Current Neuropharmacology, 2022, *20*, 1093-1115

REVIEW ARTICLE

Stem Cell-based Therapeutic and Diagnostic Approaches in Alzheimer's Disease

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ARTICLE HISTORY

Received: May 11, 2021
Revised: July 24, 2021
Accepted: September 21, 2021

DOI:
10.2174/1570159X20666211231090659

Abstract: ***Background*:** Alzheimer's disease (AD) is a neurodegenerative impairment mainly recognized by memory loss and cognitive deficits. However, the current therapies against AD are mostly limited to palliative medications, prompting researchers to investigate more efficient therapeutic approaches for AD, such as stem cell therapy. Recent evidence has proposed that extensive neuronal and synaptic loss and altered adult neurogenesis, which is perceived pivotal in terms of plasticity and network maintenance, occurs early in the course of AD, which exacerbates neuronal vulnerability to AD. Thus, regeneration and replenishing the depleted neuronal networks by strengthening the endogenous repair mechanisms or exogenous stem cells and their cargoes is a rational therapeutic approach. Currently, several stem cell-based therapies as well as stem cell products like exosomes, have shown promising results in the early diagnosis of AD.

***Objective*:** This review begins with a comparison between AD and normal aging pathophysiology and a discussion on open questions in the field. Next, summarizing the current stem cell-based therapeutic and diagnostic approaches, we declare the advantages and disadvantages of each method. Also, we comprehensively evaluate the human clinical trials of stem cell therapies for AD.

***Methodology*:** Peer-reviewed reports were extracted through Embase, PubMed, and Google Scholar until 2021.

***Results*:** With several ongoing clinical trials, stem cells and their derivatives (*e.g.*, exosomes) are an emerging and encouraging field in diagnosing and treating neurodegenerative diseases. Although stem cell therapies have been successful in animal models, numerous clinical trials in AD patients have yielded unpromising results, which we will further discuss.

Keywords: Neurodegenerative diseases, Alzheimer's disease, aging, stem cell therapy, exosomes, clinical trial.

1. INTRODUCTION

Dementia is an age-related developing neurodegeneration and cognitive impairment that leads to difficulty in daily function. Dementia is regarded as one of the leading causes of disability and dependency among elders and impacts personal and social aspects of life. Almost 50 million people have dementia worldwide, and if we consider the rapid aging of the population, about 152 million cases of Alzheimer's disease (AD) patients are expected by 2050 [1]. Among diseases with dementia, AD is the most common one, beginning with impaired memory but gradually affecting all learning and cognitive functions [2]. Even though the exact pathophysiology of AD has not been clarified yet, it consists of four main events, neuroprotective tau protein hyperphosphorylation, formation of amyloid β (Aβ) plaques due to cleavage of amyloid precursor protein (APP), microglia activation causing neuroinflammation, and finally, widespread neuronal and synaptic loss [3].

Efforts in AD treatment have a long history, but they did not lead to an effective cure; for instance, chemical drugs (*e.g.*, cholinesterase inhibitors) abate the disease progression [4]. Besides the ambiguous pathogenesis of the disease, delayed diagnosis can also contribute to the failure of AD treatment due to inefficient diagnostic methods and the long period between pathological disease onset and the clinical condition [5]. It is demonstrated that impaired neurogenesis and a toxic microenvironment are two fundamental processes in AD pathogenesis [6]. Stem cell therapy consists of endogenous repair and exogenous stem cell therapy, which opened a new horizon in AD treatment with the potential to replace lost neurons and modulate cell niches. It is expected to be the possible turning point among a broad spectrum of therapeutic methods to reduce the burden of neurodegenerative diseases such as AD [7]. Several clinical trials have been recruited due to the promising results of this method in animal studies. In AD, endogenous stem cell therapy refers to the

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1875-6190/22 $65.00+.00

strategies that enhance the proliferation, migration, and differentiation of resident neural stem cells (NSCs). Exogenous stem cell therapy refers to the procedure of transferring autologous or allogeneic stem cells including mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs) to humans or animals to reinforce the repair of injured neural circuits and restore their functions [3].

As mentioned previously, an early diagnosis and monitoring of the disease could guide clinicians to use any available treating/prophylactic approaches to attenuate disease progression [8]. Notably, the condition may progress in a clinically silent manner during the incubation period. Different biomolecules, such as microRNAs (miRNAs), tau protein, and Aβ protein fragments could reflect the disease's pathological progression and be used as diagnostic biomarkers of AD. However, some limitations exist in using these biomolecules, such as poor stability, low specificity, and lack of specific cut-off points due to different methods. Recently, solving the limitation of exosome administration has been hotly debated. Exosomes, a subgroup of extracellular vesicles, are secreted from various cells and detected in different body fluids. Cells can load exosomes with other biomolecules, such as nucleic acids and proteins [8]. Also, their potential for cell-free therapy increases their importance. Due to some limitations of cell therapy, such as tumor formation, cell-free treatment (*e.g.*, exosomes) has been emphasized in AD treatment [9]. To date, researchers examine different cell sources and their therapeutic efficacy of exosomes in animal models of AD [10, 11], which is accompanied by promising results; however, more studies are needed.

Brought together, stem cell-based therapeutic and diagnostic approaches for curing AD are ultimately encouraging due to stem cells' unique features. Poor relation between animal and human studies causes some gaps that need further investigation. This paper reviews the different aspects of stem cell therapy and its products in AD treatment with a comprehensive clinical trial assessment. Moreover, we addressed the limitations, challenges, and prospects of using stem cell therapy for curing AD.

2. SPECULATIVE MECHANISMS OF AD CONTRIBUTING TO THE AGGRAVATION OF THE PHYSIOLOGIC AGING PROCESS

Neural stem cells (NSCs) as multipotent stem cells can differentiate into neurons and glial cells. Two sites identified in the adult brain with lifelong neurogenesis- the cortical subventricular zone (SVZ) surrounding the brain's lateral ventricles and the dentate subgranular zone (SGZ) in the hippocampal formation. NSCs continuously replace damaged neurons. In the human lifespan, albeit they act inadequately and do not lead to proper "plasticity response" in practice. Tobin *et al*. showed that neurogenesis also occurs in the hippocampus of patients with cognitive impairment, even in their tenth decade of life [12, 13].

2.1. Comparison of the Physiologic and Pathologic Aging Processes for AD Progression

The exact borders between normal aging, pathological aging, and Alzheimer's specific changes are still unclear. Literature increasingly suggests that a broad array of genetic and environmental factors exacerbate the normal aging process in the pathophysiology of neurodegenerative diseases [14].

The aging process exhibits substantial changes in the brain networks, neuronal cells, and extracellular matrix. While hippocampal neurogenesis occurs throughout adulthood, aged animals have significantly less NPC proliferation, neuronal differentiation, and newborn neuron survival compared with younger animals due to a combination of intrinsic and extrinsic age-related changes. To further decipher, physiological aging causes a gradual loss of nerve function. Both the NSC and their supporting sites are adversely altered by various intrinsic and external factors, creating a toxic microenvironment that responds insufficiently to neurogenic signals [14]. Reduced cognitive function and circuit alteration exist in the normal aged brain [15]. For instance, Albertson *et al*. demonstrated that there is a general decline in cortex activity as well as a selective reduction in network connectivity in aged mice [16]. Pathological aging, a surmised preclinical stage of AD, is taken into account by misfolded protein deposition accompanied by other changes in normal aging. Controversial studies have been published in the literature on the level of neurogenesis in models of AD. To get the ball rolling, the wild-type presenilin and the soluble form of APP have both been implicated, at least in part, in the function of adult neurogenesis in AD. Studies claim that cell proliferation is increased in the SGZ of postmortem Alzheimer's patients. In the absence of clinical AD, neurofibrillary degeneration is not present or is limited to neocortical/hippocampal regions [17]. Hanseeuw *et al*. suggested that alteration of Aβ function followed by the disruption of tau proteins correlates with lower cognitive function, which could be a predisposing factor toward clinical AD [18]. Neurodegenerative diseases orchestrate the efficiency of adult neurogenesis by selective death of certain neurons and inflammation in diseased brains. Altogether, the perceived contribution of neurogenesis to the pathology of these diseases is subject to further elucidation.

Apart from the similarities, there is still much ambiguity about normal aging and AD [19]. Research has shown that all of the alterations mentioned above impairs neurogenesis and creates a toxic microenvironment of neurons and glial cells [6], which are AD facilitators.

2.2. Underlying Mechanisms Leading to AD Pathogenesis

There are two putative explanations for AD pathogenesis; the amyloid hypothesis claims that the excessive deposition of APP cleavage products (Aβ) is the leading cause of AD. On the other hand, the tau hypothesis asserts that the hyperphosphorylation of tau proteins that form neuro-fibrillary tangles (NFTs) results in an impotent manipulation, leading to AD. Nevertheless, the precise pathogenesis of AD is unclear. Still, studies have disclosed the roles of inflammation in the AD brain to form an environment that is hostile for the survival and integration of neurons into neural circuits [20]. Other genetically rooted molecular and cellular errors of functional pathways that may cause AD include apolipoprotein E (APOE), the most potent risk factor of AD, cholesterol metabolism, immune response, gene transcription, and telomerase activity [21]. Furthermore, personal characteristics

and lifestyle, including exercise, sleep, metabolism, smoking, and genetic disposition, play critical roles in aging and AD [20, 21].

2.3. Microenvironment Alteration in Association with AD Progression

Astrocytes, microglia, and endothelial cells, essential parts of the neuronal niche, undergo several morphological and signaling changes in AD that alter the neuronal niche [22]. The neurogenic niche is altered with increasing age; microglia and astrocytes transit from anti-inflammatory to proinflammatory signaling pathways with higher oxidative stress, which profoundly inhibit neurogenesis in aged animals. On a cellular level, NSCs from aged animals show lysosomal defects and increased amounts of aggregated proteins. In other words, senescence, altered signaling, dystrophy, impaired movement, proteostasis, and phagocytosis are changes in microglial cells that cause neuroinflammation and are aggravated by AD more than a normal aging process [23]. Besides, AD-induced atrophy in astrocytes instigates impaired homeostasis and neurogenesis [24]. Oligodendrocyte progenitor cells (OPCs) are also affected by this toxic niche. A study in this regard revealed that Aβ-exposed OPCs exert a senescence pattern expressing Olig2 and NG2 molecules, resulting in impaired function and aggravated inflammation [25]. It is noteworthy that NSCs cannot differentiate into functional mature neurons with insufficient concentrations of neurotrophic factors or a high level of fibrillary Aβ, fibroblast growth factor-2 (FGF-2), and other destructive factors [12]. Stem cell therapy might be a promising approach to increase stem cell growth and survival, which is critical to ease AD symptoms.

3. APPLICATION OF ENDOGENOUS REPAIR APPROACHES IN AD

NSCs from the subgranular zone (SGZ) of the hippocampus are considered a good reservoir for endogenous repair. Based on some characteristics, including morphologic features, proliferative behaviors, and specific surface antigens, NSCs have been mainly categorized into two types. Type 1 NSCs have astrocyte properties with radial processes extended around the entire granular cell layer and divaricate into the inner molecular layer of the dentate gyrus (DG). Type 1 NSCs express GFAP, Sox2, and Nestin to create the second generation of NSCs. Type 2 stem cells express the same molecules as type 1, except GFAP. Furthermore, a group of cells is developed from this type of NSCs called DCX positive neuroblasts, which differentiate into glutamatergic DG cells and populate the inner third of the granular cell layer. In the granular cell layer, these cells penetrate dendrites into the molecular layer and their axons into the stratum lucidum of the CA3, where they form synaptic connections with CA3 pyramidal cells [26].

