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Efficacy and Potential of Stem Cell Therapy for Alzheimer's Disease

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ABSTRACT

Alzheimer's Disease (AD) is characterized primarily by the buildup of beta-amyloid plaques and tau proteins. It is a very common neurodegenerative disease that is marked by cognitive decline, neuronal and synaptic loss. AD pathology is not fully understood and there is currently no cure. The disease is terminal and devastates the lives of many. Stem cell therapy involves the use of stem cell's properties of regeneration and repair to reverse the damage of many diseases. The application of stem cell therapy to AD seems to have the promise to mitigate and reverse the onset of AD. Animal models have displayed the effectiveness of stem cell therapy towards AD by improving cognitive performance and promoting neurogenesis. The abilities and applications of stem cell therapy seem to be highly promising despite having bottlenecks. The difficulties in controlling differentiation due to complexities in controlling the process is the primary issue presented. With the use of stem cell therapy for AD, it is also possible to adapt the technology to various other neurodegenerative diseases and various diseases overall.

Introduction

Dementia is the generalized term for the onset of memory loss and thinking impairment. There are over 200 subtypes of dementia with about 50 million in 2018 according to the World Alzheimer Report and that number is expected to increase [1]. Alzheimer's Disease (AD) on the other hand is the term given to a specific disease subtype that makes up approximately over 60% of dementia cases [29].

AD seems to be more likely to affect women than men. AD occurs after the age of 65 in most cases, those that are diagnosed earlier than 65 are diagnosed with early-onset AD [13]. It has been reported that Hispanic and African American populations are prone to be affected by AD more than others [13,29]. Another correlation is that those with depression are more likely to express AD. Environmental factors like neurotoxins present in cyanobacteria that reside in water like saxitoxins, ciguatoxins, anatoxins, and β-N-methylamino-L-alanine (L-BMAA) can increase risk factors for AD [3]. When looking at AD patients it is common to find these cyanotoxins in the brain possibly linking the two [3,38]. These cyanotoxins are found naturally in water coming from algal blooms and cyanobacteria. As global warming furthers, eutrophication (the overgrowth in algal and plant biomass due to increased nutrients present) will increase causing even more of these neurotoxins to be present in water. The mitigation of these effects should be further looked into as it could contribute to an increase in neurodegenerative diseases in humans [38].

AD is marked by irreversible neuronal death which results in cognitive decline mainly in areas of memory, language, reasoning, behavior, and executive function [2]. AD is also characterized by damage to the hippocampus which is responsible for memory. Other markers for AD are the presence of Tau proteins and beta-amyloid proteins (Aβ) [27]. One of the biggest challenges with AD is that it has a primarily unknown biological cause and is extremely complex [3]. AD is also a terminal illness; once diagnosed, there is not much that can be done as the disease is currently incurable. The current treatments available for AD are meant to slow down the further progression of the disease [34]. Primarily the main drug types that are clinically approved are N-methyl-D-aspartic acid (NMDA) receptor inhibitors

and acetylcholinesterase inhibitors (AChEI) [3,18]. NMDA receptor inhibitors are a class of antagonist drugs that help to mitigate the effects of NMDA excitotoxicity. NMDA receptors can cause excitotoxicity which evolves into neurodegeneration. NMDA is a glutamate receptor, and the synaptic loss in AD may be caused by this excitotoxicity [26]. The use of this drug class leads to a reduction in neuronal damage. AChEIs are an antagonist drug class that helps prevent acetylcholine breakdown. Acetylcholine is a neurotransmitter that is linked with memory. The degradation of cholinergic neurons, neurons that act on acetylcholine, is correlated with Alzheimer's [3,18,19]. Immunotherapy is also another approach utilizing the drug aducanumab, an anti-amyloid intravenous antibody. Immunotherapy involves suppressing or activating the immune system in order to fight disease. Aducanumab works by reducing Aβ plaque buildup which reduces symptoms of the disease [34,35]. The pitfall of these drug classes is that they are not cures for AD, rather they just slow down the progression of AD. As there is no cure for AD, there is a search for a possible cure.

