cells (iPSCs) are most commonly used in AD research.

**CLASSIFICATION BESED ON CELL ORIGIN**

***Embryonic stem cells***

ESCs are derived from the inner cell mass of pluripotent blastocysts[40] and classified as pluripotent because of their ability to generate cell types from the ectoderm, mesoderm, and endoderm. Studies have shown that ESCs can improve spatial learning and memory in rats with AD by differentiating into basal forebrain cholinergic neurons and γ-aminobutyric acid neurons[41]. However, the clinical application of ESCs is limited due to the high risk of teratoma formation, abnormal immune response, and rejection. In addition, ethical disputes must be clarified before they can be used in Food and Drug Administration-approved clinical trials[42]. Several reports have explored the role of ESCs in rodent models of AD. Pluripotency is one of the greatest advantages of ESCs. It represents one of the major disadvantages of ESCs because their differentiation can occur in any direction and cause tumors or teratomas[43,44]. Therefore, current research strategies focus on establishing a differentiating agreement. Mouse ESCs (mESCs) were successfully used to produce basal forebrain cholinergic neurons (BFCNs), which were severely affected in patients with AD. These neurons, when transplanted into AD rat models, drive the derivation of ESCs and induce neural precursor cell (NPC) differentiation[45].

In addition, these rats showed significant behavioral improvements in memory deficits. Human ESCs (HESCs) can also produce cholinergic neurons in the vitreous and hippocampal tissues, which are connected to existing neural network[46]. Similarly, mESCs and hESCs were introduced into mature BFCNs, and improvements in learning and memory performance were observed after transplantation into mice with AD[47]. Another method is to differentiate hESCs into medial ganglion protrusion MGE-like progenitor cells because MGE is the origin of basal forebrain neurons (including BFCNs and γ-aminobutyric acid intermediate neurons) during development. The transplantation of these MGE-like progenitor cells into the hippocampus of mice produced results similar to the findings of the present study[41].

***Mesenchymal stem cells***

MSCs are involved in the development of mesenchymal tissue types, which can be obtained from umbilical cord blood (ucb-MSCs) or the Wharton jelly. They are also found in some adult stem cell pupae, including bone marrow and adipose tissue. MSCs are classified as pluripotent cells and are capable of producing multiple cell types. These cells have a common embryonic origin: The mesoderm germ layer. Nevertheless, the phenotypic expression and differentiation potential of bone marrow MSCs may vary depending on the source tissue[23]. Umbilical cord blood is the residual blood of the placenta and umbilical cord after childbirth. The blood is rich in hematopoietic stem cells and other stem cells such as MSCs[48]. Previous studies on ucb-MSCs (mainly MSCs) using murine models of AD have shown that ucb-MSCs can improve spatial learning and prevent memory decline. Many mechanisms have also been proposed, including reduction of Aβ plaques, BACE and tau hyperphosphorylation, and reversal of microglial inflammation and promotion of anti-inflammatory cytokines[49]. Immunomodulatory and anti-inflammatory effects have also been observed by upregulating neuroprotection and downregulating pro-inflammatory cytokines. Another important way for MSCs to participate in tissue repair is the secretion of extracellular vesicles and microvesicles, which has been widely explored. Bone marrow MSCs can release extracellular vesicles that target Aβ deposition through genetic modification and are supplemented with therapeutic drugs, including siRNAs and enzymes[50,51]. Alternatively, MSCs can be regulated to overexpress cytokines and vascular endothelial growth factor, and show regeneration effects in the AD model[52]. Despite ethical issues, especially commercial cord blood banks, MSCs are the most common source of stem cells used in AD research because they are relatively easy to pick and handle if harvested after normal delivery[53,54].

***Induced pluripotent stem cells***

iPSCs were first obtained from mouse fibroblasts in 2006. They are derived *in vitro* from mature somatic cells, usually adult dermal fibroblasts, by small-molecule therapy or viral vector–mediated upregulation of transcription factors. Genetic modification makes them pluripotent and ESC-like in terms of phenotypic and differentiation capacity[55].

iPSCs are thought to differentiate into a variety of cells, including neurons[56] and neurospheres[57]. Both *in vitro* and posttransplantation into the rodent cortex studies have shown that iPSCs can be used to generate and automate neuronal subtypes[58-61]. For example, iPSC-derived glial cells can be used to study the inflammatory response of AD[62]. Another study with a mouse model of AD used iPSCs to obtain macrophages capable of expressing neprilysin, an Aβ-degrading protease[63]. An iPSC model is a powerful tool for studying the APP treatment of tissue-specific cells in mutant individuals caused by FAD[64,65]. Yagi *et al*[66] found increased levels of Aβ42 secretion in neurons with presenilin1 (PSEN1) (A246E) and PSEN2 (N141I) mutations[66]. Further research on neurons with the pathogenic PSEN1 mutation showed an increase in the ratio of Aβ42:40[67-69]. Similarly, iPSC-derived neurons with the APP V717I genotype showed an increased Aβ42:40 ratio[70-72] and an increased Aβ42:38 ratio[73]. Arber *et al*[74] used multiple patient–derived iPSC neurons to simulate APP processing and Aβ production in the context of fAD-APP and PSEN1 mutations, indicating that iPSCs provided a valuable model for studying potential cell dysfunction caused by genetic fAD mutations[74].

However, the following unresolved questions about the use of iPSCs pose huge obstacles to their clinical application: Teratoma formation, long-term safety and effectiveness, tumorigenicity, immunogenicity, patient genetic defects, optimal reprogramming and so forth[75-78].

**CLASSIFICATION BASED ON CELL TYPE**

***Neural stem cells***

NSCs are responsible for the production of all nerve cell types during development. They also exist in the adult brain and are confined to discrete neurogenic niches in the subventricular zone and the granular layer of the dentate gyrus of the hippocampus. Adult NSCs are located in the subgranular zone of the dentate gyrus and the subventricular zone of the lateral wall of the ventricle. They are self-renewing pluripotent cells that produce neurons, oligodendrocytes, or astrocytes[79].

The paracrine effect of NSCs has significant therapeutic potential. In rodent AD models[80] and senile primate brains[81], transplantation of growth factor-secreting NSCs can improve neurogenesis and cognitive function, while transplantation of human NSCs with high expression of choline acetyltransferase can reverse spatial memory and learning deficits in rodent models of alkaline neurotoxicity[82] NSC transplantation may reduce neuroinflammation in AD rodent models through the paracrine release of neuroprotective or immunomodulatory factors and also mediate neuronal differentiation[83]. These cells reduce tau and Aβ expression levels[84], promote neurogenesis and synapse formation[85,86], and reverse cognitive deficits[83,85,86], However, non-glial cells widely produced from transplanted NSCs are the main limiting factor for neural replacement strategies[87]. Studies on rodent AD models have shown that human NSCs **(**hNSCs) from the embryonic telomere, when transplanted into the lateral ventricle of the brain of mice with AD, can migrate and differentiate into neurons and glial cells in the lateral ventricle. This phenomenon reduces tau phosphorylation and Aβ–42 levels, decreases glial and astrocyte hyperplasia[84], enhances endogenous synapse formation[86], and increases neuronal, synaptic, and nerve fiber density[88], ultimately improving spatial memory in mice with AD. These effects are achieved through a variety of mechanisms, including regulation of signaling pathways, metabolic activity, secretion of anti-inflammatory factors, and cell-to-cell contact. Brain-derived neurotrophic factor (BDNF) is an important neuroprotective factor derived from NSCs. By increasing the synaptic density of the hippocampus[80] and the number of cholinergic neurons[87,89], BDNF can be used in AD rodent transplanted NSCs (obtained from the brain or hippocampus). Animal cognition plays an important role. The hNSC line that overexpresses choline acetyltransferase is transplanted into elderly Institute of Cancer Research mice. By directly producing acetylcholine and restoring the integrity of cholinergic neurons, hNSCs can increase the levels of BDNF and nerve growth factor (NGF) neurotrophins and improve the cognitive function and physical activity of elderly mice[90]. In addition, hNSCs can be genetically modified to express NGF and transplanted into mice with induced cognitive dysfunction to improve their learning and memory abilities[91].

**STEM CELLS AND AD**

***Animal experiments***

**Neural stem cells:** Researchers have used methods such as brain injury, neurotoxin-induced brain cell loss, and intraventricular injection of Aβ peptide to establish AD-like pathology and induce memory impairment models in rats and mice[92,93]. Martinez-serrano *et al*[94] transplanted forebrain cholinergic neurons into the host striatum and Meynert nuclei, and found that cells survived well in the host brain for a long time and induced hypertrophic responses of cholinergic neurons. Sinden *et al*[95] found that the transplantation of choline-rich NSCs could reduce AD symptoms in rats. Qu *et al*[96] injected human undifferentiated NSCs into the brain of 6-mo-old and 24-mo-old rats, revealing a significant improvement in cognitive function. Wu *et al*[97] found that human fetal brain–derived NSCs transplanted into adult rat brains could produce cholinergic neurons in specific regions. Wang *et al*[98] transplanted ESC-derived neurospheres into the frontal cortex of a mouse model of Meynert nuclear injury. The transplanted neurospheres survived, migrated, and differentiated into choline acetyltransferase–positive serotonin-positive neurons. The rate of working memory error in neuron- and neurosphere-transplanted mice was significantly reduced. On the contrary, ESCs in the control group developed teratomas, which did not express neurons, and the working memory significantly deteriorated.