3.1. How is it Possible that the Stimulation of Endogenous Neurogenesis Contributes to Halting AD?

Different endogenous and exogenous factors can modulate the rate of hippocampal neurogenesis. Exercise, nerve growth factors, cytokines, and miRNAs are the positive regulators of hippocampal neurogenesis, whereas aging and chronic neurodegenerative conditions are among the negative ones [12]. The primary regions affected by AD are the hippocampus, cerebral cortex, and amygdala. Various molecules, such as Aβ or soluble APPa, can positively or negatively modulate adult hippocampal neurogenesis in AD [27]. Since adult neurogenesis is crucial in learning and memory, an ideal strategy to compensate for neurodegeneration and improve cognitive disorder in AD patients is to stimulate the up-regulation of resident brain-derived neural stem cells (NSCs) [3].

3.2. Different Areas of NSC Niches and Speculative Migratory Pathways in Healthy Brain

Neuroblasts in the SGZ only migrate a short distance into the granule cell layer (GCL) of the DG and integrate into the existing circuitry of the hippocampus generating excitatory, glutamatergic granule cells. SVZ progenitors migrate over a great distance through the rostral migratory stream (RMS) and integrate into the granule cell layer and periglomerular cell layer in the olfactory bulb [28]. They differentiate into mature olfactory interneurons and acquire functional properties [29]. Also, a portion of them forms chainlike aggregates that associate with blood vessels or orient radially towards cortical regions such as the cingulate gyrus or into the prefrontal cortex through the medial migratory stream (MMS) [30].

Furthermore, neurogenesis has been witnessed in the hypothalamus and the brainstem and might exist in the neocortex, striatum, amygdala, and substantia nigra of rodents and other mammals [31]. Although it has been well established that adult neurogenesis occurs in the SVZ and SGZ. Compelling data indicated that NSCs and NPCs in or around the cerebral cortex could form new neurons upon brain damages in several subregions of the cerebral cortex, such as the anterior SVZ, white matter, gray matter, marginal zone, perivascular regions, and leptomeninges. Consistently, pathological manipulations, such as ischemia, and artificial neural degeneration, exerted high potent rerouting of neuroblasts from the anterior SVZ to injured cortical areas [32].

Taken together, neuronal migration impacts neuronal circuit formation and function throughout life and is perceived as conserved among species. Although, as outlined above, additional areas have been reported to support adult neurogenesis, we do not focus on those studies in this review.

3.3. Physiological Function of Endogenous Neurogenesis

We can say that research on adult neurogenesis has evolved from the study that attempts to ascertain its existence to one that paves to shed light on its functions. It prompts researchers to decipher what factors have proliferative, differentiative, and inhibitory effects on endogenous NSCs and NPCs at each life stage to manipulate the processes and reach optimal therapies [32].

3.3.1. Functional Importance of Newborn Neurons for DG-dependent Behavior

Hippocampal neurogenesis is vital for memory resolution and pattern separation and to enhance the creation of the temporal association in memory. Multiple independent avenues of research have declared that adult-born neurons may play a key role in hippocampus-dependent behavioral flexibility (*e.g.*, learning a novel position in the Morris water

maze). To clarify, newly generated neurons have exerted high potency to encode novel experiences and forget former experiences and memory traces [33]. Interestingly, boosting the formation and integration of new granule cells by omitting the pro-apoptotic gene Bax from adult NSCs, hinders the ventral DG, suppresses the activity of stress-responsive cells, and thus may facilitate stress resilience in mice [34]. On the other hand, comprehensive computational studies claimed that old neurons are stable and preserve an optimal encoding learned for former experiences while facilitating the plasticity of neuroblasts in a new environment [35]. Also, through computational analysis, Wiskott *et al*. have proposed that neuroblasts contribute to averting the catastrophic interference of old memories when adapting to new environments [36].

On the whole, deciphering the functional role of neurogenesis will offer us fundamental prospects concerning the olfactory and hippocampal pathways and provide us with novel approaches for neurological disorders [28].

3.4. Speculative Roles of Endogenous Neurogenesis in the Brain Injury

Researchers have witnessed dysregulated neurogenesis in animal models of, and partly in tissues from humans with, a broad spectrum of psychiatric and neurological conditions, ranging from ischemic stroke to AD, Parkinson's disease, and major depression. Deliberate data analysis suggests that neuroblasts exert high efficient responsiveness to a broad spectrum of modalities. CNS disease-triggered accumulation of blood-derived factors sway brain stem cell niche, and these factors regulate NSPC fate and brain repair. It is perceived that CNS diseases entail the endogenous adult NSPCs to proliferate, redirect their migration path towards the lesion area and preferentially differentiate into glial cells or remain in a precursor state contributing to brain repair [37, 38].

3.4.1. Association of NSC Proliferative Capacity and Cognitive Deficits in Humans

Given the obstacles associated with directly measuring neurogenesis in humans, the role of new neurons in human cognitive disorders remains in shadow. Multiple independent research concluded that the dampened neurogenesis levels are typically observed in aged or diseased mice. Both stress and aging, which choreograph neurogenesis in mice, are well known to be associated with memory impairments in clinical human populations [39]. Likewise, patients who have undergone radiation therapy for brain tumors are recognized to be afflicted by cognitive and memory deficits. Notably, radiation is one of the most robust interventions for experimentally ablating neurogenesis; thus, the witnessed cognitive deficits resonate with functions linked to neurogenesis [40].

However, research on the cerebral cortex has revealed that brain damages, such as ischemia, epilepsy, neural degeneration, and lesion, upregulate cortical adult neurogenesis. Nonetheless, in controversy of the studies claiming damage and aging hampers neurogenesis, a previous study showed NSCs and NPCs are present in the aged cerebral cortex, and the neurogenic potency of the cerebral cortex, especially damage-dependent neurogenesis, might be maintained during aging and have some neuroprotective functions against injury [41]. These findings resonate with one study that declared that fluoxetine could increase the production of new inhibitory interneurons from NPCs in advance of forebrain ischemia; thus, neuronal cell death around new neurons significantly decreased compared with the controls [42]. These findings suggest that brain tolerance to injury increases as new cells are produced in the cerebral cortex.

Future studies may reveal the molecular and cellular mechanisms underlying neuroprotection by new cells, leading to a new treatment for brain injury [39].

3.4.2. NSC Migration and Survival in Brain Injury

In an attempt to address the previously mentioned open questions in this field concerning the brain injury or diseases potential ramification on neurogenesis, herein, we try to discuss the modulating factors for NSC migration and survival upon brain injury.

3.4.2.1. Migration

Post-mortem human brain studies have witnessed an emergence of B1-integrin-expressing neuroblasts around areas of injury in association with laminin-rich blood vessels. This indicates that most migrating neuroblasts in injury sites are closely associated with a scaffold, which may be evolutionarily conserved in human brains [43]. Consistently, SVZ-derived OPCs have a prominent potency to migrate efficiently toward the corpus callosum and striatum, where they become mature oligodendrocytes and generate myelin. Upon white matter injury, such as demyelination and damage caused by hypoxia-ischemia, the production and subsequent recruitment of OPCs in the SVZ is remarkably enhanced, suggesting that the SVZ is also an essential source for oligodendrocyte regeneration and functional recovery [44]. It is critical to recognize the exact pathophysiology of neuroblasts migration and integration in the pathological environment to accelerate neuronal migration and accomplish better neuronal localization to reorder the disrupted neuronal network [45].

3.4.2.2. Survival

Most newly born neurons do not survive in the injured area; thus, promoting the survival of new neurons around the lesion is imperative. Although the underlying causes that maintain the survival of new neurons are unknown, angiogenesis, induced by growth and trophic factors, is pivotal to establishing homeostasis in the neurogenic niche and enhancing the survival of newborn neurons [34]. To further clarify, vascular endothelial growth factor (VEGF) exerts both angiogenic and neurogenic activity. Exogenous VEGF administration into the ischemic brain facilitates angiogenesis and neural progenitor proliferation and the survival of new neurons in the injured area, which causes profound enhancement in neurological performance [46].

On the other hand, NSCs are poised to receive choreographic cues from the extensive vascular plexus in the SVZ and SGZ, orchestrating their differentiation and survival. Analysis of vascular permeability in aging and patients with mild cognitive impairment revealed that progressive blood-brain barrier breakdown begins in the hippocampus and may contribute to early stages of dementia associated with AD. Fibrinogen is deposited in the AD brain resulting in gliosis intensification, and its depletion ameliorates the cognitive

decline in animal models of AD [47]. These findings suggest that such a clinically feasible approach can lead to developing new treatments for brain injury.

3.4.3. Modulating the Role of the Host Microenvironment on the Grafted Stem Cells

NSCs exert regenerative and restorative capacity by replacing damaged neurons and severed axons and forming a permissive microenvironment to promote CNS tissue repair. However, toxic aggregates and the hostile inflammatory microenvironment of the injured CNS may provide a fertile ground for dampened survival and integration of transplanted stem cells, leading to a poor outcome in tissue repair [48].

In this realm, transplanted NSCs demonstrated a secretory protein profile distinct from other brain cells and secret a broad spectrum of immune and neurotrophic factors and extracellular vesicles encompassing protein and microRNA cargoes, which predominantly target microglia, regulating their activation, proliferation, and phagocytosis [49]. More to the point, upon chronic inflammation, NSCs exhibit anti-inflammatory responses by detecting the extracellular succinate secreted by inflammatory microglia. The uptake of extracellular succinate upregulates the expression and release of prostaglandin E2 by the NSCs with the consequential abate of the inflammation [50].

NSCs proliferate in ectopic areas of the adult CNS beside the SVZ and SGZ, albeit the cells do not differentiate into neurons, becoming oligodendrocytes and astrocytes instead. However, NSCs isolated from non-neurogenic sites in the adult brain, such as the spinal cord and optic nerve, retain potency to differentiate into neurons upon transplantation into the DG [51] or by administration of FGF-2 inhibitors, which further support the proposal that extrinsic factors from the local microenvironment regulate the neurogenesis fate [52].

Overall, taking into account the inextricable interconnection between activated NSCs and niche cells, such as microglia under homeostatic and pathological conditions, will pave the way for novel therapeutic targets for modifying NSC-based stem cell therapies to reach the optimal results.

3.4.4. Outlook of the Progressively Prominent Role of Endogenous Neurogenesis in Brain Diseases

Although a damaged area attempts to emulate the permissive target-like environment, the natural repair mechanisms do not fully recover the lesioned brain, especially in adults with less capacity for post-injury neurogenesis than neonates. To shed light on this, large numbers of neuroblasts migrate to the damaged brain and mature there, which is put into context by considering the amount in the neonatal period; however, only about 0.2% of dead neurons can be replaced by these cells [53]. Neuroblasts in the injured brain migrate in an inconsistent direction and disproportionately reach the injured area [35, 44].

These findings raise the possibility that the enhancement of regenerative potential could be a remarked modality for harnessing regenerative therapies after brain injury [54]. Providing an appropriate migratory scaffold in combination with administration of growth factors and neurotrophic factors that promote each step of neuronal regeneration, including proliferation, migration, survival, and maturation of newly formed neurons in the injured brain contributes to subsequent functional recovery [53]. However, it is noteworthy that understanding the mechanisms that underlie migration, final positioning, and circuit integration of neuroblasts after an injury is still in its infancy.