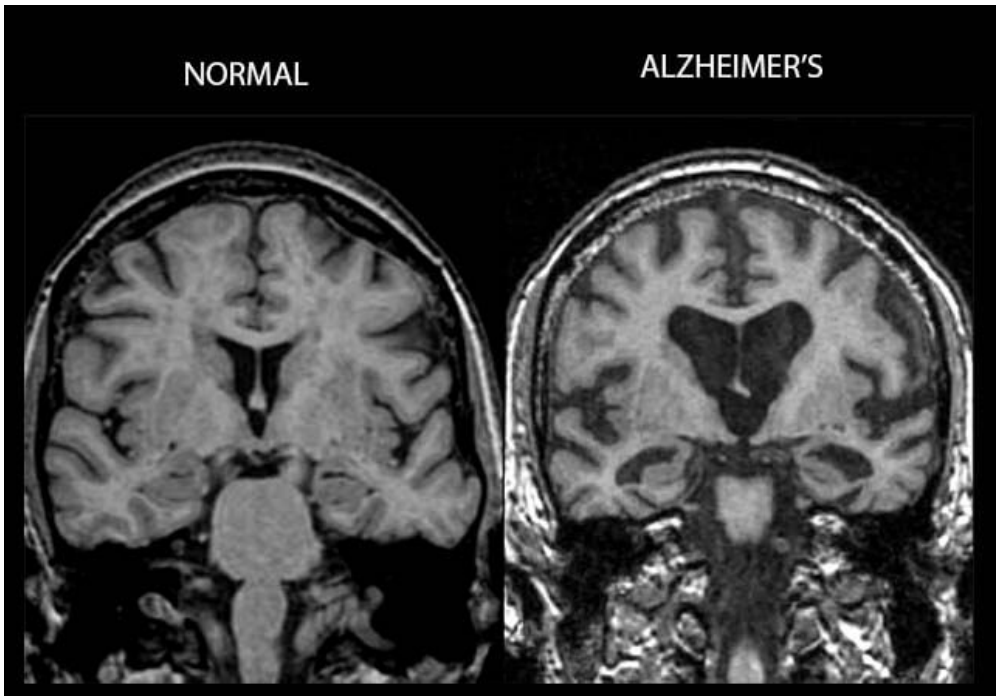

Fig. 1 MRI imaging of human brains. Image of the human brain (left) healthy and (right) affected by Alzheimer's Disease, dark spaces in the AD image represent the accelerated neurodegeneration - Adapted from John Hopkins University [59].

In the past couple of decades, researchers have been exploring the potential of stem cells and their ability to regenerate and have found a wide variety of therapeutic applications [9]. As anticipated, over the past decade, multiple research groups have initiated efforts to generate stem cell therapies in the context of Alzheimer's disease [4,5,6,24,25,44]. Stem cells are precursor cell types that are able to differentiate into various specialized cell types. They are most often associated with turning germ cells into a full organism. This ability of stem cells seems to have promise in reversing the effects of AD. With stem cells differentiating into different neural cell types, it is possible to utilize this, and repair and reverse damage caused by AD.

Neural Cell Types Affected in AD

Stem cells being able to differentiate into various neural cell types offers promise for the reversal of AD. With AD affecting various cell types, it is important to discuss what AD affects and what the function of those cell types are to understand the disease and stem cell therapy better. While AD pathology is a complex process and is not completely understood, it is understood that Aβs, tau proteins, and other AD influencing factors lead to various toxic mechanisms which result in neural cell death [30]. AD mainly attacks the hippocampus and cerebral neocortex [30]. The main cell types affected during AD are astrocytes, microglia, oligodendrocytes, pericytes, and endothelial cells.