Animal models related to Aβ-induced memory loss are widely used in exploring the pathophysiology of AD and the efficacy of therapeutic targets. Prakash *et al*[99] used a lateral ventricular injection of Aβ to observe the effect of peroxisome proliferator–activated receptor γ agonist pioglitazone on BDNF and found that Aβ-injured animals showed obvious memory impairment; BDNF levels were reduced, and this situation was reversed by pioglitazone[99]. Tang and others showed that the Aβ-40 fiber was neurotoxic in the hippocampus of rats, characterized by Congo erythema and degeneration neurons at the injection site; the Morris water maze test showed impaired cognitive function in rats[100]. Transplanted cells improved Aβ-induced cognitive dysfunction in rats; they further survived, integrated, and differentiated into neuronal cells 16 wk after transplantation[101]. Blurton Jones and others transplanted NSCs into aged transgenic mice expressing mutant presenilin, tau, and APP, and found that transplanted NSCs could improve spatial learning and memory function in mice with dementia without altering the pathology of Aβ. In addition, NSCs underwent BDNF-mediated regeneration and promoted a decrease in synaptic density. When recombinant BDNF was additionally supplemented, memory loss was restored[80]. When NSCs were genetically engineered to stably release the Aβ-degrading enzyme neprilysin, synaptic plasticity could be enhanced and the potential Aβ pathological characteristics of transgenic mice could be improved[102].

The cells either replace degenerated neurons or secrete trophic factors to provide a protective environment for endogenous cells. They secrete a variety of neurotrophic factors to regulate synaptic function in the brain. In particular, BDNF is synthesized by neurons and is highly expressed in the cerebral cortex and hippocampus; these regions are essential for brain learning and memory[103]. Therefore, it is reasonable to conclude that these preliminary studies point to a potentially viable treatment for AD and that the effect of stem cell transplantation into the brain is supported by a combination of methods and mediated, or at least significantly affected, by paracrine effects to a large extent.

**Mesenchymal stem cells:** MSCs have been widely studied due to their accessibility and relative ease of operation. They have three main roles in AD treatment: (1) Immune regulation; (2) Reduction of Aβ plaque burden through internalization and Aβ degradation of endosomal–lysosomal pathway oligomers; and (3) Neurotrophic/regenerative potential[104]. Systematic injection of green fluorescent protein–labeled bone marrow MSCs has been shown to reduce the size of Aβ plaques in the hippocampus of animal models of AD[105] and function in an immunomodulatory manner. Transplantation of placental-derived MSCs in the lateral ventricle in Aβ1-42 perfused mice has also been shown to have beneficial effects, including improving memory deficit function and reducing Aβ1–42 levels, APP and BACE1 expression levels, alpha- and beta-secretase activity, and gliomas[106]. After injecting MSCs in AD animal models, NPCs were induced to differentiate into hippocampal mature neurons by activating the Wnt pathway, providing evidence for MSCs supporting the growth and differentiation of local stem and progenitor cells[107]. In another study, human MSCs transplanted into aged rats have been shown to reach the brain and differentiate into nerve cells, restoring motor and cognitive activity[90]. It is worth noting that the encouraging clinical results obtained under different pathological conditions and the preclinical results of MSCs in animal models of AD[108] facilitated the start of clinical trials of MSCs in patients with AD (https: //clinical trials.gov, using MSCs and AD as keywords). One of these trials has completed the first phase of the study, confirming the feasibility and safety of MSC injection in human brains in nine patients[38].

**Embryonic stem cells:** ESCs are totipotent and self-renewing. They can differentiate into NPCs *in vitro*, hence serving as therapeutics when transplanted into animal models of AD[38]. Generally, the direct transplantation of ESCs into animal models of AD results in the formation of teratomas rather than neurons. However, the safety level of ESC-derived NPC and neuron transplantation has been demonstrated[38]. They can differentiate into astrocytes and neuron-like cells and improve neurodegenerative diseases *in vivo*[101]. In the AD rat model, mESCs-derived NPCs were transferred to unilateral meynert basal nucleus with and without pretreatment, improving learning and memory abilities. The mainstream cells of transplanted NPCs maintain a neuronal phenotype, but nearly 40% of these cells show a cholinergic phenotype[45]. Despite no report on the potential of hESCs for treating AD, hESCs can be considered as a new factor in treating different types of neurodegenerative diseases and brain damage[110]. However, these cells are derived from pre-implantation human embryos, and therefore ethical issues must be addressed before using hESCs in AD clinical trials. In addition, the possibility of the use of immune rejection in ESC-based AD cell therapy remains a controversial issue[110].

**Induced pluripotent stem cells:** In some AD models, attempts to regulate endogenous neurogenesis, replace lost neurons, or reverse pathological changes throughiPSCs have demonstrated early effectiveness. In a Parkinson (PD) APP transgenic mouse model, an ipsilateral injection of cholinergic neuron precursors in humans stimulated endogenous neurogenesis and reversed spatial memory disorders[111]. Human iPSC–derived macrophage-like cells were genetically modified to express neprilysin-2, an Aβ-degrading protease, differentiate into functional neurons, and therapeutically reduce Aβ levels in a five familial AD (5 × FAD) transgenic mouse model[63]. In addition, the inoculation of human iPSC-derived NSCs into the hippocampus of a mouse model of stroke could significantly improve neural function, which might be explained by the transition from the pro-inflammatory cytokine response to the anti-inflammatory cytokine response through neurotrophin-related reprogramming effects[112]. In a recent study, the use of protein-induced iPSCs and ferritin released by mESCs greatly promoted the differentiation and maturation of oligodendrocytes, thereby reducing plaque deposition and improving bilateral brain transplantation in 5 × FAD transgenic mice with AD. Cognitive dysfunction highlights the significance of stem cells that promote the differentiation of transplanted cells into different cell lines[113]. Despite these successful studies, autologous iPSCs may show genetic instability and phenotypic neuropathology, such as significant Aβ load rates, shortened axon lengths, and increased tau phosphorylation, hindering their clinical application in AD[73,78,114]. However, healthy neurons can be transplanted into patients with AD by implementing genome-editing techniques, such as recombinant homologs, transcription activator-like effect nucleases, and regularly spaced short palindromic repeats (CRISPR-cas9)[115]. To date, the efficiency and repeatability of automated iPSC reprogramming procedures have resulted in stable, high-quality cell lines for major disease modeling or cell therapy. Studies have shown efficient production of neuronal subtypes, such as cortical pyramids and BFCNs[59].

***Clinical trials***

In 2015, human umbilical cord blood MSCs were used for the first phase of a clinical trial in nine patients with mild-to-moderate AD[38]. In an attempt to treat AD, patients were stereotactically injected with human umbilical cord blood MSCs into the hippocampus and anterior hippocampus, confirming that the method of stem cell administration was safe and feasible without any adverse reactions. However, the clinical effect of the method on the pathogenesis of AD needs to be further verified. Several clinical trials are ongoing on patients with AD; however, the results have not been published (Clinicaltrials.gov, NCT01547689, NCT02672306, NCT02054208, and NCT02600130). Since 2011, preclinical trials of bone marrow MSCs in animal models of AD have achieved good results and are sufficient to authorize patients with AD to begin clinical trials (Table 1). Intravenous infusion is the most ideal method for stem cell implantation, and cord blood stem cells are the most commonly used source of cells. Kim *et al*[38] stereotactically transplanted human umbilical cord blood–derived MSCs into the hippocampus and anterior thalamus.

Despite no serious adverse events, no significant clinical effects on cognitive decline were observed (Clinicaltrials.gov, NCT01297218, NCT01696591)[116]. In addition, no pathological changes or neuroprotective effects have been observed[106,116,117]. These results might be partly attributed to neuroimaging, which is an insensitive method for detecting these changes compared with postmortem biochemical analysis. Stem cell therapy using both MSCs and iPSCs reveals great potential in the treatment of several neurodegenerative disorders (AD and PD). Their use has shown promising results with regard to modulation of inflammation. Moreover, they can promote other beneficial effects, such as neuronal growth. In a recent AD clinical trial, intracranially injected MSCs were evaluated for safety and tolerability. Nine patients participated in this study. The criteria for inclusion in the study involved a Mini-Mental Status Examination score range from 10 to 24, indicating mild to moderate dementia. The patients were also confirmed to have Aβ pathology using PET scans. The patients were divided into two groups, one of them received a low dose while the other received a higher dose of the same injection. MSCs were directly injected into the hippocampus of the patients surgically. Follow-up examinations were taken at the 3- and 24-mo time points. No slowing of cognitive decline was found at the 24 mo, and no decrease of AB pathology was observed. None of the patients showed adverse side effects from the surgery and transplantation[118]. Although preclinical trials in animal models demonstrated neuroprotective effects, they did not translate clinically.