3.5. The Clinical Feasibility of Endogenous Repair

The neurotrophin gene family (NGF) enhances the survival of a specific population of nerve cells (those affected by AD), which consists of brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3 (NT-3). NGF maintains and supports the survival of cholinergic neurons in the basal forebrain system [55]. NGF levels are disrupted in AD pathogenesis. Engineering encapsulated cell bio delivery could offer significant potential to maintain the level of NGF (NCT01163825, NCT00017940). BDNF levels drop in patients with AD [56]. BDNF attenuates the formation of APP through the tropomyosin receptor kinase signaling pathway. Administration of BDNF to animal models showed neuroprotective effects. On the other hand, brain hydrolysate enhances BDNF levels in the brain (Table **1**). Therefore, an oral supplement of brain peptide diet derived from brain proteolytic products may enhance neural differentiation and metabolism and protect nerve cells from ischemia and improve cognition in human beings (NCT03978338) (Fig. **1**).

As discussed before, research claims robustness in the association between endogenous stem cell therapies, promising facilitation in neurogenesis, migration, and maturation. Overall, various therapeutic approaches have been developed for different stages of NSC development (Table **1**). Recent research demonstrated the capability of PMZ-1620 (Sovateltide), an endothelin-B receptor agonist, in reducing neural damage through, in part, it's capacity to promote the formation of neural progenitors. The results indicated a robust neuro-regeneration by the development of new mature neurons (NCT04052737). GV1001 has prompted a new set of research on endogenous stem cell therapy for AD. Indeed, GV1001 significantly prevents neurotoxicity and apoptosis associated with the harmful accumulation of Aβ particles in NSCs (Fig. **1**), achieved by mimicking the extra-telomeric activities of human telomerase reverse transcriptase (hTERT). hTERT is the catalytic subunit of telomerase and is assumed to modulate tumor progression, NSC development, and apoptosis, leading to a dramatic increase in survival, proliferation, and migration of NSCs.

Inflammation in AD patients' brains creates an environment that is hostile to the function and survival of neurons. Specifically, as the association between hTERT (the catalytic subunit) and mitochondria has recently come to light along with hTERT translocation from the nucleus to the mitochondria following increased oxidative stress, GV1001 diminishes inflammation by reducing ROS (NCT03959553). In line with the studies outlined above, the supposed neurotrophic role of LM11A-31 (LM11A-BHS) has recently been explained. It binds to the p75 neurotrophic receptor (p75NTF) and selectively inhibits the apoptosis pathway, leading to promising neuronal growth and survival (NCT03069014).

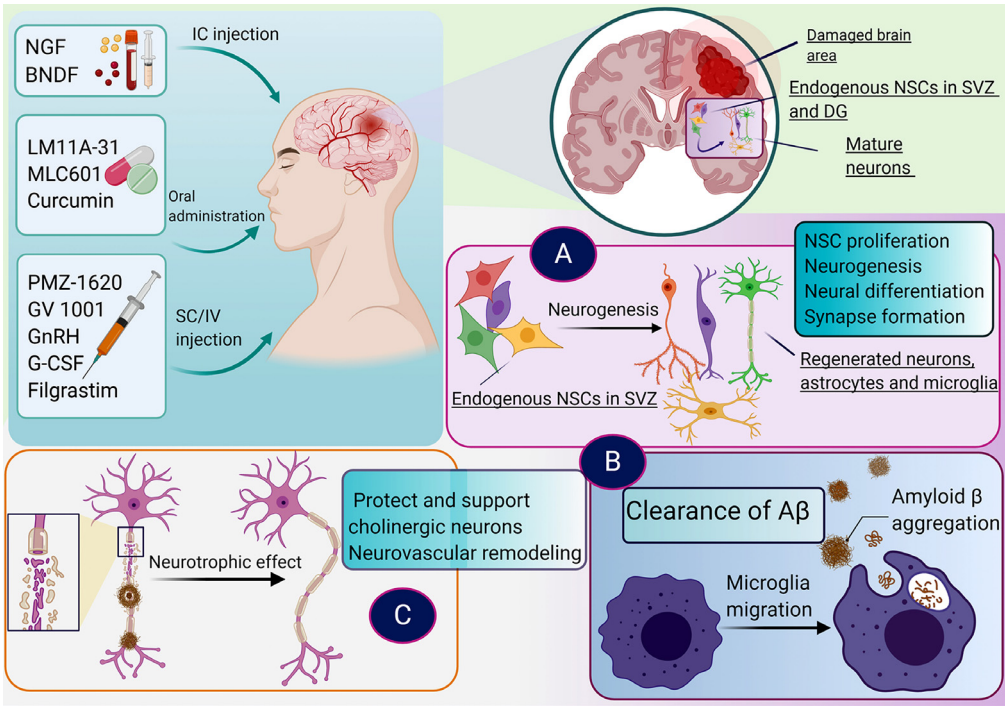

Fig. (1). Endogenous repair in Alzheimer's disease; Some drugs and growth factors have treating effects on patients with Alzheimer's disease (AD). These drugs can be administrated in different ways, including oral, nasal, injected intracranial (IC), subcutaneous (SC), and intravenous (IV). **A**) These neurotrophic drugs or substances can affect the sub-ventricular zone and dentate gyrus (DG), leading to neurogenesis and neural stem cell (NSC) proliferation and differentiation. **B**) Administration of these substances induces microglia migration, leading to amyloid β (Aβ) clearance. **C**) Moreover, administration of these factors enhances synapse formation by protecting cholinergic neurons and neurovascular remodeling. Stem cells (SCs) migration from bone marrow (BM) can also be triggered following the administration of these factors. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

Recent experimental work has attempted to shed light on the role of disrupted GnRH pulsatile secretion, the cornerstone for mammalian reproduction, in providing a situation for senescence-associated AD symptoms. GnRH is considered to open a new horizon for treating AD by toning up adult neurogenesis. Thus, a recent clinical trial has initiated an assessment of the efficiency of clinical administration of GnRH to patients afflicted with AD (NCT04390646).

Furthermore, curcumin's therapeutic benefits on a wide range of diseases have prompted researchers to investigate its speculative efficacy in rehabilitating AD patients, and a phase 2 clinical trial is recruiting on this case. The critical mechanism is exponential adult neurogenesis and the activation of NSCs through the notch signaling pathway (NCT01811381). MLC601 (NeuroAid), derived from a Chinese herbal reagent, is perceived to have neuroprotective and neuro-proliferative attributes. A clinical trial evaluated its efficacy in patients intolerant to rivastigmine (NCT01696123). Some data suggested a protective role for granulocyte colony-stimulating factor (G-CSF) in ameliorating conditions such as myocardial infarction (MI) and cerebrovascular accident (CVA). Concerning AD, G-CSF boosts the migration of hematopoietic stem cells (HSCs) from the bone marrow to the injured area, promoting neurological recovery. Two recently accomplished clinical trials demonstrated the efficiency of G-CSF (filgrastim) in reducing the symptoms of patients afflicted with mild to moderate AD (NCT03656042, NCT01617577) (Fig. **1**). Table **1** summarizes some completed and ongoing clinical trials on enhancing endogenous neurogenesis in AD.

4. EXOGENOUS STEM CELL THERAPY IN AD

Exogenous stem cell therapy (EC therapy) transfers autologous or allogeneic stem cells to injured tissue to reinforce the tissue's repair response by various methods and processes [57]. In 1987, neurodegenerative stem cell therapy was performed on a Parkinson's disease patient (PD). Madrazo *et al.* transplanted the adrenal tissue of two young PD patients into their brains, which resulted in their recovery. Stem cell therapy expanded to other neurodegenerative diseases, such as AD and multiple sclerosis [58]. Animal studies have shown that AD progressions decrease adult hippocampal neurogenesis (AHN). However, the pathogenic role of AHN has not been clarified yet. Endogenous neurogenesis is inadequate in regenerating damaged neuronal circuits [59, 60]. Therefore, EC therapy replaces damaged neural networks and amplifies the neurogenesis capability [3]. Transplanted exogenous stem cells also have a paracrine effect called the "bystander effect," in which the cells either secrete or induce different mediators, such as neurotrophic factors, which modulate the host niche [3, 61-63]. The neural niche has an essential role in managing the stem cell paths and secreting the factors required for their self-renewal [64]. As mentioned before, AD patients demonstrate pathologic changes in stem cell niches. For example, Hamilton *et al.* found a derangement of fatty acid metabolism in NSCs' niche in mice model of AD, which altered their normal functions [65].

Table 1. Some completed and ongoing clinical trials on enhancing endogenous neurogenesis in Alzheimer's disease.

Trial ID	NCT04052737	NCT03959553	NCT03069014	NCT04390646	NCT01811381	NCT01696123
Date	August 2019 to August 2021	May 2019 to February 2022 (approximately)	March 2017 to September 2020	May 2020 to March 2024 (approximately)	March 2013 to December 2020 (approximately)	January 2011 to August 2012
Study design	Phase II Safety and the efficacy intervention, multicentric, randomized, double-blind, placebo-controlled	Phase IIa Safety and efficacy intervention, Double-blind, Multicenter, Randomized, Double-Blind, Placebo-Controlled	Phase IIa evaluates Safety, Tolerability and Exploratory Endpoints in the intervention, Multi-center, Double-blind, Placebo-controlled, Randomized study	Phase not applicable; feasibility and the efficacy; Intervention, pilot study, Placebo-controlled	Phase II Safety and efficacy Intervention Randomized Placebo-controlled	Phase II Safety and efficacy; Intervention
Stage	Recruiting	Not yet recruiting	Completed	Recruiting	Active, not recruiting	Completed
Main effective pathway	Neuroregeneration/neurovascular remodeling	Inhibit neurotoxicity and apoptosis in neural stem cells	Neurogenesis/ neurotrophic	Neurogenesis	Adult neural stem cell proliferation	Neuroprotective and neuron proliferative
Inclusion criteria	Age 45-85 Probable AD MMSE: 11 - 26 The positive result of MRI/CT imaging; absence of major depressive disease according to GDS of < 57	Age 55-85 diagnosis of AD based on NINCDS-ADRDA criteria; Diagnosis of dementia based on DSM-V criteria; MMSE score ≥10 to <20	Age 50-85 CSF AD specific biomarker profile; positive (CSF Aβ42 < 550 ng l-1 or an Aβ 40/42 ratio < 0.89), MMSE ≥ 18 and ≤ 26; Absence of major depressive disease according to GDS of < 5	Age 20-40, male, Diagnosis of trisomy 21, Olfactory impairment (Sniffin' Sticks, identification score: for men ≤11, for women ≤12)	Age 50-90 Probable AD MMSE > 24; essentially intact activities of daily living (FAQ scores < 6)	Age ≥ 50 probable mild-to-moderate AD due to DSM-IV, failed treatment with the cholinesterase inhibitor Rivastigmine
Delivery route	IV bolus injection	SC injection	Oral capsule uptake	Subcutaneous pump	Oral capsule uptake	Oral capsule uptake
Arms	n=80 Experimental group: injection of 3 doses of PMZ-1620, at 0.3 µg/kg body weight in 3 hours, repeated every month for 6 months post randomization Control group: 3 doses of equal volume of normal saline in 3 hours and repeated every month for six months	n = 90 administration once weekly for 4 weeks, then every 2 weeks through Week 24 Low-dose group: GV1001 0.56 mg High-dose group: GV1001 1.12 mg Placebo group: placebo administration	n = 242 1 capsule, twice daily (morning & evening) for 26 weeks Active Comparator Group : 400 mg LM11A-31-BHS and 400 mg Placebo per day Active Comparator Group: 800 mg LM11A-31-BHS Placebo Comparator: 800 mg (microcrystalline cellulose with 0.5 - 1% magnesium stearate)	n = 32 dosage of 75 ng/kg/pulse, giving a pulse every 90 minutes in women and every 120 minutes in men for 24 weeks Active Comparator: Pulsatile GnRH (gonadorelin acetate) pump treatment Placebo Comparator: Pulsatile placebo (0.9% NaCl) pump treatment	n = 80 Experimental: Curcumin and either aerobic or non-aerobic exercise; Subjects will take 800 mg of curcumin in 4 capsules BID per day prior to meals Placebo Comparator: Placebo and either aerobic or non-aerobic exercise: Subjects will take 4 capsules x BID of placebo	n = 125 MLC601 (NeuroAid) prescribed as one capsule (0.4 mg MLC601 per capsule) three times daily
Outcome measures	160 day FU primary outcomes: Tolerability and drug-related adverse events Secondary outcomes: Statistically relevant changes in clinical progression of AD, as measured by MMSE, NPI Score and ADAS-Cog, after 3 and 6 months of treatment; Evaluation of EEGs and hippocampal atrophy using MRI/CT.	26 weeks FU No. of adverse events Change from baseline: ADAS-Cog, K-MMSE, CIBIC-plus, CDR-SB, NPI, ADCS-ADL	26 week FU primary outcomes: number of subjects with AEs/SAEs, alterations in vital signs, and laboratory tests Secondary outcomes: the alteration from baseline: CSF-Biomarkers (tau, ptau, Aβ40, Aβ42, AchE activity), working memory ability assessed with COWAT, word fluency assessed with CFT, processing speed assessed with the Coding Test (Subtest of the Wechsler Adult Intelligence Scale)	Primary: RBANS test for evaluating cognition Secondary: Change from baseline: HRQoL test, brain MRI signals, amyloidosis biomarkers (Aβ1-40, Aβ1-42, and truncated forms), The "Sniffin' Sticks" test	6-12 months FU Primary outcomes: AD plasma markers change from baseline Secondary outcomes: Change from baseline: FDG-PET glucose metabolism neuroimaging, Neuropsychological parameter evaluated by a neuropsychological battery, behavioral - symptoms assessed by a Neuropsychiatric Inventory Questionnaire (NPI-Q), adverse events	18 months FU Primary outcomes: Change from baseline: MMSE score, ADAS-cog Secondary outcome: assessment of adverse events