Astrocytes are responsible for numerous processes in the brain. They support many of the brain's functions, providing energy for the brain's metabolism, aiding in wound healing, controlling blood flow, and interacting with neurons and synapses. The microglia are the innate immune cells that reside in the central nervous system (CNS) and they regulate neuroinflammation. Oligodendrocytes are the cells that develop the myelin sheath, the fatty insulation around axons that speed up neural signals. Pericytes are responsible for blood vessel formation in the CNS. Endothelial cells provide structural support in blood vessels and are responsible for the regulation of the permeability of the blood-stream to surrounding tissues. Fig.2 explains the various cell types in a healthy individual as compared to an AD affected individual.

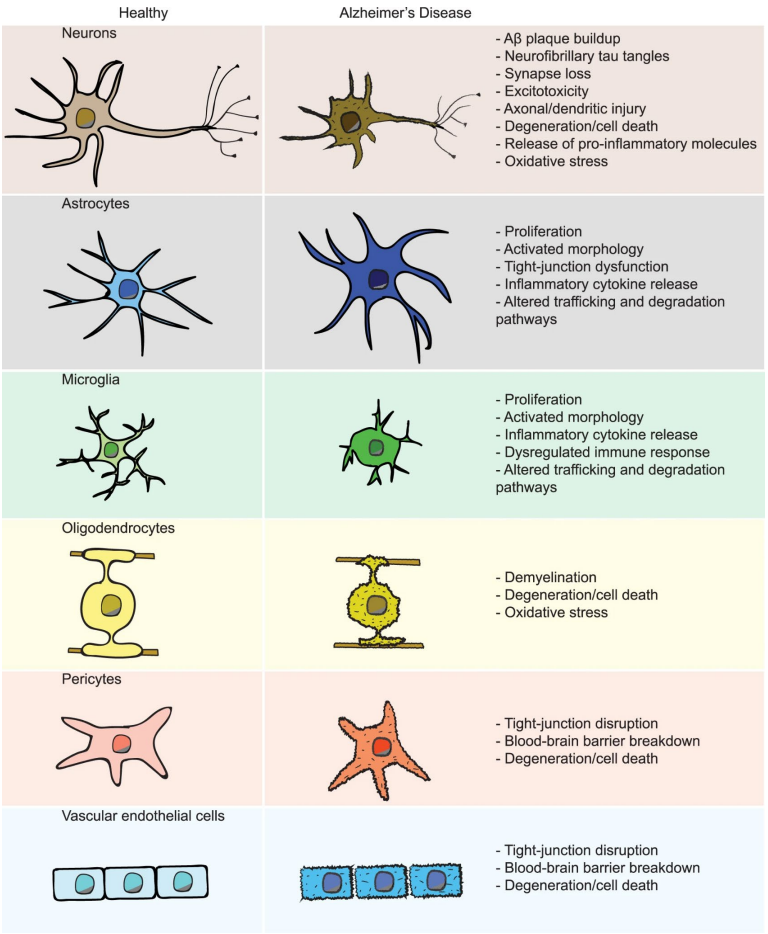

Fig. 2 Neural cell types in the human brain. Different cell types of the brain comparing healthy (left) with AD-affected (right) - Adapted from "Modeling Alzheimer's disease with iPSC-derived brain cells" [31]

Stem Cell Therapies and Clinical Trials

Stem cells can be derived from either embryos or adult stem cells [9]. The main stem cell types that will be discussed are mesenchymal stem cells (MSCs) [39], induced pluripotent stem cells (iPSCs) [40], embryonic stem cells (ESCs) [41], and neural stem cells [42] (NSC) [4]. These four exhibit the highest potential for differentiation into neural cells. Other stem cell types like adult stem cells or somatic stem cells do not have the same differentiation potential. Other stem cell types like olfactory ensheathing cells and hematopoietic stem cells have limited research when it comes to Alzheimer's but they do seem to have some promise in differentiation [2,4,20]. MSCs, iPSCs, ESCs, and NSCs are the most promising for differentiation purposes because they express pluripotency and/or multipotency meaning that they can differentiate into varied types of cells [2,4].