In addition, specific issues such as the specific cell stage to be transplanted, dose, route of administration, and duration of therapeutic effect must be solved[119]. Thus, there are still numerous open questions which have to be answered before clinical trials can be initiated. Preclinical evidence of the efficacy and safety of stem cells from different sources is necessary for the development of clinically useful therapies. Extensive cell characterization, more efficient modelling of human diseases, and better comprehension of the interaction with resident and immune/scavenging cells are some of the key points that still need to be properly addressed by researchers.

**DISCUSSION**

The field of cell therapy awaits the results of many ongoing clinical trials on AD. Scientists are still working to solve some of the small technical issues in this area to pave the way for effective treatment of AD and accelerate the pace of development. In addition to insufficient survey funding, the question of participant registration is undoubtedly the most critical obstacle to the development of clinical investigations. First, the appropriate timing of stem cell transplantation for AD has not been determined. Some intervention trials for AD have failed because they have not been conducted at the appropriate time. AD is a progressive chronic disease that usually begins several years before diagnosis. Therefore, an individual's brain is severely damaged by the time symptoms or signs appear and a large number of central neurons in the brain are dead, resulting in an irreversible loss. CSF biomarkers are being used more and more widely, to increase the diagnostic certainty, provide comprehensive patient information, and optimize management, from the beginning of clinical symptoms. Most ongoing therapeutic trials target subjects with MCI due to biomarker-confirmed AD, since many recent longitudinal studies have demonstrated the ability of biomarkers to predict the progression of cognitive impairment and the development of overt dementia[120,121]. In MCI, identifying AD lesions helps to predict the progression towards AD dementia. The evidence that CSF biomarkers could identify or exclude AD is strong in patients with mild dementia, but weaker in ambiguous cases. However, there are still uncertainties regarding the individual course of cognitive decline, even though the biomarkers show a typical AD profile. There is no precise framework for the use of biomarkers with regards to the age and general health status of the patient. The multiple causes of cognitive impairment in elderly and very elderly subjects make their interpretation difficult and ethical and clinical reflection must be systematically conducted. Conversely, in some cases, brain imaging showed that a few study participants did not have a trial treatment plan for amyloidosis, suggesting an urgent need for early detection technology (ClinicalTrials.gov, Reg. No. NCT01163825). Given that clinical trials lasted for several years, patients with dementia received several injections and went through some difficult follow-up procedures; some participants withdrew before the end of the trial, making it difficult to evaluate the results (NCT02600130, NCT03117738, *etc.*). Unfortunately, another subtle point not considered in clinical trials was sex-related differences. It is estimated that women account for about two thirds of the patients with AD. Therefore, to obtain meaningful data and hence develop effective treatments, randomized controlled trials targeting specific populations need to adapt and evolve to cope with sex-related differences.

**CONCLUSION**

Animal research is difficult to translate into human trials. The transgenic model used in preclinical research is based on the familial AD hypothesis, and the clinical distribution of AD has genetic heterogeneity. In addition, results from rodent models or from models using higher-order animals may not be sufficient to support the clinical use of stem cells in AD because of significant differences in neuronal function and anatomy in rodents and primates. None have successfully replicated the complex microenvironment of the human brain or the precise pathophysiological conditions of AD. Consequently, it is challenging to precisely characterize the beneficial effects of stem cells in AD.

Another important area that requires further research is the role of stem cells in the lymphatic system. This system, which is composed mainly of astrocytes, is a recently discovered macroscopic waste removal system[122]. It plays an important role in eliminating potentially neurotoxic waste, including Aβ. In addition, previous studies have shown that Aβ clearance disorder due to a dysfunctional lymphatic system is a cause of AD pathology[123]. Therefore, vigorous research is needed to elucidate the interactions between stem cells, astrocytes, Aβ clearance, and the lymphatic system.

AD is a progressive neurodegenerative disease with no effective treatment currently. Because of their regenerative potential, stem cells may be an effective treatment option (compared with traditional therapies). Although the mechanism of action of stem cell therapy has not been fully elucidated, many preclinical studies have provided promising results. However, human clinical trials are still in their infancy. Further relevant animal research and clinical trials (with standardized protocols) are needed for the successful clinical transformation of this technology.

Stem cells used in AD and animal models have achieved certain results, but there are still many problems to be solved before they can be extended to clinical applications. One of the disadvantages of stem cell therapy is the requirement for a neurosurgical procedure and immunosuppression. Human and rodent studies have reported tumor formation resulting from autologous haematopoietic stem cell[124], allogeneic fetal NSC[125], and genetically engineered MSC[126] transplantation. At this point, the major concerns are related to controlling the proliferation and differentiation of stem cells, controlling the targeting of molecular markers, and developing cell delivery systems, as well as understanding and exploiting the heterogeneity of AD patients. Related to the heterogeneity of AD, transgenic animal models to date have been developed for the familial type of AD. However, most human AD cases are sporadic. Regarding these issues, researchers will continue to attempt to optimize cells by genetic engineering approaches to improve safety, efficacy, and patient-specific individualization of cell therapy. Furthermore, the recent technological developments of stem cells, involving the use of hydrogels, nano-technology, and light therapies have made drug delivery and regeneration treatments more efficient neural replacement, and regeneration therapy can soon be translated into the clinical setting with further research combining these recent advancements. Stem cell therapy for AD carries enormous promise but remains under development. Many problems such as uncertainty about the amyloid hypothesis, differing objectives such as preventing progression from MCI to AD *vs* symptomatic treatment of established AD, and methodological designs of the trials themselves have been mentioned. Additionally, temporary recovery of behavior is relatively easily obtained, but often fail to be linked to a complete cure. Curative treatment is likely dependent upon sufficiently early diagnosis (MCI) to prevent further cell death and brain deterioration. A combination of NSC transplantation alongside administrating existing approved medication and preventing further Aβ aggregation may be the most effective way. It is important to note that whilst behavioral or cognitive improvement is interpreted as positive outcomes, it can be frequently misinterpreted as permanent arrest or even reversal of AD progression. Alternatively, due to the complex nature of AD pathophysiology, a multimodal approach may be required, incorporating pharmacological targeting of pathology, stimulation of endogenous neurogenesis and synaptogenesis, as well as exogenous neuroreplacement.

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**REFERENCES**

1 **Ferri CP**, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M; Alzheimer's Disease International. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005; **366**: 2112-2117 [PMID: 16360788 DOI: 10.1016/S0140-6736(05)67889-0]

2 **Alzheimer's Disease International.** World Alzheimer Report 2018 (cited 30 September 2018). Availableat: https: //www.alz.co.uk/research/ world-report2018)

3 **Kang JM**, Yeon BK, Cho SJ, Suh YH. Stem Cell Therapy for Alzheimer's Disease: A Review of Recent Clinical Trials. *J Alzheimers Dis* 2016; **54**: 879-889 [PMID: 27567851 DOI: 10.3233/jad-160406]

4 **Briggs R**, Kennelly SP, O'Neill D. Drug treatments in Alzheimer's disease. *Clin Med (Lond)* 2016; **16**: 247-253 [PMID: 27251914 DOI: 10.7861/clinmedicine.16-3-247]

5 **Kumar V**, Jahan S, Singh S, Khanna VK, Pant AB. Progress toward the development of in vitro model system for chemical-induced developmental neurotoxicity: potential applicability of stem cells. *Arch Toxicol* 2015; **89**: 265-267 [PMID: 25537189 DOI: [10.1007/s00204-014-1442-0](https://doi.org/10.1007/s00204-014-1442-0)]

6 **Huang Y**, Mucke L. Alzheimer mechanisms and therapeutic strategies. *Cell* 2012; **148**: 1204-1222 [PMID: 22424230 DOI: 10.1016/j.cell.2012.02.040]

7 **Rygiel K**. Novel strategies for Alzheimer's disease treatment: An overview of anti-amyloid beta monoclonal antibodies. *Indian J Pharmacol* 2016; **48**: 629-636 [PMID: 28066098 DOI: 10.4103/0253-7613.194867]

8 **Golde TE**, Schneider LS, Koo EH. Anti-aβ therapeutics in Alzheimer's disease: the need for a paradigm shift. *Neuron* 2011; **69**: 203-213 [PMID: 21262461 DOI: 10.1016/j.neuron.2011.01.002]

9 **Iqbal K**, Alonso AC, Gong CX, Khatoon S, Pei JJ, Wang JZ, Grundke-Iqbal I. Mechanisms of neurofibrillary degeneration and the formation of neurofibrillary tangles. *J Neural Transm Suppl* 1998; **53**: 169-180 [PMID: 9700655 DOI: 10.1007/978-3-7091-6467-9\_15]

10 **Zhan Y**, Zheng H, Wang C, Rong Z, Xiao N, Ma Q, Zhang YW. A novel presenilin 1 mutation (F388L) identified in a Chinese family with early-onset Alzheimer's disease. *Neurobiol Aging* 2017; **50**: 168.e1-168.e4 [PMID: 27836335 DOI: 10.1016/j.neurobiolaging.2016.10.010]