(Table 1) contd….

Trial ID	NCT03656042	NCT01617577	NCT01163825	NCT00017940	NCT03978338
Date	March 2009 to August 2014	June 2009 to February 2012	January 2008 to December 2011	June 2001 to November 2003	July 2019 to September 2020
Study design	Phase II Safety and efficacy Intervention Open-label, No-treatment-controlled, Parallel, Pilot Phase	Phase I/II efficacy and safety Intervention, Randomized, Crossover Assignment	Phase I Safety and tolerability Intervention, open-label, single-center	Phase I open-label, prospective clinical trial	Phase not applicable; safety and efficacy Multi-center, Randomized, Double-blind, Controlled Study, Parallel Assignment
Stage	Completed	Completed	Active, not recruiting	Completed	Not yet recruiting
Main effective pathway	Neuroregeneration	Neuroregeneration, stem cell migration from bone marrow	Neural growth factor to support and maintain the function of cholinergic neurons	Protect cholinergic neurons from degeneration, augment the process of remaining cholinergic neurons by directly elevating the function of ChAT neurons	Adjust and improve neural metabolism, promote synapse formation, neural differentiation, protect nerve cells, reduce the loss of cognition in the aging process
Inclusion criteria	Age 50-85 surmised AD patients due to DSM-IV, NINCDS - ADRDA results and CT/MRI brain scan assessments, MMSE: 12-26, CDR score of 1 (mild) or 2 (moderate), Modified Hachinski Ischemic score of 4	Age ≥ 55 Probable AD due to NINDS/ADRDA criteria, MMSE: 10-24	Age 50-80 diagnosis of AD based on NINCDS-ADRDA criteria MMSE 15-24	Age ≥ 50 AD diagnosis of the neurologist Early-stage of AD Average speaking ability and moderate ability to understand	Age 50-85 completed the cognitive ability measurement, meeting the criteria of AD NINCDS/ADRDA, patients with mild dementia: MMSE: illiteracy ≤1, primary school ≤20 secondary school ≤22 universities ≤23, CDR = 1, HIS <4, Hamilton depression scale <7, brain MRI likelihood hood of AD
Delivery route	SC injection	SC injection	Oral capsule uptake	Ex vivo gene therapy then intracerebral injection	Oral solution uptake
Arms	n = 21 Experimental group: 10 mic/kg/day Filgrastim (75 mcg/0.3 ml), for five successive days for the first week, rest for 11 weeks. It will be administered 12-weekly (12 weeks/cycle) for two cycles. Control group: no treatment	n = 8 Subjects took G-CSF at a dose of 10 micron/kg daily for five days and after seven weeks, they took a placebo (D5W or 5% dextrose solution) for 5 successive days	n=6 Experimental: Dose 1 Encapsulated cell biodelivery of NGF to the basal forebrain nuclei of the brain by multiple implantable devices housing NGF-secreting human cells Experimental: Dose 2 Encapsulated cell biodelivery to the basal forebrain nuclei of the brain by multiple implantable devices housing NGF-secreting human cells	n=8 Genetically modified autologous NGF secreting fibroblasts and a subsequent intracerebral injection of their own fibroblasts into the region of basal forebrain cholinergic neurons	n=200 Experimental group: brain polypeptide solution 60 ml per day containing nitrogen 90 mg, soybean oil, glycerin and soybean phospholipids in 84 days. Control group: treated with the same package of placebo 60 ml per day, which contains soybean oil, glycerin and soybean phospholipids in 84 days.
Outcome measures	12, 24, 48 weeks FU Primary outcomes: Change from baseline: ADAS-Cog-C Secondary outcomes: Change from baseline: TMT-Part A, TPCT, NPI, Lawton and Brody Scale for IADL, ADCS-CGIC, CDR, MMSE	2, 4 and 14 weeks FU Change from baseline: ADAS-cog, Selected CANTABS Tests, PAL	12 month FU Primary outcomes: assessment of Adverse events Secondary outcomes: measures Cognition using ADAS-Cog, neuropsychologic test battery, ADL, PET, EEG	18 month FU assessment of safety and toxicity	6, 12 week FU Primary outcome: Change from baseline: ADAS-cog Secondary outcome: change from baseline: ADCS-ADL, PSQI, NPI, MMSE, MoCA

Abbreviations: AD: Alzheimer's disease, ADAS-Cog: Alzheimer's disease Assessment Scale-Cognitive Subscale, ADAS-Cog-C: Alzheimer's disease Assessment Scale-Cognitive Subscale-Chinese version, ADCS-ADL: Alzheimer's disease cooperative study-activities of daily living, ADCS-CGIC: AD cooperative study-clinical global impression of change, AEs/SAEs: Adverse events/serious adverse events, CANTABS: Cambridge neuropsychological test automated battery, CIBIC-plus: Clinician interview-based impression of change plus, CDR-SB: Clinical dementia rating scale-sum of boxes, CFT: Category fluency test, COWAT: Controlled oral word association test, CSF: Cerebrospinal fluid, CT: Computed tomography, DSM-V criteria: Diagnostic and statistical manual of mental disorders-V criteria, EEGs: Electroencephalograms, FAQ: Fair average quality, FDG-PET: 18F-fluorodeoxyglucose- positron emission tomography, FU: Follow-up, GDS: Geriatric Depression Scale, GnRH: Gonadotropin releasing hormone, HRQoL: Health-related quality of life, IADL: Instrumental activities of daily living, IV: Intravenous, MMSE: Mini-Mental State Examination, MRI: Magnetic resonance imaging, NINCDS-ADRDA criteria: National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association, NPI: Neuropsychiatric inventory, NPI-Q: Neuropsychiatric Inventory Questionnaire, PAL: Paired associate learning, RBANS: Repeatable battery for the assessment of neuropsychological status, TMT: Trail making test, TPCT: Ten-point clock test TPCT, ChAT: Choline acetyltransferase. PSQI: Pittsburgh sleep quality index, MoCA: Montreal Cognitive Assessment.

Currently, two influential groups of stem cells are being transplanted for EC therapy, which are as follows:

1) Neural stem cells (NSCs): They are obtained from two types of sources; directly isolating them from rodent or human brain stem cell pools (primary source) or indirectly differentiating pluripotent cells like embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) or transdifferentiation of somatic cells into NSCs (secondary source) [66].

2) Mesenchymal stem cells (MSCs): Each type has particular attributes, making it difficult to decide which therapeutic protocol is suitable for each disease [3, 7]. Details on the clinical trials of exogenous stem cell therapy are summarized in Table **2**.

4.1. Brain-derived NSCs (BD-NSCs)

Neural stem/progenitor cells (NSCs) are extracted from human or rodent fetal brain tissue, which undergoes different cell culture methods [67]. Suspension of tiny clusters of stem cells in a specific medium contains epidermal growth factor (EGF), fibroblast growth factor (FGF), and other factors are needed to form adherent monolayer cells or neurospheres [68]. There are ongoing research studies on BD-NSCs' potential to regenerate affected areas of the central nervous system (CNS) in neurodegenerative diseases. When BD-NSCs were grafted into a 1-year-old mice model of AD, hippocampal NSCs induced normal endogenous neurogenesis, differentiating all three types of neuron, oligodendrocyte, and astrocyte with a high percent of microtubule-associated protein-2 (MAP-2) positive cells and improvement in memory and learning abilities [68]. In another experimental study in a 5-month-old rat model of status epilepticus (SE), transplanted BD-NSCs diminished disease progression and ameliorated memory function; moreover, the majority of grafted cells secreted neurotrophic factors including FGF-2, BDNF, insulin-like growth factor-1, and glial cell line-derived neurotrophic factor (GDNF) [69]. However, one of the significant hurdles for clinical application of BD-NSCs is their low yield proliferation, differentiation, and migration, which can be reinforced by various ways of manipulation, including gene editing and co-administration of different agents. For example, multi-loci gene editing using CAS9 mRNA and synthetic guide RNAs can convert NSCs into a more potent therapeutic agent, with the preservation of their self-renewing, migration, and differentiation abilities [67]. Furthermore, adding fingolimod (FTY720), an analog of sphingosine-1-phosphate (S1P), to the culture medium of NSCs showed dose-dependent amplification in quoted capabilities of NSCs [70]. Noteworthy, BD-NSCs are uneconomical since they are a limited source with potential ethical problems [71].

4.2. Human Pluripotent Stem Cells (hPSCs)

Pluripotent stem cells encompass ESCs and iPSCs, differentiate into a broad spectrum of cell types, and compose the CNS and peripheral nervous system (PNS) from neural progenitors to specialized mature neurons, oligodendrocytes, and astrocytes (4). In 2006, Takahashi *et al*. induced mouse differentiated fibroblasts into a pluripotent-like state by integrating the transcription factors OCT3/4, SOX2, C-MYC, and KLF4 into cell genomes, creating iPSCs [72]. iPSCs are autologous and more resistant to immune rejection [73]. The development of human embryonic stem cell (hESC) and human induced pluripotent stem cell (hiPSC)-derived cells led to a growing strand of literature evaluating the cell therapies in multiple neurodegenerative disease models [4]. Over ten years, hPSC-based treatments have advanced into clinical trials, with hundreds of patients undergoing hPSC-derived cells transferring [74]. Researchers speculated a potential for dopaminergic neuron transplants upon transplants of human fetal stem cells in past decades. Thus, recruitment of hiPSC-based therapy for the treatment of PD clinical trial ensued in 2018 [75].