Current research on utilizing stem cells as a treatment modality for AD demonstrates higher potential as compared to prior methods evident from several recent studies. The furthest testing for stem cell therapies for AD has been involving mice studies. Mice are often chosen for their genetic similarity to humans [22]. In a 2013 study, iPSCs differentiated into cholinergic neuronal precursors were grafted into the hippocampus of an AD mouse and matured into mature cholinergic cells resulting in a reversal of spatial memory impairment [5,23]. In another mouse study done in 2015, mice embryonic stem cells were differentiated into basal forebrain cholinergic neurons (BFCNs) and then grafted into existing BFCNs, which are neurons that are involved with acetylcholine by producing the main source of cortical cholinergic input and are often degraded with AD. Damage to BFCNs substantially reduces cognitive potential with AD [43]. The result of this experiment was a gradual improvement in learning and memory performances [21]. However, it is unclear whether there was further research on this front for BFCN differentiation. Furthermore, a mouse study conducted in 2021 involving the injection of MSCs into the hippocampus resulted in the reduction of neuro-inflammation and also reduced tau protein levels, a reduction in tau protein levels means relief in symptoms of AD [24,36]. As evident from these above AD-related studies, it should also be noted that a large amount of research comes from rodent/mice models, and as time progresses more human clinical trials should advance further. Current human trial research has presented issues that will be discussed later in the text below. The following are some of the main stem cell types that have been studied extensively for therapeutic applications to AD.

Mesenchymal Stem Cells:

MSCs are one of the more promising stem cell types for therapy options as they are easier to handle and utilize, multipotent, and can be used intravenously. They are derived primarily from the umbilical cord, bone marrow, adipose tissue, amniotic fluid, lungs and muscle, and peripheral blood [4]. Because of its ability to be injected intravenously, it allows for the hastening of the transfer to the treatment site past the blood-brain barrier. This promotes higher success rates of transfer and reversing damage from AD. MSC transplantation has demonstrated a reduction of Aβ and phosphorylation of tau protein buildup in mice models [4,24,25]. This leads to neurogenesis and improved learning and memory [4]. In addition, it has been shown to stimulate synaptogenesis and neuronal differentiation. It is important to note that the primary demonstration of these abilities was from rodent and mice models, and unfortunately, the majority of human trials have been largely unsuccessful [5]. The low success rate of human trials could possibly be attributed to the level of progression in AD for those chosen for human trials. Another factor could be the lack of using *in vivo* transferring of stem cells as that has shown the highest success for stem cell therapy to AD [2]. It may also be that the transfer from mice to human models is an inappropriate transition and that research should be conducted on higher neural order organisms such as canines or primates before going to humans [5,37]. Further, it could be an issue of development and procedure that will continue to get better as more trials occur. MSCs also seem to have a low rate of differentiation into neural cells [4]. Although this should not be discouraging as these trials are in the very early stages and the research for stem cells is ever-growing.

Induced Pluripotent Stem Cells:

iPSCs are the next subset of stem cells that derive primarily from adult stem cells but are altered so that they are brought to an embryonic stem cell-like state [6]. It has been established that it is possible to differentiate iPSCs into astrocytes, microglia, oligodendrocytes, endothelial cells, and pericytes [7]. Using iPSCs it is possible to create 3D co-cultures to further model AD and cell-cell interactions in terms of AD as well as other diseases [7,44]. iPSC 3D Co-Cultures allow for a view of neurodegeneration and allows for interactions that 2D models would not allow for [7]. These stem cells allow for advancements in modeling AD to further research. The primary benefit of iPSCs is to use them for autologous transplantation, replacing the damaged cell with iPSC differentiated cells. Another use of iPSCs is that they have been shown to differentiate into forebrain acetylcholine neurons, which means that researchers can inject them into AD patients [1]. As acetylcholine plays a role in memory as mentioned prior, iPSCs can be used to improve memory function [1]. Injectable forms of acetylcholine have been shown to improve memory degradation caused by AD [1]. It is important to mention that iPSCs have a safety concern as they are more susceptible to causing tumorigenicity and are more susceptible to genetic variations and mutations [11].