11 **Farrer LA**, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. 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**: 1349-1356 [PMID: 9343467]

12 **Neve RL**, Harris P, Kosik KS, Kurnit DM, Donlon TA. Identification of cDNA clones for the human microtubule-associated protein tau and chromosomal localization of the genes for tau and microtubule-associated protein 2. *Brain Res* 1986; **387**: 271-280 [PMID: 3103857 DOI: 10.1016/0169-328x(86)90033-1]

13 **Scott CW**, Blowers DP, Barth PT, Lo MM, Salama AI, Caputo CB. Differences in the abilities of human tau isoforms to promote microtubule assembly. *J Neurosci Res* 1991; **30**: 154-162 [PMID: 1795399 DOI: 10.1002/jnr.490300116]

14 **Trinczek B**, Biernat J, Baumann K, Mandelkow EM, Mandelkow E. Domains of tau protein, differential phosphorylation, and dynamic instability of microtubules. *Mol Biol Cell* 1995; **6**: 1887-1902 [PMID: 8590813 DOI: 10.1091/mbc.6.12.1887]

15 **Kins S**, Kurosinski P, Nitsch RM, Götz J. Activation of the ERK and JNK signaling pathways caused by neuron-specific inhibition of PP2A in transgenic mice. *Am J Pathol* 2003; **163**: 833-843 [PMID: 12937125 DOI: 10.1016/s0002-9440(10)63444-x]

16 **An WL**, Cowburn RF, Li L, Braak H, Alafuzoff I, Iqbal K, Iqbal IG, Winblad B, Pei JJ. Up-regulation of phosphorylated/activated p70 S6 kinase and its relationship to neurofibrillary pathology in Alzheimer's disease. *Am J Pathol* 2003; **163**: 591-607 [PMID: 12875979 DOI: 10.1016/s0002-9440(10)63687-5]

17 **Spillantini MG**, Murrell JR, Goedert M, Farlow MR, Klug A, Ghetti B. Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. *Proc Natl Acad Sci U S A* 1998; **95**: 7737-7741 [PMID: 9636220 DOI: 10.1073/pnas.95.13.7737]

18 **Jadhav S**, Cubinkova V, Zimova I, Brezovakova V, Madari A, Cigankova V, Zilka N. Tau-mediated synaptic damage in Alzheimer's disease. *Transl Neurosci* 2015; **6**: 214-226 [PMID: 28123806 DOI: 10.1515/tnsci-2015-0023]

19 **Sontag E**, Nunbhakdi-Craig V, Lee G, Brandt R, Kamibayashi C, Kuret J, White CL 3rd, Mumby MC, Bloom GS. Molecular interactions among protein phosphatase 2A, tau, and microtubules. Implications for the regulation of tau phosphorylation and the development of tauopathies. *J Biol Chem* 1999; **274**: 25490-25498 [PMID: 10464280 DOI: 10.1074/jbc.274.36.25490]

20 **La Joie R**, Visani AV, Baker SL, Brown JA, Bourakova V, Cha J, Chaudhary K, Edwards L, Iaccarino L, Janabi M, Lesman-Segev OH, Miller ZA, Perry DC, O'Neil JP, Pham J, Rojas JC, Rosen HJ, Seeley WW, Tsai RM, Miller BL, Jagust WJ, Rabinovici GD. Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET. *Sci Transl Med* 2020; **12**: [PMID: 31894103 DOI: 10.1126/scitranslmed.aau5732]

21 **Bakota L**, Brandt R. Tau Biology and Tau-Directed Therapies for Alzheimer's Disease. *Drugs* 2016; **76**: 301-313 [PMID: 26729186 DOI: 10.1007/s40265-015-0529-0]

22 **Nikolaev A**, McLaughlin T, O'Leary DD, Tessier-Lavigne M. APP binds DR6 to trigger axon pruning and neuron death via distinct caspases. *Nature* 2009; **457**: 981-989 [PMID: 19225519 DOI: 10.1038/nature07767]

23 **Hass R**, Kasper C, Böhm S, Jacobs R. Different populations and sources of human mesenchymal stem cells (MSC): A comparison of adult and neonatal tissue-derived MSC. *Cell Commun Signal* 2011; **9**: 12 [PMID: 21569606 DOI: 10.1186/1478-811X-9-12]

24 **Benilova I**, Karran E, De Strooper B. The toxic Aβ oligomer and Alzheimer's disease: an emperor in need of clothes. *Nat Neurosci* 2012; **15**: 349-357 [PMID: 22286176 DOI: 10.1038/nn.3028]

25 **Zlokovic BV**, Yamada S, Holtzman D, Ghiso J, Frangione B. Clearance of amyloid beta-peptide from brain: transport or metabolism? *Nat Med* 2000; **6**: 718-719 [PMID: 10888892 DOI: 10.1038/77397]

26 **Silverberg GD**, Messier AA, Miller MC, Machan JT, Majmudar SS, Stopa EG, Donahue JE, Johanson CE. Amyloid efflux transporter expression at the blood-brain barrier declines in normal aging. *J Neuropathol Exp Neurol* 2010; **69**: 1034-1043 [PMID: 20838242 DOI: 10.1097/NEN.0b013e3181f46e25]

27 **Deo AK**, Borson S, Link JM, Domino K, Eary JF, Ke B, Richards TL, Mankoff DA, Minoshima S, O'Sullivan F, Eyal S, Hsiao P, Maravilla K, Unadkat JD. Activity of P-Glycoprotein, a β-Amyloid Transporter at the Blood-Brain Barrier, Is Compromised in Patients with Mild Alzheimer Disease. *J Nucl Med* 2014; **55**: 1106-1111 [PMID: 24842892 DOI: 10.2967/jnumed.113.130161]

28 **Boncristiano S**, Calhoun ME, Howard V, Bondolfi L, Kaeser SA, Wiederhold KH, Staufenbiel M, Jucker M. Neocortical synaptic bouton number is maintained despite robust amyloid deposition in APP23 transgenic mice. *Neurobiol Aging* 2005; **26**: 607-613 [PMID: 15708435 DOI: 10.1016/j.neurobiolaging.2004.06.010]

29 **Spires TL**, Meyer-Luehmann M, Stern EA, McLean PJ, Skoch J, Nguyen PT, Bacskai BJ, Hyman BT. Dendritic spine abnormalities in amyloid precursor protein transgenic mice demonstrated by gene transfer and intravital multiphoton microscopy. *J Neurosci* 2005; **25**: 7278-7287 [PMID: 16079410 DOI: 10.1523/JNEUROSCI.1879-05.2005]

30 **Counts SE**, Alldred MJ, Che S, Ginsberg SD, Mufson EJ. Synaptic gene dysregulation within hippocampal CA1 pyramidal neurons in mild cognitive impairment. *Neuropharmacology* 2014; **79**: 172-179 [PMID: 24445080 DOI: 10.1016/j.neuropharm.2013.10.018]

31 **Cao J**, Hou J, Ping J, Cai D. Advances in developing novel therapeutic strategies for Alzheimer's disease. *Mol Neurodegener* 2018; **13**: 64 [PMID: 30541602 DOI: 10.1186/s13024-018-0299-8]

32 **Pinheiro L**, Faustino C. Therapeutic Strategies Targeting Amyloid-β in Alzheimer's Disease. *Curr Alzheimer Res* 2019; **16**: 418-452 [PMID: 30907320 DOI: 10.2174/1567205016666190321163438]

33 **Schneider LS**, Mangialasche F, Andreasen N, Feldman H, Giacobini E, Jones R, Mantua V, Mecocci P, Pani L, Winblad B, Kivipelto M. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. *J Intern Med* 2014; **275**: 251-283 [PMID: 24605808 DOI: 10.1111/joim.12191]

34 **Kumar A**, Tiwari A, Sharma A. Changing Paradigm from one Target one Ligand Towards Multi-target Directed Ligand Design for Key Drug Targets of Alzheimer Disease: An Important Role of In Silico Methods in Multi-target Directed Ligands Design. *Curr Neuropharmacol* 2018; **16**: 726-739 [PMID: 29542413 DOI: 10.2174/1570159X16666180315141643]

35 **Ibrahim MM**, Gabr MT. Multitarget therapeutic strategies for Alzheimer's disease. *Neural Regen Res* 2019; **14**: 437-440 [PMID: 30539809 DOI: 10.4103/1673-5374.245463]

36 **Traynor K**. Effective drug therapy for Alzheimer's disease remains elusive. *Am J Health Syst Pharm* 2015; **72**: 516, 518 [PMID: 25788503 DOI: 10.2146/news150026]

37 **Morris GP**, Clark IA, Vissel B. Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease. *Acta Neuropathol Commun* 2014; **2**: 135 [PMID: 25231068 DOI: 10.1186/s40478-014-0135-5]