Moreover, in a study, hiPSC-NPCs of the cholinergic phenotype were injected into the hippocampus of the PDGF promoter-driven amyloid precursor protein (PDAPP) transgenic mouse model of dementia. By 1.5 months post-transferring, prominent signs of hiPSC-NPCs survival culminated in marked improvement in spatial memory. Based on this, hiPSC-NPCs can be differentiated into cholinergic and GABAergic neurons in the brain [54, 76]. Researchers modified human ESCs to differentiate into basic forebrain cholinergic neurons (BFCN) progenitors and implemented cells into the brain of AD rodent models. By 60 days post-transplant, transferred BFCN progenitors differentiated into mature cholinergic neurons revealed their functional integrity into the host endogenous cholinergic system. HESC-BFCN therapy showed promise in rehabilitating cholinergic circuitry and attenuating AD mouse models' cognitive deficits six months after transplantation [77, 78].

Despite immense *in vitro* and *in vivo* efforts spanning several decades, there has been intense debate on the clinical implementation of hPSCs due to the ethical and safety concerns associated with hPSC transplantation. For example, hPSC-based therapies' clinical application hurdles include the risk of rapid immune rejection, tumorigenesis, and challenges in regenerating the heterogeneous cell types in the CNS [79]. Two studies have reported oncogenic mutations in hiPSC [80] and hESC [81], highlighting the necessity of developing principal methods for safe and efficient production of hPSC-derived cells for transplantation.

4.3. Mesenchymal Stem Cells (MSCs)

MSCs are immune-privileged multipotent stem cells from mesodermal germ lines that naturally exist in human tissues, creating adipocyte, osteoblast, myocyte, chondrocyte, and other cells with mesodermal origin. However, a few studies showed that they could also exhibit pluripotency in differentiating into ectodermal and endodermal germ lineages like neurons [82] and pancreatic islet cells [83]. MSCs can be derived from many sources, such as adult stem cell pupae of the bone marrow, adipose tissue [84], the dental pulp [85], and perinatal structures, such as the umbilical cord placenta and amniotic fluid [71]. MSCs can be extracted from pluripotent stem cells (PSC-MSCs) [86]. Based on their various sources, MSCs have different manners. For example, giving the more primitive nature of perinatal sources provides better expansion potential for MSCs [87]. Besides, PSC-MSCs have better self-renewal and therapeutic capacities than adult tissue-driven MSCs [86].

Table 2. Completed or ongoing clinical trials on exogenous stem cell transplantation in Alzheimer's disease.

Trial ID	NCT01297218	NCT02054208	NCT02833792	NCT02600130	NCT02899091	NCT03117738	NCT03172117
Date	February 2011 to April 23, 2012	March 2014 to August 28, 2020	June 2016 to June 2020	October 2016 to September 2020	September 2016 to December 2021	April 2017 to June 2019	May 2017 to December 2021
Study design	Phase 1 Safety and the Efficacy Intervention Open-Label, Single-Center	Phase 1/2a Safety and Efficacy, Intervention Double-blind, Single-center	Phase 2a Safety and Efficacy Intervention, multi-center, randomized, single-blind, placebo-controlled, crossover	Phase 1 Safety and efficacy Intervention Randomized Double-blind Placebo-controlled	Phase 1/2a Safety and efficacy, Intervention, Randomized Double-blind Placebo-controlled	Phase 1/2 Safety and efficacy Intervention Randomized Double-blind Placebo-controlled	Follow-up Study of Safety and Efficacy in Subjects Who Completed NCT02054208 phase 1/2a Clinical Trial.
Stage	Completed	Completed	Recruiting	Active, Not recruiting	Recruiting	Completed	Recruiting
Cell type	hUCB-MSCs	hUCB-MSCs	Allogeneic human MSCs	LMSCs	CB-AC-02 (hPD-MSCs)	AstroStem (Ad-MSCs)	hUCB-MSCs
Inclusion criteria	Age ≥ 50 Probable AD K-MMSE: 10 to 24 The positive result of PIB-PET imaging (SUV > 1.5, comparing the result for the cerebellum with frontal lobe)	Stage 1: Age 50-85 Probable AD K-MMSE: 18-26 Amyloid+ PIB/florbetaben-PET Stage 2: Age 50-85 Probable AD K-MMSE > 18 Amyloid+ florbetaben-PET Neurodegeneration (mild atrophy)+ MRI	Age 55-80 Mild-moderate AD Related Disorders Association (NINDS-ADRDA) Alzheimer's criteria K-MMSE 12-24 Amyloid+ florbetapir-PET	Age 50-80 Diagnosed AD K-MMSE 18-24 Amyloid+ PET	Age ≥50 Probable AD K-MMSE 10-26 Amyloid+ PET Brain atrophy/↓ Glucose metabolism MRI/PET Stable dose of AD medication lasting two months or more	Age ≥ 50 probable mild-to-moderate AD MMSE 16-26 Stable dose of AD medication lasting three months or more	Stage 1: Age 50-85 Probable AD K-MMSE: 18-26 Amyloid+ PIB/florbetaben-PET Stage 2: Age 50-85 Probable AD K-MMSE > 18 Amyloid+ florbetaben-PET Neurodegeneration (mild atrophy)+ MRI
Delivery route	Stereotactic brain injection	Intraventricular administrations via an Ommaya Reservoir	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intravenous infusion	Intraventricular administrations via an Ommaya Reservoir
Arms	n=9 Single-injection Low-dose group: 3.0×10^6 cells/60 mL per brain High-dose group: 6.0×10^6 cells/60 mL per brain	n = 45 Three injections at 4-week intervals Low-dose group: 1×10^7 cells/2 mL per injection High-dose group: 3×10^7 cells/2 mL per injection Placebo group: saline 2 mL	n = 40 Single infusion Crossover at six months post-infusion Group 1: 1.5×10^6 cells/kg body-weight Group 2: lactated Ringer's Solution	n = 33 Single infusion Low-dose group: 2×10^7 cells High-dose group: 1×10^8 cells Placebo group: Plasmalyte A and 1% human serum albumin	n = 24 Single (S) or repeat (R) infusion (day 0 and weak 4) stage 1: group 1: 2×10^8 cells group 2: two infusions two $\times 10^8$ cells stage 2: Arm 1: K-MMSE 20-26, 2×10^8 cells Arm 2: K-MMSE 10-19, two infusions two $\times 10^8$ cells	n = 21 Nine infusions at 2-week intervals drug group: dosage not mentioned placebo group: Saline with 30% auto-serum	n = 45 Three injections at 4-week intervals Low-dose group: 1×10^7 cells/2mL per injection High-dose group: 3×10^7 cells/2mL per injection Placebo group: saline 2 mL
Outcome measures	12 weeks FU No. of adverse events Change from baseline: ADAS-cog, S-IADL, K-MMSE, CGA-NPI, serum transthyretin, Aβ and tau in cerebrospinal fluid, PIB-PET and FDG-PET	24 weeks FU No. of adverse events Change from baseline: ADAS-Cog, S-IADL, K-MMSE, CIBIC-plus, CGA-NPI, CDR-SOB, CSF biomarkers MRI DTI mapping, Florbetaben-PET and FDG-PET	18 months FU No. of adverse events Change from baseline: Neurological examinations	30 days FU No. of adverse events 2, 4, 13, 26, 39, and 52 weeks FU Change from baseline: ADAS-cog, MMSE, NPI, UPSIT, GDS, CSF inflammatory biomarkers (Aβ and tau), Blood inflammatory and AD biomarkers MRI brain volumetry	48 weeks FU No. of adverse events Change from baseline: ADAS-cog, K-MMSE, GDS, CDR, K-IADL, CGA-NPI, CIBIC and SF-36 CSF Aβ and tau, Brain MRI, amyloid-PET, CMRglc FDG-PET Quantitative EEG	32 and 52 weeks FU No. of adverse events Change from baseline: ADAS-Cog, MMSE, CDR-SOB, NPI, GDS, ADCS-ADL, C-SSRS, MRI, Aβ 40, Aβ 42, AICD, sNRG-1	12, 24, 36 months FU Change from baseline: ADAS-Cog, S-IADL, K-MMSE, CGA-NPI, CDR-SOB, CIBIC-plus, Florbetaben-PET, FDG-PET, MRI (DTI), CSF biomarkers

(Table 2) cont….

Trial ID	NCT03724136	NCT04040348	NCT03899298	NCT04228666	NCT04482413	NCT03297177
Date	October 2018 to October 2023	October 2019 to September 2021	September 2019 to March 2029	March 2020 to February 2021	December 2020 to December 2023	January 2020 to January 2023
Study design	Phase 1 Safety and efficacy Intervention Non-Randomized Open-Label Parallel Assignment	Phase 1 Safety and the Efficacy Intervention Open-label Single group	Phase 1 Safety and the Efficacy Intervention Non-Randomize Open-label	Phase 1/2a Safety and the Efficacy Intervention Non-Randomize Open-label	Phase 2 Safety and the Efficacy Intervention randomized, double-blind, active-controlled	Not Applicable; Safety and the Efficacy Intervention Non-Randomize Open-label Single Group Assignment
Stage	Recruiting	Recruiting	Not yet recruiting	Active, Not recruiting	Not yet recruiting	Not yet recruiting
Cell type	BM-MSCs ± Infrared light	hUCB-MSCs	hUCB-MSCs and hAMSCs	Ad-MSCs	AstroStem (Ad-MSCs)	AD-tSVF
Inclusion criteria	Age ≥ 18 Diagnosed AD/ documented cognitive impairment Stable medical treatment	Age 55-80 probable AD K-MMSE 20-26 Amyloid+ PET scan /CSF Aβ 1-42+, stable dose of a cholinesterase inhibitor medication last three months or more, no significant Lab Test abnormality	Age > 18 Diagnosed AD MMSE	Age 50-85 probable AD (early stage) Amyloid+ PET scan, a stable dose of medication, last one month or more	Age > 50 Probable mild AD MMSE 20-24 No AD medication since diagnosis	Age 18-90 Documented Functional Neurological Damage, at least six months after onset or diagnosis of disease
Delivery route	Intravenous infusion/ intranasal topical administration	Intravenous infusion	hUCB-MSCs and hAMSCs Infusion, Injection, Nebulizer, Intranasal (based on patient condition)	Intravenous infusion	Intravenous infusion	Intravenous infusion
Arms	n = 100 Single administration Arm 1: 14cc BM-MSCs fraction I.V Arm 2: 14cc BM-MSCs fraction I.V and Near-Infrared Light pre & postoperative day Arm 3: 14cc BM-MSCs fraction Intravenous and 1cc BM-MSCs administered to the nasal mucosa topically	Four infusions at about 13-week intervals Treatment group: 10^8 cells	n= 5000	Four infusions on weeks 0, 2, 6, 8 Treatment group: 2 × 10^8 cells	n= 24 Four infusions at 4-week intervals Treatment group: 2 × 10^8 cells/20 mL of saline with 30% auto-serum Active control group: 5 mg Donepezil and Asrtostem placebo	n= 300 Single fusion Treatment group: AD-tSVF with sterile normal saline 500 cc
Outcome measures	1, 3, 6, 12 months FU Change from baseline: MMSE, Activities of Daily Living	Up to 65 weeks FU No. of adverse events Change from baseline: ADAS-cog, MMSE, GDS, Oder test (olfactory function), ADRQL-40, ADCS-ADL, NPI-Q, Caregiver Quality of life, Blood biomarkers, serum/ CSF ApoE, PRA and Tau level, CSF biomarkers, MRI (hippocampal volume)	Up to 120 months FU No. of adverse events Change from baseline: MMSE, AQOL	52 weeks FU No. of adverse events Change from baseline: Blood biomarkers, Aβ-40/42, MMSE, ADCS-ADL, Q-LES-Q, Altoids NMI, CDR, MRI (volume changes)	28 weeks FU No. of adverse events Change from baseline: ADAS-cog, MMSE, C-SSRS, NPI, ADCS-CGIC	Five years FU No. of adverse events Change from baseline: Neurological Function, MRI