Embryonic Stem Cells:

As the name suggests ESCs derive from embryos, and as embryos are the precursor to an organism ESCs promise enormous differentiation potential. ESCs are most commonly derived near the fourth to the seventh day of an embryo and taken from the inner mass of the blastocyst [4,28]. The current procedures for human ESCs are taken from donated *in vitro* fertilized cells. One mouse study was conducted in 2009 where human ESCs were injected into the hippocampal region of mice that had experienced radiation-induced cognitive impairment [45]. The result of this study was a success in the mice with a significant improvement in hippocampal tasks. The predominant issue with ESCs are the ethical concerns with using a human embryo [10]. The difficulty in targeting differentiation is another challenge to be addressed with the use of ESCs. Because ESCs can differentiate into the three germ layer types and can differentiate so freely it is hard to target that differentiation [33]. In 2018, a mouse study was conducted that illustrated the efficacy of mouse ESCs to create neural-like cells. These cells were transplanted into AD rat brains and found that neurogenesis was expressed significantly more in the AD rats with the ESCs than in the control, suggesting the efficacy of this stem cell type [50].

Neural Stem Cells:

NSCs demonstrate multipotency and can have been shown to differentiate into neurons, oligodendrocytes, or astrocytes. NSCs are derived from the brain as the name suggests and they are self-renewing [3,4]. A 2009 study indicates that NSC transplantation was effective in repairing cognitive function. The study found that the transplanted NSCs did not work by reducing Tau or Aβ plaque levels, but rather by increasing synaptic density in the hippocampus by elevating levels of a molecule called a brain-derived neurotrophic factor (BDNF) in the hippocampus. BDNF is a molecule that plays a role in the maturation and growth of neurons [57,58]. In an experiment with AD mice, human NSCs were injected into the lateral ventricles of the mouse, and the cells differentiated into glial and neuronal cells. The results of this experiment illustrated that the mouse had increased spatial memory, decreased tau phosphorylation, and a decrease in Aβ42 levels. This experiment demonstrates promise for this cell type. NSCs also seem to have a lower survival rate in transplantation and are more susceptible to an immune rejection response [3,4]. A 2018 study was interested in investigating NSC therapy for hypoxic-ischemic brain injuries, which are injuries caused by lack of oxygenated blood flow to the brain resulting in cell death, and ischemic strokes, strokes that occur due to lack of oxygenated blood. This study involves repairing damaged or decayed neuronal cells which can be applied to AD as

the utilization of NSCs is for the same purpose. The study found that exogenous transplantation of NSCs proved to be effective in repairing cognitive, behavioral, and sensorimotor functions [46].