38 **Kim HJ**, Seo SW, Chang JW, Lee JI, Kim CH, Chin J, Choi SJ, Kwon H, Yun HJ, Lee JM, Kim ST, Choe YS, Lee KH, Na DL. Stereotactic brain injection of human umbilical cord blood mesenchymal stem cells in patients with Alzheimer's disease dementia: A phase 1 clinical trial. *Alzheimers Dement (N Y)* 2015; **1**: 95-102 [PMID: 29854930 DOI: 10.1016/j.trci.2015.06.007]

39 **Cummings JL**, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimers Res Ther* 2014; **6**: 37 [PMID: 25024750 DOI: 10.1186/alzrt269]

40 **Martello G**, Smith A. The nature of embryonic stem cells. *Annu Rev Cell Dev Biol* 2014; **30**: 647-675 [PMID: 25288119 DOI: 10.1146/annurev-cellbio-100913-013116]

41 **Liu Y**, Weick JP, Liu H, Krencik R, Zhang X, Ma L, Zhou GM, Ayala M, Zhang SC. Medial ganglionic eminence-like cells derived from human embryonic stem cells correct learning and memory deficits. *Nat Biotechnol* 2013; **31**: 440-447 [PMID: 23604284 DOI: 10.1038/nbt.2565]

42 **Jin X**, Lin T, Xu Y. Stem Cell Therapy and Immunological Rejection in Animal Models. *Curr Mol Pharmacol* 2016; **9**: 284-288 [PMID: 26415913 DOI: 10.2174/1874467208666150928153511]

43 **Fujikawa T**, Oh SH, Pi L, Hatch HM, Shupe T, Petersen BE. Teratoma formation leads to failure of treatment for type I diabetes using embryonic stem cell-derived insulin-producing cells. *Am J Pathol* 2005; **166**: 1781-1791 [PMID: 15920163 DOI: 10.1016/s0002-9440(10)62488-1]

44 **Richards M**, Fong CY, Chan WK, Wong PC, Bongso A. Human feeders support prolonged undifferentiated growth of human inner cell masses and embryonic stem cells. *Nat Biotechnol* 2002; **20**: 933-936 [PMID: 12161760 DOI: 10.1038/nbt726]

45 **Moghadam FH**, Alaie H, Karbalaie K, 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**: 59-68 [PMID: 19616885 DOI: 10.1016/j.diff.2009.06.005]

46 **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**: 802-811 [PMID: 21381151 DOI: 10.1002/stem.626]

47 **Yue W**, Li Y, Zhang T, Jiang M, Qian Y, Zhang M, Sheng N, Feng S, Tang K, Yu X, Shu Y, Yue C, Jing N. ESC-Derived Basal Forebrain Cholinergic Neurons Ameliorate the Cognitive Symptoms Associated with Alzheimer's Disease in Mouse Models. *Stem Cell Reports* 2015; **5**: 776-790 [PMID: 26489896 DOI: 10.1016/j.stemcr.2015.09.010]

48 **Ding DC**, Chang YH, Shyu WC, Lin SZ. Human umbilical cord mesenchymal stem cells: a new era for stem cell therapy. *Cell Transplant* 2015; **24**: 339-347 [PMID: 25622293 DOI: [10.3727/096368915X686841](https://doi.org/10.3727/096368915X686841)]

49 **Lee HJ**, Lee JK, Lee H, Carter JE, Chang JW, Oh W, Yang YS, Suh JG, Lee BH, Jin HK, Bae JS. Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation. *Neurobiol Aging* 2012; **33**: 588-602 [PMID: 20471717 DOI: 10.1016/j.neurobiolaging.2010.03.024]

50 **Alvarez-Erviti L**, Seow Y, Yin H, Betts C, Lakhal S, Wood MJ. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nat Biotechnol* 2011; **29**: 341-345 [PMID: 21423189 DOI: 10.1038/nbt.1807]

51 **Katsuda T**, Tsuchiya R, Kosaka N, Yoshioka Y, Takagaki K, Oki K, Takeshita F, Sakai Y, Kuroda M, Ochiya T. Human adipose tissue-derived mesenchymal stem cells secrete functional neprilysin-bound exosomes. *Sci Rep* 2013; **3**: 1197 [PMID: 23378928 DOI: 10.1038/srep01197]

52 **Garcia KO**, Ornellas FL, Martin PK, Patti CL, Mello LE, Frussa-Filho R, Han SW, Longo BM. 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 [PMID: 24639647 DOI: 10.3389/fnagi.2014.00030]

53 **Yang H**, Yang H, Xie Z, Wei L, Bi J. Systemic transplantation of human umbilical cord derived mesenchymal stem cells-educated T regulatory cells improved the impaired cognition in AβPPswe/PS1dE9 transgenic mice. *PLoS One* 2013; **8**: e69129 [PMID: 23935936 DOI: 10.1371/journal.pone.0069129]

54 **Lee HJ**, Lee JK, Lee H, Shin JW, Carter JE, Sakamoto T, Jin HK, Bae JS. The therapeutic potential of human umbilical cord blood-derived mesenchymal stem cells in Alzheimer's disease. *Neurosci Lett* 2010; **481**: 30-35 [PMID: 20600610 DOI: 10.1016/j.neulet.2010.06.045]

55 **Takahashi K**, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006; **126**: 663-676 [PMID: 16904174 DOI: 10.1016/j.cell.2006.07.024]

56 **Cooper O**, Hargus G, Deleidi M, Blak A, Osborn T, Marlow E, Lee K, Levy A, Perez-Torres E, Yow A, Isacson O. Differentiation of human ES and Parkinson's disease iPS cells into ventral midbrain dopaminergic neurons requires a high activity form of SHH, FGF8a and specific regionalization by retinoic acid. *Mol Cell Neurosci* 2010; **45**: 258-266 [PMID: 20603216 DOI: 10.1016/j.mcn.2010.06.017]

57 **Nori S**, Okada Y, Yasuda A, Tsuji O, Takahashi Y, Kobayashi Y, Fujiyoshi K, Koike M, Uchiyama Y, Ikeda E, Toyama Y, Yamanaka S, Nakamura M, Okano H. Grafted human-induced pluripotent stem-cell-derived neurospheres promote motor functional recovery after spinal cord injury in mice. *Proc Natl Acad Sci U S A* 2011; **108**: 16825-16830 [PMID: 21949375 DOI: 10.1073/pnas.1108077108]

58 **Kim TG**, Yao R, Monnell T, Cho JH, Vasudevan A, Koh A, Peeyush KT, Moon M, Datta D, Bolshakov VY, Kim KS, Chung S. Efficient specification of interneurons from human pluripotent stem cells by dorsoventral and rostrocaudal modulation. *Stem Cells* 2014; **32**: 1789-1804 [PMID: 24648391 DOI: 10.1002/stem.1704]

59 **Paull D**, Sevilla A, Zhou H, Hahn AK, Kim H, Napolitano C, Tsankov A, Shang L, Krumholz K, Jagadeesan P, Woodard CM, Sun B, Vilboux T, Zimmer M, Forero E, Moroziewicz DN, Martinez H, Malicdan MC, Weiss KA, Vensand LB, Dusenberry CR, Polus H, Sy KT, Kahler DJ, Gahl WA, Solomon SL, Chang S, Meissner A, Eggan K, Noggle SA. Automated, high-throughput derivation, characterization and differentiation of induced pluripotent stem cells. *Nat Methods* 2015; **12**: 885-892 [PMID: 26237226 DOI: 10.1038/nmeth.3507]

60 **Maroof AM**, Keros S, Tyson JA, Ying SW, Ganat YM, Merkle FT, Liu B, Goulburn A, Stanley EG, Elefanty AG, Widmer HR, Eggan K, Goldstein PA, Anderson SA, Studer L. Directed differentiation and functional maturation of cortical interneurons from human embryonic stem cells. *Cell Stem Cell* 2013; **12**: 559-572 [PMID: 23642365 DOI: 10.1016/j.stem.2013.04.008]

61 **Nicholas CR**, Chen J, Tang Y, Southwell DG, Chalmers N, Vogt D, Arnold CM, Chen YJ, Stanley EG, Elefanty AG, Sasai Y, Alvarez-Buylla A, Rubenstein JL, Kriegstein AR. Functional maturation of hPSC-derived forebrain interneurons requires an extended timeline and mimics human neural development. *Cell Stem Cell* 2013; **12**: 573-586 [PMID: 23642366 DOI: 10.1016/j.stem.2013.04.005]

62 **Holtman IR**, Raj DD, Miller JA, Schaafsma W, Yin Z, Brouwer N, Wes PD, Möller T, Orre M, Kamphuis W, Hol EM, Boddeke EW, Eggen BJ. Induction of a common microglia gene expression signature by aging and neurodegenerative conditions: a co-expression meta-analysis. *Acta Neuropathol Commun* 2015; **3**: 31 [PMID: 26001565 DOI: 10.1186/s40478-015-0203-5]

63 **Takamatsu K**, Ikeda T, Haruta M, Matsumura K, Ogi Y, Nakagata N, Uchino M, Ando Y, Nishimura Y, Senju S. Degradation of amyloid beta by human induced pluripotent stem cell-derived macrophages expressing Neprilysin-2. *Stem Cell Res* 2014; **13**: 442-453 [PMID: 25460605 DOI: 10.1016/j.scr.2014.10.001]