Abbreviations: AD: Alzheimer's disease, FU: Follow-up, hUCB-MSCs: Human umbilical cord blood-derived mesenchymal stem cells, LMSCs: Leukemia mesenchymal stem cells, Ad-MSCs: Adipose-derived mesenchymal stem cells, hPD-MSCs: Human placenta-derived mesenchymal stem cells, BM-MSCs: Bone Marrow Mesenchymal Stem Cells, hAMSCs: Human amniotic mesenchymal cells, AD-tSVF: Adipose-derived tissue stromal vascular fraction, Aβ: Amyloid-beta, sNRG-1: Plasma soluble neuregulin-1, ApoE: Apolipoprotein E, PRA: Plasma Renin Activity, CSF: Cerebrospinal fluid, MRI: Magnetic resonance imaging, MRI DTI: Diffusion tensor imaging -magnetic resonance imaging, PIB-PET: Pittsburgh compound B -positron emission tomography, FDG-PET: Fluorodeoxyglucose -positron emission tomography, CMRglc: Regional cerebral glucose consumption, EEG: Electroencephalography, MMSE: Mini-Mental State Examination, K-MMSE: Korean Mini-Mental State Examination, NINCDS-ADRDA: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association, ADAS-Cog: Alzheimer's disease Assessment Scale-Cognitive Subscale, ADRQL-40: The Alzheimer's Disease-Related Quality of Life (40-item version), ADCS-ADL: Alzheimer's disease cooperative study - activities of daily living, ADCS-CGIC: AD cooperative study-clinical global impression of change, K/S-IADL: Korean/Seoul-Instrumental Activities of Daily Living, CIBIC-plus: clinician interview-based impression of change plus, UPSIT: The University of Pennsylvania Smell Identification Test, CGA-NPI: Caregiver-Administered Neuropsychiatric Inventory, GDS: Geriatric Depression Scale, CDR-SB: Clinical dementia rating scale-sum of boxes, C-SSRS: The Columbia-Suicide Severity Rating Scale, AICD: Australian Institute of Company Directors, SF-36: 36-Item Short Form Survey, NPI: Neuropsychiatric inventory, NPI-Q: Neuropsychiatric Inventory Questionnaire, CGA-NPI: Caregiver-Administered Neuropsychiatric Inventory, AQOL: Assessment of Quality of Life, Q-LES-Q: Satisfaction questionnaire, Altoida NMI: The Altoida Neuro-Motor Index, CDR: Clinical Dementia Rating, SUV: Standardized uptake value.

MSCs have attracted interest in regenerative medicine as the most appropriate and safe stem cell therapy for AD clinical trials (Table **2**). MSCs are more accessible and abundant than other types of stem cells, owing to their various sources and ease of handling [3]. Besides, their autologous sources overcome the ethical issues related to ESCs [88]. Their ability to move toward the site of injury after receiving extracellular matrix signals makes it possible to administer them intravenously in a place far from the pathologic area [89]. MSCs are recognized for their high inherent secretory ability, known as secretome and bystander effects, which establish tissue homeostasis [90, 91]. MSCs enhance neurogenesis in neurodegenerative diseases and induce angiogenesis, immunomodulation, and increase neural cell survival by the secretion of various neuroprotective agents [92]. The immunomodulatory and neuroprotective activity of MSCs have been demonstrated in several studies. Nakano *et al*. found changes in bone marrow-derived MSC (BM-MSC) treated mice's brains, which included increased synaptic density, decreased ratio of M1/M2 activated microglia, and elevated concentration of anti-inflammatory and neuroprotective cytokines like CXCL5, MCP-1, β-NGF, TIMP-1, VEGF-A, TGF-β, and IL-10 [93]. The secretion of cytokines and exosomes causes regulatory effects of MSCs. Recent findings show that the cytokine-mediated effects may be the result of inactivated and apoptotic MSCs [94]. It seems that T regulatory cells and monocytes play a fundamental role in the regulatory impact of MSCs [90]. Besides that, MSCs express no or low major histocompatibility complex II (MHC II) or costimulatory molecules [95]; suppressing T and B cells is another function of MSCs, therefore, allogeneic MSCs can be a therapeutic tool free of immune rejection concerns [96].

Recently, manipulating MSCs (*e.g.*, gene engineering, prearranging by different factors, using extracellular vesicles) brought a great deal of interest due to the wide range of changing possibilities of these cells [86]. Next to all its advantages, MSC therapy certainly has its disadvantages, including limited cell survival, risk of malignant transformation, and low neuronal differentiation rates [89, 97].

5. ONGOING CLINICAL TRIALS

So far, twenty clinical trials (CT) have been registered in clinicaltrials.gov for AD treatment based on exogenous stem cell therapy (Table **2**). In the first clinical trial (NCT01297218), nine patients with non severe AD received 3.0×10^6 and 6.0×10^6 cells/60 mL in low and high dose groups. No dose-related toxicity and serious adverse events were observed in any of the patients. Pain from the surgical wound was the most common acute side effect reported, followed by headaches, dizziness, and postoperative delirium. Howsoever, no detectable changes were found in the patients' clinical course. This result may be due to the small sample size of the study, inappropriate route of transplantation, differences in analyzing human and animal data on the effect of transplantation (*i.e.*, imaging versus immunohistochemical), and the different neural microenvironments between humans and rodents [98].

Other clinical trials have not published their results yet, but they are also expected to find safe and effective transplantation (Table **2**). From the beginning, scientists gradually became more inclined to use adipose-derived mesenchymal stem cells (Ad-MSCs) instead of umbilical cord blood (UCB)-derived mesenchymal stem cells (UCB-MSCs) (Table 2), possibly because of their accessibility and abundance [99]. Additionally, a comparison of Ad-MSCs and UCB-MSCs derived from pregnant women who had undergone C-section demonstrated the superior response of Ad-MSCs, due to their higher differentiation rate toward neural lineage over a shorter period compared with UCB-MSCs [100].

Previous MSCs' clinical trials concluded intravenous injection and 100-150 million cells/patient/dose to be the ideal delivery route [1] and optimal effective dose [101]. However, other delivery routes, including intracranial injection, intranasal topical administration (NCT03724136), inhalation (nebulizer) (NCT03899298), and different administration frequencies or dosages are still under investigation. Furthermore, epidemiological differences should be reconsideration as about two-thirds of AD patients are women [102]. Still, none of the clinical trials considered sex differences in their inclusion criteria (Table **2**).

Several combinations of methods have been studied to enhance the therapeutic effect of MSCs. Lim *et al*. showed that combination therapy using MSCs and T regulatory cells has a synergistic immunomodulatory impact in the murine model of acute graft versus host disease (GVHD) [103]. Therefore, combination therapy has also been examined in AD clinical trials. In the trial with NCT03899298 ID, mixtures of amniotic and umbilical cord tissue-derived stem cells were applied. In another ongoing clinical trial, infrared light was used as a companion treatment (NCT03724136). One of the underlying reasons can be the boosted migration of BM-MSCs to the hypoxic-ischemic damaged areas of the mouse model's brain when exposed to 660 nm red light [104].

6. STEM CELLS DERIVED EXOSOME-BASED APPROACHES IN AD

Despite the compelling therapeutic potentials of stem cells, their cell structure has limitations, such as ethical considerations, tumorigenesis, cell rejections, and poor differentiation potential [105]. Exosomes (<100 nm), microvesicles (<1000 nm), and apoptotic bodies (>1000 nm) are a group of stem cell secretions known as extracellular vesicles (EV) [106, 107]. They are bilayer lipid membrane-bounded structures secreted by various cell types, including stem cells, which encapsulate and deliver several functional biomolecules to neighbor and remote cells [108, 109].

It is demonstrated that stem cells' therapeutic effects are mainly exerted through EVs [110-112] since they resemble parent stem cells' phenotype [113], modulate cell-to-cell communication [114, 115], and inhibit bioactive molecules' destruction in the ECM [116]. Indeed, exosomes are small EVs with a diameter of about 30-100 nm [117]. They act as paracrine messengers and exist in all body fluids, especially blood, cerebrospinal fluid, breast milk, saliva, ascites fluid, and urine, prompting researchers to assess their potentiality to develop as diagnostic markers [118]. Besides, EVs can be loaded with different compounds, known as cargo (*e.g.*, proteins and nucleic acids) [119]. Hence, they are suggested as an ideal candidate for cell-free therapy [113].

Application of stem cell-secreted EVs, especially exosomes, can diminish stem cells' several ethical and safety concerns. Leaving aside the necessity of an effective treatment for AD, detecting the disease in the early stage of progression should be researchers' priority [117]. Besides their therapeutic role, exosomes are used as diagnostic biomarkers for AD, which will be discussed in more detail in the following sections.

6.1. Exosome Biogenesis

Exosomes originate from the inward budding of the membrane in the endosomal system, which forms early endosomes. Further invagination of the endosomal membrane generates intraluminal vesicles (ILVs) or exosomes in the multi-vesicular bodies (MVBs), which are now referred to as late endosomes (LEs). Then, the MVBs become subject to one of the following three fates: (1) fusion with the plasma membrane, where they are freed into the extracellular space as exosomes, (2) delivery to lysosomes for the degradation of the material they carry, or (3) transport to the trans-Golgi network (TGN) for endosome recycling (Fig. **2**) [120, 121].

During exosome maturation, the cargoes are stored in the ILV through two significant pathways, including (1) the endosomal sorting complex required for transporting (ESCRT)-dependent and (2) ESCRT-independent pathways (Fig. **2**) [122]. The ESCRT-dependent pathway includes four distinct ESCRT protein complexes (ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III) and concomitant proteins (ALIX, VPS4, and Tsg101). ESRT-0 sequesters ubiquitinated proteins into the endosomal domain. ESCRT-I and -II induce membrane budding and recruit ESCRT-III, which finally drives vesicle neck scission [123, 124]. In the ESCRT-independent pathway, which depends on raft-based microdomains, cargoes' loading into the exosomes relies on the self-organization of lipid and cargo microdomains is perceived to be highly enriched in sphingomyelinase (Fig. **2**) [125].

6.2. Recent Therapeutic Application of Stem Cell-derived Exosomes in AD Models

Exosomes originate from almost every cell in the body, and specific exosomes are produced from different cells [126]. In recent years, stem cell-derived exosomes have been studied in AD precisely. Mesenchymal stem cell-derived exosomes (MSC-Exos) have been claimed to improve memory functions and neural plasticity in an animal model of AD. The impact of MSC-Exos was compared with MSC therapy's effect in a β-amyloid 1−42-induced mouse model of AD. Intriguingly, improvement in novel object recognition tests and Morris water maze showed cognitive restoration in both MSC and MSC-Exo-administered groups.

Moreover, the MSC-Exos have the same effect as mesenchymal stem cells on subventricular zone neurogenesis [11]. Another cell source for the exosome-based treatment of AD is adipose tissue-derived MSCs (ADSCs). Katsuda *et al*. reported that ADSCs secrete exosomes with Neprilysin (NEP)-specific activity [127]. NEP and insulin-degrading enzymes are found in exosomes secreted from ADSC and microglia [128, 129]. These exosomes are involved in β-amyloid clearance and inhibit their oligomerization in the brain [130]. Higher levels of NEP expression in ADSCs than BM-MSCs prompted scientists to investigate the ADSCs' efficacy as an appropriate source for the exosome-based treatment of AD [10]. Of interest, Aβ clearing by exosome administration, as a novel therapeutic approach for AD, is documented in Yuyama *et al*.'s study. They evaluated the effect of intracerebral injection of neuroblastoma-derived exosomes enriched with glycosphingolipids (GSLs), as a potent Aβ scavenger, into Aβ precursor protein transgenic mice. Notably, a significant reduction of Aβ levels occurred, and a dampening of Aβ-mediated synaptic toxicity was observed in the hippocampus of treated mice [10].