64 **Israel MA**, Yuan SH, Bardy C, Reyna SM, Mu Y, Herrera C, Hefferan MP, Van Gorp S, Nazor KL, Boscolo FS, Carson CT, Laurent LC, Marsala M, Gage FH, Remes AM, Koo EH, Goldstein LS. Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells. *Nature* 2012; **482**: 216-220 [PMID: 22278060 DOI: 10.1038/nature10821]

65 **Raja WK**, Mungenast AE, Lin YT, Ko T, Abdurrob F, Seo J, Tsai LH. Self-Organizing 3D Human Neural Tissue Derived from Induced Pluripotent Stem Cells Recapitulate Alzheimer's Disease Phenotypes. *PLoS One* 2016; **11**: e0161969 [PMID: 27622770 DOI: 10.1371/journal.pone.0161969]

66 **Yagi T**, Ito D, Okada Y, Akamatsu W, Nihei Y, Yoshizaki T, Yamanaka S, Okano H, Suzuki N. Modeling familial Alzheimer's disease with induced pluripotent stem cells. *Hum Mol Genet* 2011; **20**: 4530-4539 [PMID: 21900357 DOI: 10.1093/hmg/ddr394]

67 **Mahairaki V**, Ryu J, Peters A, Chang Q, Li T, Park TS, Burridge PW, Talbot CC Jr, Asnaghi L, Martin LJ, Zambidis ET, Koliatsos VE. Induced pluripotent stem cells from familial Alzheimer's disease patients differentiate into mature neurons with amyloidogenic properties. *Stem Cells Dev* 2014; **23**: 2996-3010 [PMID: 25027006 DOI: 10.1089/scd.2013.0511]

68 **Sproul AA**, Jacob S, Pre D, Kim SH, Nestor MW, Navarro-Sobrino M, Santa-Maria I, Zimmer M, Aubry S, Steele JW, Kahler DJ, Dranovsky A, Arancio O, Crary JF, Gandy S, Noggle SA. Characterization and molecular profiling of PSEN1 familial Alzheimer's disease iPSC-derived neural progenitors. *PLoS One* 2014; **9**: e84547 [PMID: 24416243 DOI: 10.1371/journal.pone.0084547]

69 **Woodruff G**, Young JE, Martinez FJ, Buen F, Gore A, Kinaga J, Li Z, Yuan SH, Zhang K, Goldstein LS. The presenilin-1 ΔE9 mutation results in reduced γ-secretase activity, but not total loss of PS1 function, in isogenic human stem cells. *Cell Rep* 2013; **5**: 974-985 [PMID: 24239350 DOI: 10.1016/j.celrep.2013.10.018]

70 **Moore S**, Evans LD, Andersson T, Portelius E, Smith J, Dias TB, Saurat N, McGlade A, Kirwan P, Blennow K, Hardy J, Zetterberg H, Livesey FJ. APP metabolism regulates tau proteostasis in human cerebral cortex neurons. *Cell Rep* 2015; **11**: 689-696 [PMID: 25921538 DOI: 10.1016/j.celrep.2015.03.068]

71 **Ochalek A**, Mihalik B, Avci HX, Chandrasekaran A, Téglási A, Bock I, Giudice ML, Táncos Z, Molnár K, László L, Nielsen JE, Holst B, Freude K, Hyttel P, Kobolák J, Dinnyés A. Neurons derived from sporadic Alzheimer's disease iPSCs reveal elevated TAU hyperphosphorylation, increased amyloid levels, and GSK3B activation. *Alzheimers Res Ther* 2017; **9**: 90 [PMID: 29191219 DOI: 10.1186/s13195-017-0317-z]

72 **Sun L**, Zhou R, Yang G, Shi Y. Analysis of 138 pathogenic mutations in presenilin-1 on the in vitro production of Aβ42 and Aβ40 peptides by γ-secretase. *Proc Natl Acad Sci U S A* 2017; **114**: E476-E485 [PMID: 27930341 DOI: 10.1073/pnas.1618657114]

73 **Muratore CR**, Rice HC, Srikanth P, Callahan DG, Shin T, Benjamin LN, Walsh DM, Selkoe DJ, Young-Pearse TL. The familial Alzheimer's disease APPV717I mutation alters APP processing and Tau expression in iPSC-derived neurons. *Hum Mol Genet* 2014; **23**: 3523-3536 [PMID: 24524897 DOI: 10.1093/hmg/ddu064]

74 **Arber C**, Toombs J, Lovejoy C, Ryan NS, Paterson RW, Willumsen N, Gkanatsiou E, Portelius E, Blennow K, Heslegrave A, Schott JM, Hardy J, Lashley T, Fox NC, Zetterberg H, Wray S. Familial Alzheimer's disease patient-derived neurons reveal distinct mutation-specific effects on amyloid beta. *Mol Psychiatry* 2019 [PMID: 30980041 DOI: 10.1038/s41380-019-0410-8]

75 **Araki R**, Uda M, Hoki Y, Sunayama M, Nakamura M, Ando S, Sugiura M, Ideno H, Shimada A, Nifuji A, Abe M. Negligible immunogenicity of terminally differentiated cells derived from induced pluripotent or embryonic stem cells. *Nature* 2013; **494**: 100-104 [PMID: 23302801 DOI: 10.1038/nature11807]

76 **Hibaoui Y**, Feki A. Human pluripotent stem cells: applications and challenges in neurological diseases. *Front Physiol* 2012; **3**: 267 [PMID: 22934023 DOI: 10.3389/fphys.2012.00267]

77 **Lister R**, Pelizzola M, Kida YS, Hawkins RD, Nery JR, Hon G, Antosiewicz-Bourget J, O'Malley R, Castanon R, Klugman S, Downes M, Yu R, Stewart R, Ren B, Thomson JA, Evans RM, Ecker JR. Hotspots of aberrant epigenomic reprogramming in human induced pluripotent stem cells. *Nature* 2011; **471**: 68-73 [PMID: 21289626 DOI: 10.1038/nature09798]

78 **Tolosa L**, Pareja E, Gómez-Lechón MJ. Clinical Application of Pluripotent Stem Cells: An Alternative Cell-Based Therapy for Treating Liver Diseases? *Transplantation* 2016; **100**: 2548-2557 [PMID: 27495745 DOI: 10.1097/tp.0000000000001426]

79 **Shimada IS**, LeComte MD, Granger JC, Quinlan NJ, Spees JL. Self-renewal and differentiation of reactive astrocyte-derived neural stem/progenitor cells isolated from the cortical peri-infarct area after stroke. *J Neurosci* 2012; **32**: 7926-7940 [PMID: 22674268 DOI: [10.1523/JNEUROSCI.4303-11.2012](https://doi.org/10.1523/JNEUROSCI.4303-11.2012)]

80 **Blurton-Jones M**, Kitazawa M, Martinez-Coria H, Castello NA, Müller FJ, Loring JF, Yamasaki TR, Poon WW, Green KN, LaFerla FM. Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. *Proc Natl Acad Sci U S A* 2009; **106**: 13594-13599 [PMID: 19633196 DOI: 10.1073/pnas.0901402106]

81 **Kordower JH**, Winn SR, Liu YT, Mufson EJ, Sladek JR Jr, Hammang JP, Baetge EE, Emerich DF. The aged monkey basal forebrain: rescue and sprouting of axotomized basal forebrain neurons after grafts of encapsulated cells secreting human nerve growth factor. *Proc Natl Acad Sci U S A* 1994; **91**: 10898-10902 [PMID: 7971980 DOI: 10.1073/pnas.91.23.10898]

82 **Park D**, Yang YH, Bae DK, Lee SH, Yang G, Kyung J, Kim D, Choi EK, Lee SW, Kim GH, Hong JT, Choi KC, Lee HJ, Kim SU, Kim YB. Improvement of cognitive function and physical activity of aging mice by human neural stem cells over-expressing choline acetyltransferase. *Neurobiol Aging* 2013; **34**: 2639-2646 [PMID: 23731954 DOI: 10.1016/j.neurobiolaging.2013.04.026]

83 **Zhang Q**, Wu HH, Wang Y, Gu GJ, Zhang W, Xia R. Neural stem cell transplantation decreases neuroinflammation in a transgenic mouse model of Alzheimer's disease. *J Neurochem* 2016; **136**: 815-825 [PMID: 26525612 DOI: 10.1111/jnc.13413]

84 **Lee IS**, Jung K, Kim IS, Lee H, Kim M, Yun S, Hwang K, Shin JE, Park KI. Human neural stem cells alleviate Alzheimer-like pathology in a mouse model. *Mol Neurodegener* 2015; **10**: 38 [PMID: 26293123 DOI: 10.1186/s13024-015-0035-6]