There are various exosome delivery routes, including intracerebral, intravenous, and intranasal administrations [131]. In the noninvasive intranasal administration of Wharton's jelly mesenchymal stem cells (WJ-MSCs)-derived exosomes to the olfactory bulbectomized (OBE) mice, the development of spatial memory loss was inhibited, and labeled exosomes were detected in the neocortex and hippocampus, the areas for the memory and learning process. Compared with WJ-MSCs, exosomes are smaller in size, lower in immunogenicity, and have higher therapeutic efficacy without inducing cell transformation. Furthermore, intranasal administration makes it possible to enhance the effectiveness with lower doses of exosomes [132]. Intravenous injection is another administration route; howsoever, exosomes could be disseminated in other organs rather than the targeted areas in the brain. To facilitate the specific delivery of exosomes to the brain, a CNS-specific rabies viral glycoprotein (RVG)-tagged MSC-derived Exosome (RVG-MSC-Exo) was intravenously injected into the transgenic APP/PS1 mice. As a result, reduction in plaque deposition, astrocyte activation, improvement in learning and memory function, and modulation of inflammatory cytokines were more significant in RVG-MSC-Exo than in the MSC-Exo group [131].

Although the results of the application of exosomes in AD-animal models were promising, we did not find any published clinical trials about their therapeutic applicant on humans. There is just one ongoing single-center, open-label phase I/ clinical trial (NCT04388982), which aims to evaluate the efficacy and safety of allogenic ADSC-derived exosomes in the treatment of AD patients with mild to moderate dementia. Collectively, due to different promising traits of exosomes, such as facile storage, autologous source, minimal immunogenicity, and low risks of tumorigenicity [133], it is of interest to provide more attention to evaluate their therapeutic applicant in human studies.

6.3. Exosomes are Ideal Diagnostic Biomarkers as a Liquid Biopsy for AD

6.3.1. Early Diagnosis of AD Pronouncedly Enhances the Success of Treatments

AD has a long-dormant period (up to 17 years). The progressive disease course is categorized into three major stages; firstly, the asymptomatic period constitutes neuronal dysfunction onset and initiation of impaired cognition. Secondly, in the prodromal phase, mild cognitive impairment ensues as the disease rapidly progresses. Thirdly, the symptomatic stage is recognized by prominent dementia [5]. Noteworthy, owing to long preclinical stages, the early diagnosis of the disease in its latent phase merits vast exploration to prevent or at least delay the disease's deterioration by early implementation of

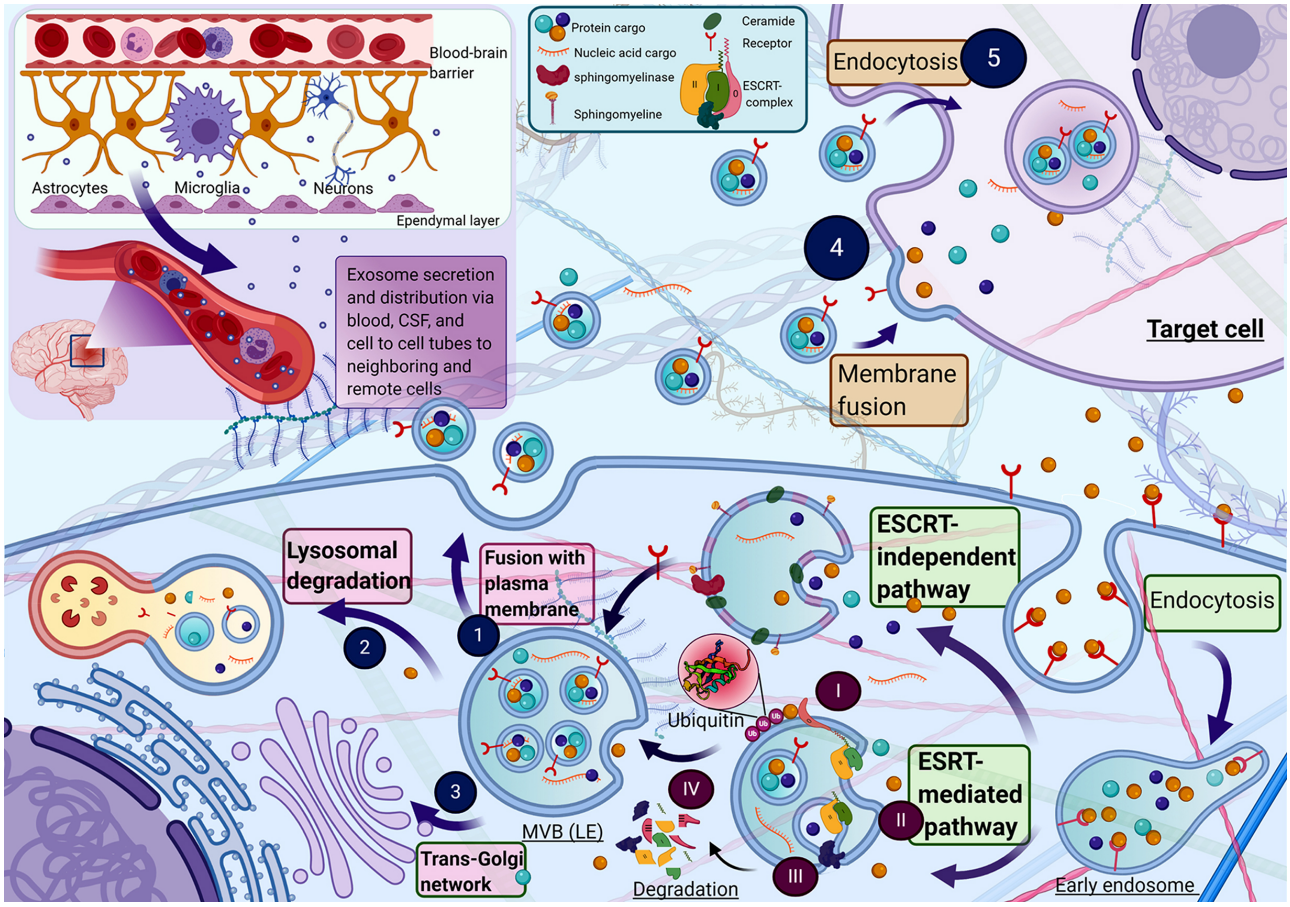

Fig. (2). Exosome biogenesis: Exosomes originate from ILVs in MVBs (*i.e.*, LE), which are generated by early endosomes. Either ESCRT-dependent or ESCRT-independent pathways modulate exosome biogenesis. In the ESRCT dependent pathway, (I) ESRT-0 sequesters ubiquitinated proteins into the endosomal domain, and (II) ESCRT-I and -II induce membrane budding, and (III) recruit ESCRT-III, which finally drives vesicle neck scission. (IV) After ILVs formation, ESCRT-III is separated from the MVB. However, in the ESCRT-independent pathway, exosomes and ILVs are generated by converting sphingomyelin to ceramide mediated by the sphingomyelinase enzyme on the endosomal membrane. Then, ceramide accumulation induces microdomain coalescence and triggers ILV formation. ILVs finally (1) fuse with the plasma membrane to form exosomes or (2) are degraded by lysosomes, or (3) are transported to the TGN for endosome recycling. Once exosomes reach their destination in the extracellular space, they may (4) fuse into the plasma membrane of the recipient cell and release their contents directly to the cytosol, or (5) be taken up by the target cell's endocytic pathway and delivered back via a back-fusion event. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

available and novel treatments [134]. To further clarify, low CSF levels of Aβ1-42, high CSF levels of P-tau, and positive CNS images of amyloid deposits are prognostic markers for developing mild cognitive impairment (MCI) and herald AD. However, repetitive CSF sampling and neuroimaging are expensive, and CSF sampling increases intracranial infection susceptibility [135]. Overall, the overlap between these AD biomarkers and other forms of dementia underscores the urgent need for a more accurate, less costly, and less invasive blood-based test to predict AD development.

It is noteworthy that the circulating microRNAs are easily isolated and detected from plasma, serum, CSF, urine, and saliva and are tissue-specific [136, 137]. Furthermore, they are closely associated with AD (as opposed to non-AD patients); therefore, there has also been an intense debate on their utilization as AD screening biomarkers. Nevertheless, the complexity of mixtures of microRNAs derived from different cell types in human blood and their poor stability are significant hurdles for their clinical application.

6.3.2. Exosome as a Novel, Sensitive and Specific Biomarker for Diagnosis of AD

There is a body of ongoing experimental work attempting to shed new light on the prominently progressing role of exosomes as promising diagnostic biomarkers for various diseases, including AD. Notably, exosomes can be reliably detected at low concentrations [138]. To get the ball rolling, *in vivo* studies have revealed exosomes involvement in the pathophysiology of AD, including APP metabolism and Aβ secretion, in addition to pathogenic proteins, such as γ/β secretases. Also, exosomes are implicated in Aβ peptides and tau protein delivery to adjacent neurons and their subsequent propagation [139-143]. For Instance, Aβ-oligomers can be transferred in the brains of AD patients through exosomes enriched with high quantities of Aβ-oligomers [8]. Moreover, researchers have found that injured cell-derived exosomes dramatically impact glial cells, leading to astrocytes' failure to support neurons [144] and astrocytic-mediated apoptosis [145]. Leaving aside the destructive effects, exo-

somes play some beneficial roles, such as accelerating the degradation of Aβ1-42 and hindering Aβ and BACE-1 expression [146].

Overall, brain-derived exosomes originate from different cells, including neurons, astrocytes, microglia, and oligodendrocytes [147]. These exosomes cross the blood-brain barrier (BBB) and appear in peripheral body fluids, such as blood, cerebrospinal fluid, saliva, urine, ascites fluid, and breast milk. Therefore, brain cell-derived exosomes can reflect the physiological or pathological state of a brain suffering from neurodegenerative disorders, such as AD, and they are considered for liquid biopsy in AD. Among different body fluids, blood is cheaper, less invasive, and more accessible, making it an attractive source for exosome measurement.

6.3.3. Recent Diagnostic Application of Exosomes Enriched with Different Biomolecules

Exosomes can be enriched with different cargoes, such as mRNA, miRNAs, long non-coding RNAs (LncRNA), and various proteins associated with AD pathogenesis (Aβ and tau proteins). To further clarify the diagnostic potentialities of exosomes, Fiandaca *et al.,* in a deliberate study, evaluated the profile of neural-derived blood exosomes containing pathogenic proteins in patients with AD, frontotemporal dementia (FTD), and cognitively normal matched case controls. They concluded that increased levels of blood exosomal Aβ1-42 and P-T181-tau suggest the presence of or future susceptibility to AD and FTD variants to some extent. Also, increased exosomal PS396-tau implies the presence or propensity to AD [148].

On the other hand, in the case of utilizing microRNAs as diagnostic biomarkers, circulating ex-miRNAs possess some advantages compared to free circulating miRNAs. Unlike circulating miRNAs, circulating ex-miRNAs are highly stable and resistant to degradation. CNS-derived ex-miRNAs can mirror their cellular origins, which provides a better view of the nervous system's condition [149]. In this context, one study assessed the diagnostic value of serum miRNAs compared to serum exosomal miRNAs. Three neuroinflammation-related miRNAs, including miR-137, miR-155, and miR-223, were examined in dementia-afflicted people and a healthy control group. Among these three miRNAs, serum miR-223 and serum exosomal miR-223 were significantly lower in dementia patients than in healthy individuals. Specifically, the level of exosomal miR-223 was significantly lower in AD patients in their first clinic visit compared with those who had already received medical care [150]. Thus, indicating that serum exosomal miR-223 is an efficient diagnostic marker to determine the progression of dementia.