85 **Lilja AM**, Malmsten L, Röjdner J, Voytenko L, Verkhratsky A, Ögren SO, Nordberg A, Marutle A. Neural Stem Cell Transplant-Induced Effect on Neurogenesis and Cognition in Alzheimer Tg2576 Mice Is Inhibited by Concomitant Treatment with Amyloid-Lowering or Cholinergic α7 Nicotinic Receptor Drugs. *Neural Plast* 2015; **2015**: 370432 [PMID: 26257960 DOI: 10.1155/2015/370432]

86 **Ager RR**, Davis JL, Agazaryan A, Benavente F, Poon WW, LaFerla FM, Blurton-Jones M. Human neural stem cells improve cognition and promote synaptic growth in two complementary transgenic models of Alzheimer's disease and neuronal loss. *Hippocampus* 2015; **25**: 813-826 [PMID: 25530343 DOI: 10.1002/hipo.22405]

87 **Xuan AG**, Luo M, Ji WD, Long DH. Effects of engrafted neural stem cells in Alzheimer's disease rats. *Neurosci Lett* 2009; **450**: 167-171 [PMID: 19070649 DOI: 10.1016/j.neulet.2008.12.001]

88 **Li X**, Zhu H, Sun X, Zuo F, Lei J, Wang Z, Bao X, Wang R. Human Neural Stem Cell Transplantation Rescues Cognitive Defects in APP/PS1 Model of Alzheimer's Disease by Enhancing Neuronal Connectivity and Metabolic Activity. *Front Aging Neurosci* 2016; **8**: 282 [PMID: 27932977 DOI: 10.3389/fnagi.2016.00282]

89 **Xuan AG**, Long DH, Gu HG, Yang DD, Hong LP, Leng SL. BDNF improves the effects of neural stem cells on the rat model of Alzheimer's disease with unilateral lesion of fimbria-fornix. *Neurosci Lett* 2008; **440**: 331-335 [PMID: 18579298 DOI: 10.1016/j.neulet.2008.05.107]

90 **Park D**, Yang G, Bae DK, Lee SH, Yang YH, Kyung J, Kim D, Choi EK, Choi KC, Kim SU, Kang SK, Ra JC, Kim YB. Human adipose tissue-derived mesenchymal stem cells improve cognitive function and physical activity in ageing mice. *J Neurosci Res* 2013; **91**: 660-670 [PMID: 23404260 DOI: 10.1002/jnr.23182]

91 **Lee HJ**, Lim IJ, Park SW, Kim YB, Ko Y, Kim SU. Human neural stem cells genetically modified to express human nerve growth factor (NGF) gene restore cognition in the mouse with ibotenic acid-induced cognitive dysfunction. *Cell Transplant* 2012; **21**: 2487-2496 [PMID: 22526467 DOI: [10.3727/096368912X638964](https://doi.org/10.3727/096368912X638964)]

92 **Anand A**, Banik A, Thakur K, Masters CL. The animal models of dementia and Alzheimer's disease for pre-clinical testing and clinical translation. *Curr Alzheimer Res* 2012; **9**: 1010-1029 [PMID: 22698073 DOI: 10.2174/156720512803569055]

93 **Banik A**, Anand A. Preclinical non-human models to combat dementia. *Ann Neurosci* 2013; **20**: 24-29 [PMID: 25206006 DOI: 10.5214/ans.0972.7531.200109]

94 **Martinez-Serrano A**, Hantzopoulos PA, Björklund A. Ex vivo gene transfer of brain-derived neurotrophic factor to the intact rat forebrain: neurotrophic effects on cholinergic neurons. *Eur J Neurosci* 1996; **8**: 727-735 [PMID: 9081624 DOI: 10.1111/j.1460-9568.1996.tb01258.x]

95 **Sinden JD**, Stroemer P, Grigoryan G, Patel S, French SJ, Hodges H. Functional repair with neural stem cells. *Novartis Found Symp* 2000; **231**: 270-83; discussion 283-8, 302-306 [PMID: 11131543 DOI: 10.1002/0470870834.ch16]

96 **Qu T**, Brannen CL, Kim HM, Sugaya K. Human neural stem cells improve cognitive function of aged brain. *Neuroreport* 2001; **12**: 1127-1132 [PMID: 11338178 DOI: 10.1097/00001756-200105080-00016]

97 **Wu P**, Tarasenko YI, Gu Y, Huang LY, Coggeshall RE, Yu Y. Region-specific generation of cholinergic neurons from fetal human neural stem cells grafted in adult rat. *Nat Neurosci* 2002; **5**: 1271-1278 [PMID: 12426573 DOI: 10.1038/nn974]

98 **Wang Q**, Matsumoto Y, Shindo T, Miyake K, Shindo A, Kawanishi M, Kawai N, Tamiya T, Nagao S. Neural stem cells transplantation in cortex in a mouse model of Alzheimer's disease. *J Med Invest* 2006; **53**: 61-69 [PMID: 16537997 DOI: 10.2152/jmi.53.61]

99 **Prakash A**, Kumar A. Role of nuclear receptor on regulation of BDNF and neuroinflammation in hippocampus of β-amyloid animal model of Alzheimer's disease. *Neurotox Res* 2014; **25**: 335-347 [PMID: 24277156 DOI: 10.1007/s12640-013-9437-9]

100 **Seaberg RM**, van der Kooy D. Stem and progenitor cells: the premature desertion of rigorous definitions. *Trends Neurosci* 2003; **26**: 125-131 [PMID: 12591214 DOI: 10.1016/s0166-2236(03)00031-6]

101 **Tang J**, Xu H, Fan X, Li D, Rancourt D, Zhou G, Li Z, Yang L. Embryonic stem cell-derived neural precursor cells improve memory dysfunction in Abeta(1-40) injured rats. *Neurosci Res* 2008; **62**: 86-96 [PMID: 18634835 DOI: 10.1016/j.neures.2008.06.005]

102 **Blurton-Jones M**, Spencer B, Michael S, Castello NA, Agazaryan AA, Davis JL, Müller FJ, Loring JF, Masliah E, LaFerla FM. Neural stem cells genetically-modified to express neprilysin reduce pathology in Alzheimer transgenic models. *Stem Cell Res Ther* 2014; **5**: 46 [PMID: 25022790 DOI: 10.1186/scrt440]

103 **Ernfors P**, Wetmore C, Olson L, Persson H. Identification of cells in rat brain and peripheral tissues expressing mRNA for members of the nerve growth factor family. *Neuron* 1990; **5**: 511-526 [PMID: 2206535 DOI: 10.1016/0896-6273(90)90090-3]

104 **Elia CA**, Losurdo M, Malosio ML, Coco S. Extracellular Vesicles from Mesenchymal Stem Cells Exert Pleiotropic Effects on Amyloid-β, Inflammation, and Regeneration: A Spark of Hope for Alzheimer's Disease from Tiny Structures? *Bioessays* 2019; **41**: e1800199 [PMID: 30919493 DOI: 10.1002/bies.201800199]

105 **Naaldijk Y**, Jäger C, Fabian C, Leovsky C, Blüher A, Rudolph L, Hinze A, Stolzing A. Effect of systemic transplantation of bone marrow-derived mesenchymal stem cells on neuropathology markers in APP/PS1 Alzheimer mice. *Neuropathol Appl Neurobiol* 2017; **43**: 299-314 [PMID: 26918424 DOI: 10.1111/nan.12319]

106 **Yun HM**, Kim HS, Park KR, Shin JM, Kang AR, il Lee K, Song S, Kim YB, Han SB, Chung HM, Hong JT. Placenta-derived mesenchymal stem cells improve memory dysfunction in an Aβ1-42-infused mouse model of Alzheimer's disease. *Cell Death Dis* 2013; **4**: e958 [PMID: 24336078 DOI: 10.1038/cddis.2013.490]

107 **Oh SH**, Kim HN, Park HJ, Shin JY, Lee PH. Mesenchymal Stem Cells Increase Hippocampal Neurogenesis and Neuronal Differentiation by Enhancing the Wnt Signaling Pathway in an Alzheimer's Disease Model. *Cell Transplant* 2015; **24**: 1097-1109 [PMID: 24612635 DOI: [10.3727/096368914X679237](https://doi.org/10.3727/096368914X679237)]

108 **Galipeau J**, Sensébé L. Mesenchymal Stromal Cells: Clinical Challenges and Therapeutic Opportunities. *Cell Stem Cell* 2018; **22**: 824-833 [PMID: 29859173 DOI: 10.1016/j.stem.2018.05.004]

109 **Rikhtegar R**, Yousefi M, Dolati S, Kasmaei HD, Charsouei S, Nouri M, Shakouri SK. Stem cell-based cell therapy for neuroprotection in stroke: A review. *J Cell Biochem* 2019; **120**: 8849-8862 [PMID: 30506720 DOI: 10.1002/jcb.28207]

110 **Schwartz SD**, Hubschman JP, Heilwell G, Franco-Cardenas V, Pan CK, Ostrick RM, Mickunas E, Gay R, Klimanskaya I, Lanza R. Embryonic stem cell trials for macular degeneration: a preliminary report. *Lancet* 2012; **379**: 713-720 [PMID: 22281388 DOI: [10.1016/S0140-6736(12)60028-2](https://doi.org/10.1016/S0140-6736(12)60028-2)]

111 **Fujioka K**, Hanada S, Inoue Y, Sato K, Hirakuri K, Shiraishi K, Kanaya F, Ikeda K, Usui R, Yamamoto K, Kim SU, Manome Y. Effects of silica and titanium oxide particles on a human neural stem cell line: morphology, mitochondrial activity, and gene expression of differentiation markers. *Int J Mol Sci* 2014; **15**: 11742-11759 [PMID: 24992594 DOI: 10.3390/ijms150711742]

112 **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**: 841-851 [PMID: 26025980 DOI: 10.5966/sctm.2014-0184]

113 **Cha MY**, Kwon YW, Ahn HS, Jeong H, Lee YY, Moon M, Baik SH, Kim DK, Song H, Yi EC, Hwang D, Kim HS, Mook-Jung I. Protein-Induced Pluripotent Stem Cells Ameliorate Cognitive Dysfunction and Reduce Aβ Deposition in a Mouse Model of Alzheimer's Disease. *Stem Cells Transl Med* 2017; **6**: 293-305 [PMID: 28170178 DOI: 10.5966/sctm.2016-0081]

114 **Balez R**, Steiner N, Engel M, Muñoz SS, Lum JS, Wu Y, Wang D, Vallotton P, Sachdev P, O'Connor M, Sidhu K, Münch G, Ooi L. 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 [PMID: 27514990 DOI: 10.1038/srep31450]

115 **Brookhouser N**, Raman S, Potts C, Brafman DA. May I Cut in? Gene Editing Approaches in Human Induced Pluripotent Stem Cells. *Cells* 2017; **6**: [PMID: 28178187 DOI: 10.3390/cells6010005]

116 **Kim KS**, Kim HS, Park JM, Kim HW, Park MK, Lee HS, Lim DS, Lee TH, Chopp M, Moon J. Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model. *Neurobiol Aging* 2013; **34**: 2408-2420 [PMID: 23623603 DOI: [10.1016/j.neurobiolaging.2013.03.029](https://doi.org/10.1016/j.neurobiolaging.2013.03.029)]

117 **Yang H**, Xie Z, Wei L, Yang H, Yang S, Zhu Z, Wang P, Zhao C, Bi J. Human umbilical cord mesenchymal stem cell-derived neuron-like cells rescue memory deficits and reduce amyloid-beta deposition in an AβPP/PS1 transgenic mouse model. *Stem Cell Res Ther* 2013; **4**: 76 [PMID: 23826983 DOI: 10.1186/scrt227]

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

119 **Xiao J**, Yang R, Biswas S, Qin X, Zhang M, Deng W. Mesenchymal stem cells and induced pluripotent stem cells as therapies for multiple sclerosis. *Int J Mol Sci* 2015; **16**: 9283-9302 [PMID: 25918935 DOI: [10.3390/ijms16059283](https://doi.org/10.3390/ijms16059283)]

120 **Vos SJ**, Verhey F, Frölich L, Kornhuber J, Wiltfang J, Maier W, Peters O, Rüther E, Nobili F, Morbelli S, Frisoni GB, Drzezga A, Didic M, van Berckel BN, Simmons A, Soininen H, Kłoszewska I, Mecocci P, Tsolaki M, Vellas B, Lovestone S, Muscio C, Herukka SK, Salmon E, Bastin C, Wallin A, Nordlund A, de Mendonça A, Silva D, Santana I, Lemos R, Engelborghs S, Van der Mussele S; Alzheimer’s Disease Neuroimaging Initiative, Freund-Levi Y, Wallin ÅK, Hampel H, van der Flier W, Scheltens P, Visser PJ. Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage. *Brain* 2015; **138**: 1327-1338 [PMID: 25693589 DOI: 10.1093/brain/awv029]

121 **Villemagne VL**, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, Szoeke C, Macaulay SL, Martins R, Maruff P, Ames D, Rowe CC, Masters CL; Australian Imaging Biomarkers and Lifestyle (AIBL) Research Group. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol* 2013; **12**: 357-367 [PMID: 23477989 DOI: 10.1016/S1474-4422(13)70044-9]

122 **Jessen NA**, Munk AS, Lundgaard I, Nedergaard M. The Glymphatic System: A Beginner's Guide. *Neurochem Res* 2015; **40**: 2583-2599 [PMID: 25947369 DOI: 10.1007/s11064-015-1581-6]

123 **Peng W**, Achariyar TM, Li B, Liao Y, Mestre H, Hitomi E, Regan S, Kasper T, Peng S, Ding F, Benveniste H, Nedergaard M, Deane R. Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. *Neurobiol Dis* 2016; **93**: 215-225 [PMID: 27234656 DOI: 10.1016/j.nbd.2016.05.015]

124 **Thirabanjasak D**, Tantiwongse K, Thorner PS. Angiomyeloproliferative lesions following autologous stem cell therapy. *J Am Soc Nephrol* 2010; **21**: 1218-1222 [PMID: 20558536 DOI: 10.1681/ASN.2009111156]

125 **Amariglio N**, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R, Trakhtenbrot L, Paz N, Koren-Michowitz M, Waldman D, Leider-Trejo L, Toren A, Constantini S, Rechavi G. Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. *PLoS Med* 2009; **6**: e1000029 [PMID: 19226183 DOI: 10.1371/journal.pmed.1000029]

126 **Fazel SS**, Angoulvant D, Butany J, Weisel RD, Li RK. Mesenchymal stem cells engineered to overexpress stem cell factor improve cardiac function but have malignant potential. *J Thorac Cardiovasc Surg* 2008; **136**: 1388-1389 [PMID: 19026843 DOI: 10.1016/j.jtcvs.2007.11.068]

**Footnotes**

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**Table 1 Completed clinical trial trials of stem cells in patients with Alzheimer’s disease**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study name (study date)** | **Current state** | **Length (phase)** | **Site** | **Subjects (age)** | **Design** | **Stem cell** | **Route (*n*)** | **Dosage (participants)** | ***n*1** | **Outcome measures** | |
| **Primary** | **Secondary** |
| NCT03117738 (4/2017-9/2019) | Active, NR | 32 wk (I/II) | United States | AD (> 50) | PBO-control, Double-blind | AD-MSC | IV (9) | NA | 21 | ADAS-cog | MMSE, CDR-SB, NPI, GDS, ADL, biomarkers (MRI, Aβ, *etc*.) |
| NCT04040348 (4/2019-9/2021) | Recruiting | 65 wk (I) | United States | AD (50-85) | Open label | H-MSC | IV (NA) | 1 × 108 (5), 2 × 108 (5) | 10 | AE number | ADAS-cog, MMSE, GDS, ADL, NPI, diverse biomarkers |
| NCT02600130 (4/2019-9/2021) | Active, NR | 65 wk (II) | United States | AD (50-80) | PBO-control, Double-blind | L-MSC | IV (1) | 2 × 107 (10), 1 × 108 (10), PBO (5) | 25 | AE number | ADAS-cog, ADL, biomarkers (CSF, Aβ) |
| NCT02672306 (10/2017-10/2019) | Active, NR | 36 wk (I/II) | China | AD (50-85) | PBO-control, Double-blind | HUC-MSC | IV (8) | 0.5 × 106/kg (NA), PBO (NA) | 16 | ADAS-cog | ADAS-cog, CIBIC, CIBIC plus, MMSE, ADL, NPI biomarkers (plasma Aβ, *etc.*) |
| NCT03724136 (10/2018-10/2022) | Recruiting | 12 mo | United States | AD+ other neurological disease (> 18) | Open label, Three groups | B-MSC | IV (NA) | NA | 100 | MMSE, ASQ-SE | Activities of daily living |
| NCT01547689 (2012.3-2016.12) | Unknown status | 10 wk (I/II) | China | AD (50-85) | Open label, Single-center, Self-control | HUC-MSC | IV (8) | 0.5 × 106/kg | 30 | AE number | ADAS-cog, MMSE, CIBIC, ADL, NPI biomarkers (Aβ, tau, *etc.*) |

1Number of total participants. Aβ: Amyloid-beta; AD: Dementia due to Alzheimer’s disease; ADAS-Cog: Alzheimer’s Disease Assessment Scale-Cognitive Subscale; AE: Adverse events; NPI: Neuropsychiatric Inventory; CSF: Cerebrospinal fluid; AD-MSC: Autologous adipose tissue-derived mesenchymal stem cells; H-MSC: Human mesenchymal stem cells; L-MSC: Leukemia mesenchymal stem cells; B-MSC: Bone marrow mesenchymal stem cells; HUC-MSC: Human umbilical cord blood-derived mesenchymal stem cells; ADL: Activities of daily living; NA: Not available; CDR-SB: Clinical Dementia Rating-Sum of the Boxes scale; GDS: Geriatric Depression Scale; MMSE: Minimum Mental State Examination; CIDIC: Composite International Diagnostic Interview Core; PBO: Placebo; IV: Intravenous; ASQ-SE: Ages and stages questionnaires-social-emotional.