Besides, other clinical studies have evaluated the different expression patterns of exosomal miRNAs in different stages of AD compared to dementia with Lewy body (DLB) patients and healthy controls. Plasma levels of ex-miR-21-5p and ex-miR-451a were remarkedly downregulated in the AD group compared to the DLB group and healthy controls [151]. In another study, fourteen exosomal miRNAs including miR-15a-5p, miR-18b-5p, miR-361-5p, miR-30e-5p, miR-106b-5p, miR-101-3p, miR-106a-5p, miR-93-5p, miR-143-3p, miR-335-5p, miR-20a-5p, miR-3065-5p, miR-582-5p, miR-424-5p) and three exosomal miRNAs (miR-15b-3p, miR-342-3p, and miR-1306-5p) were upregulated and downregulated in AD patients, respectively [152]. Cha *et al*. also reported that ex-miR-212 and ex-miR-132 were downregulated in AD patients compared to healthy controls [153]. The low levels of exosomal miR-193b observed in patients with MCI and dementia of Alzheimer-type (DAT) suggest that exosomal miR-193b is an ideal biomarker of MCI and DAT [154]. Ex-miRNAs may act as diagnostic biomarkers to observe the progression of both the early and late onset of AD. Mckeever *et al.* evaluated the different ex-miRNAs expression in young-onset AD and late-onset AD patients (YOAD and LOAD, respectively). In this study, CSF-derived ex-miRNAs (ex-miR-125b-5p, ex-miR-605-5p, ex-miR-451a, and ex-miR-16-5p) were expressed in different levels in YOAD patients compared to miR-605-5p, miR-451a and miR-125b-5p in healthy patients showed similar alteration pattern in LOAD compared with control groups, but miR-16-5p showed similar expression pattern to the control [155]. These studies suggest that exosomes, especially ex-miRNAs, have emerged as an attractive biomarker for diagnosing AD in its different preclinical and clinical stages. However, more studies are required to validate the specificity and sensitivity of these small EVs.

7. CHALLENGES AND FUTURE RESEARCH AVENUES

Accelerating neurogenesis with different methods, such as administration of stem cell-derived components, growth factors, cytokines, and drugs, has garnered attention as an igniting therapeutic approach to compensate for the neural loss in AD. Many challenges remain in reaching the desired results in stem cell therapy as a developing novel tool. To commence, the significant reduction in hippocampal neurogenesis that occurs along with the normal aging process is the major hurdle. Meanwhile, AD pathogenesis deteriorates endogenous repair capacity and implicates in prominent neuronal loss in the dentate gyrus and CA1 regions of the hippocampus. Of note, neuronal loss in the CA1 is never compensated by adult hippocampal neurogenesis [3].

Transferring exogenous stem cells is an excellent solution for tuning up the endogenous repair, owing to their unlimited source and diverse nature. Indeed, this method has opened a new avenue of research in approaching neurodegenerative diseases by showing sufficiently pronounced effects in animal models of AD [156]. Howsoever, it has failed to show promise in phase III trials related to AD [157]. To clarify, several issues have to be addressed before achieving success in clinical trials, which are as follows:

1) Rodent brains are at a different level of complexity than humans since neuropathology-associated genes are absent in rodent brains. Thus, experimental studies on more human-like models or even rodents may be illuminators [158].

2) Subclinical pathological changes in the neuronal niches in the dormant phase of the disease before the burst of inflammation impede stem cells from showing a vigorous response. Thus, shortening the preclinical phase by developing accurate diagnostic methods for early detection of AD could establish more promising results in clinical trials.

3) AD clinical trials are in a germination stage, and there are controversies regarding the optimal administration method. Consequently, many trials underway assess various delivery routes, frequencies, dosages, and types of stem cells to bring about the most effective design.

Altogether, the clinical application of stem cells stays a daunting task since most grafted stem cells fail to integrate appropriately with resident circuits with an elusive mechanism [159]. To solve this issue, researchers have developed multiple laboratory methods to empower stem cells' performance and modulate neural niches. For instance, the administration of nanoparticles (*e.g.*, silver, silica, liposome) in drug delivery, modifying extracellular matrix (ECM), and imaging has exponentially boosted the efficiency of the process [160]. Intriguingly, gene-editing is also a highly flexible technology to overcome the problems mentioned above. Collectively, further investigation on combining various methods can lead to better therapeutic approaches in the future.

Overall, stem cell therapy through tissue repair has emerged as a promising method for treating AD. However, the risk of tumorigenesis, cellular rejection, and thrombosis formation in exogenous cell therapy remains unresolved [67]. Another approach to treat AD is the utilization of stem cell derivatives, such as exosomes. Exosomes can cross the BBB; thus, they carry therapeutic cargoes with high specificity, low immunogenicity, and less-cytotoxic effects for host tissues. Exosomes are originated from various cell types that make them an ideal cell-free therapy for neurodegenerative disorders, including AD. Several ongoing *in vivo* research studies on the essential role of MSC-derived exosomes disclose their pronounced capability to exchange information between neighbor and remote cells, abate neuroinflammation, attenuate learning impairment, enhance neurogenesis, and improve functional recovery. Notably, despite the preclinical studies conducted on the therapeutic effects of exosomes in AD, there are few clinical trials regarding their therapeutic role in diseases, such as macular degeneration [161], ischemic stroke [162], chronic kidney disease [163], and diabetes [164]. Remarkably, despite the beneficial effects of exosomes in treating AD, they can participate in pathogenic pathways such as spreading and forming SP and NFT, making them a double-edged sword for therapeutic application. Therefore, further clinical studies are needed to evaluate the long-term safety, complications, and efficacy of exosomes in AD's target-specific therapy.

Since exosomes are being utilized as diagnostic biomarkers of AD, more studies must find less time-consuming designs. Indeed, the major hinderance for the clinical application of exosome-based therapeutic strategies is their low yield when produced under standard culture conditions. Moreover, due to several variable parameters, such as different biological fluids and different exosomal miRNAs isolation and quantification procedures, there is a slight overlap and considerable variation between ex-miRNAs detected in various studies, demonstrating the need for multicenter studies with large sample sizes [165] to optimize and standardize the ex-miRNAs analysis, storage, isolation, and purification protocols. Further investigations are needed to reveal the different specific ex-miRNAs expressed in different AD stages [166]. Furthermore, although exosomes' capacity to act as drug vehicles is beneficial, more studies are required to identify appropriate strategies for increasing their specificity and drug loading capacity and reducing their immunogenicity and probable cytotoxic effects.

CONCLUSION

With several ongoing clinical trials, stem cells and their derivatives (*e.g.*, exosomes) are an emerging and encouraging approach for diagnosing and treating neurodegenerative diseases. Of various therapeutic strategies, stem cell-based approaches, including endogenous repair and exogenous transplantation, have been lately exponentially garnering attractions; they will, therefore, need to play an increasingly prominent role in managing AD. Despite poor current coherence between animal and human studies, these methods are expected to yield promising results in the future. The latter is surmised in accordance with many *in vitro* and *in vivo* techniques, including pretreating stem cells with various agents, gene editing, co-administration of drugs, and applying different delivery routes to boost their functions. Exosomes secreted from different cells exhibit the originating cell phenotype and eliminate cell-related concerns in stem cell therapy, such as tumorigenesis and immunogenicity. They have versatile therapeutic potential due to their ability to cross BBB and carry therapeutic cargoes. Moreover, since exosomes can be detected at low concentrations and are enriched with AD-related proteins, they are valuable diagnostic biomarkers. A deeper understanding of stem cells' critical role in the neurodegenerative diseases prospect and the development of better stem cell therapies is needed to treat neurodegenerative diseases.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's Disease
Aβ	=	Amyloid β
APP	=	Amyloid Precursor Protein
NSCs	=	Neural Stem Cells
MSCs	=	Mesenchymal Stem Cells
ESCs	=	Embryonic Stem Cells
iPSCs	=	Induced Pluripotent Stem Cells
miRNAs	=	microRNAs
SVZ	=	Subventricular Zone
SGZ	=	Dentate Subgranular Zone
NFTs	=	Neuro-fibrillary Tangles
APOE	=	Apolipoprotein E
OPCs	=	Oligodendrocyte Progenitor Cells
FGF-2	=	Fibroblast Growth Factor-2
DG	=	Dentate Gyrus
GCL	=	Granule Cell Layer
RMS	=	Rostral Migratory Stream
MMS	=	Medial Migratory Stream
VEGF	=	Vascular Endothelial Growth Factor

NGF	=	Neurotrophin Gene Family
BDNF	=	Brain-derived Neurotrophic Factor
NGF	=	Nerve Growth Factor
NT-3	=	Neurotrophin-3
hTERT	=	Human Telomerase Reverse Transcriptase
ROS	=	Reactive Oxygen Species
G-CSF	=	Granulocyte Colony-stimulating Factor
MI	=	Myocardial Infarction
CVA	=	Cerebrovascular Accident
HSCs	=	Hematopoietic Stem Cells
EC therapy	=	Exogenous Stem Cell Therapy
PD	=	Parkinson's Disease
AHN	=	Adult Hippocampal Neurogenesis
BD-NSCs	=	Brain-Derived Neural Stem Cells
EGF	=	Epidermal Growth Factor
FGF	=	Fibroblast Growth Factor
CNS	=	Central Nervous System
MAP-2	=	Microtubule-associated Protein-2
SE	=	Status Epilepticus
IGF-1	=	Insulin-like Growth Factor-1
GDNF	=	Glial Cell Line-derived Neurotrophic Factor
S1P	=	Sphingosine-1-Phosphate
hPSCs	=	Human Pluripotent Stem Cells
PNS	=	Peripheral Nervous System
hESC	=	Human Embryonic Stem Cell
hiPSC	=	Human Induced Pluripotent Stem Cell
PDAPP	=	PDGF Promoter-driven Amyloid Precursor Protein
BFCN	=	Basic Forebrain Cholinergic Neurons
PSC-MSCs	=	Pluripotent Stem Cells-derived MSCs
BM-MSC	=	Bone Marrow-derived MSC
MHC II	=	Major Histocompatibility Complex II
CT	=	Clinical Trials
Ad-MSCs	=	Adipose-derived Mesenchymal Stem Cells
UCB-MSC	=	Umbilical Cord Blood (UCB)-derived Mesenchymal Stem Cell
GVHD	=	Graft Versus Host Disease
EV	=	Extracellular Vesicle
ILVs	=	Intraluminal Vesicles
MVBs	=	Multi-Vesicular Bodies
LEs	=	Late Endosomes
TGN	=	Trans-Golgi Network
ESCRT	=	Endosomal Sorting Complex Required For Transporting
MSC-Exo	=	Mesenchymal Stem Cell-derived Exosomes
ADSCs	=	Adipose Tissue-derived MSCs
NEP	=	Neprilysin
GSLs	=	Glycosphingolipids
WJ-MSCs	=	Wharton's Jelly Mesenchymal Stem Cells
OBE	=	Olfactory Bulbectomized
RVG-MSC-Exo	=	Rabies Viral Glycoprotein (RVG)-tagged MSC-derived Exosome
MCI	=	Mild Cognitive Impairment
BBB	=	Blood-Brain Barrier
LncRNA	=	Long Non-coding RNAs
FTD	=	Frontotemporal Dementia
DLB	=	Dementia with Lewy Body
DAT	=	Dementia of Alzheimer-type
YOAD	=	Young-onset AD
LOAD	=	Late-onset AD
ECM	=	Extracellular Matrix

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This study was approved at Babol University of Medical Sciences (No: 140013043).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

All figures and graphical abstract were prepared by BioRender.com.

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