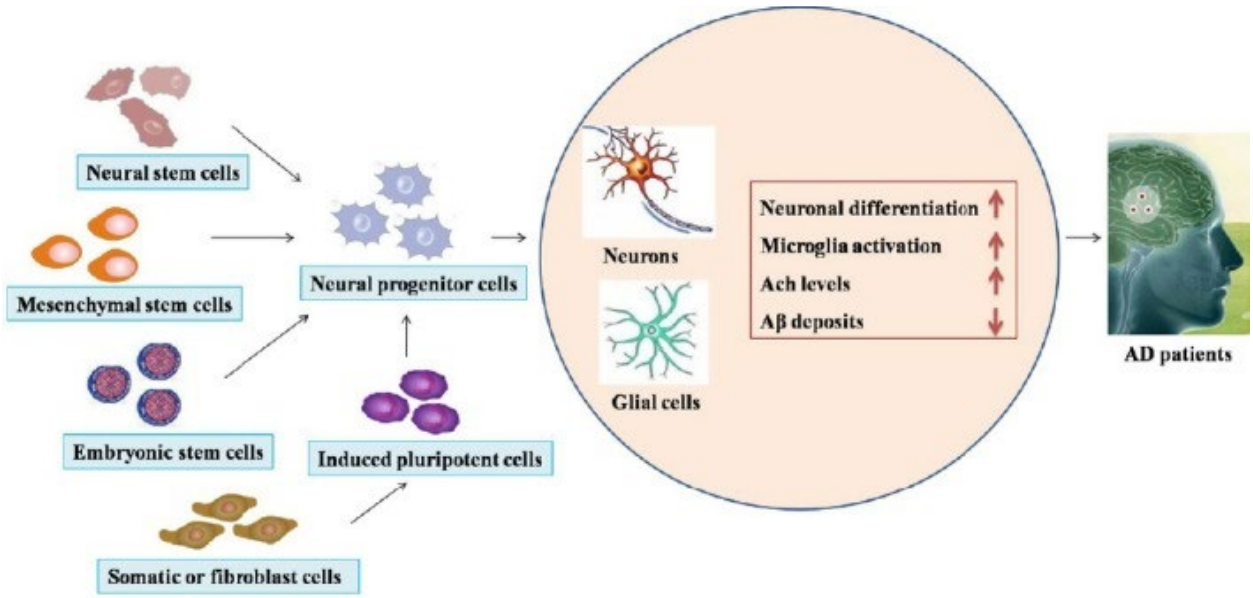

Fig. 3 Types of stem cell types utilized for AD therapy. The four main types of stem cells that have been explored to have a treatment potential for AD are NSCs, MSCs, ESCs, and iPSCs - Adapted from "Current status and future prospects of stem cell therapy in Alzheimer's disease" [32]

Bottlenecks of Stem Cell Therapy

As time and research have advanced stem cell research and therapy, several bottlenecks have been found with stem cell therapy for AD. One of the biggest issues with stem cells is trying to control their differentiation [3]. The highest success rate for stem cell translation has been found to be through *in vivo* which complicates the process further [3]. The current human clinical trial research of stem cell transplantation to AD patients is not the most promising, but it is important to note that these trials are in very early stages, most are in phase 1 and some are awaiting phase 2 [8]. Another issue is trying to control the Yamanaka factors that control translation [3,12]. The method of creating iPSCs involves utilizing these Yamanaka factors. The next bottleneck is that the rate of stem cell transplantation is low in human trials because the research for stem cells is in its early phases. A concern is the possibility of stem cells causing tumorigenesis and possibly teratomas. Stem cells also have rejection issues when transplanted into host cells [3].

Stem Cell Applications to Other Neurodegenerative Diseases:

Stem cell therapies can also be applied to other neurodegenerative diseases. Some of the most prominent, incurable and often terminal ones are diseases like multiple sclerosis (MS), Parkinson's Disease (PD), and Huntington's Disease (HD). These diseases severely reduce the quality of life and are often terminal. Stem cell therapy, like with AD, has also shown promise to combat these diseases. These diseases are also similar to AD in the way that they all degrade the brain.

Table 1

Disease Type	Effects and Pathology
Alzheimer's Disease	Characterized primarily by the buildup of beta-amyloid plaques and tau proteins, leads to neuronal and synaptic damage, cognitive decline in executive function and memory [1,2,34].
Parkinson's Disease	Parkinson's Disease leads to neuronal damage specifically in dopamine-producing pathways in the basal ganglia, resulting in an overall decrease in dopamine which impairs movement and causes tremors[47].
Huntington's Disease	Characterized by the inherited degradation of neurons in the cerebral cortex and basal ganglia, the disease leads to uncontrolled emotions, movements, and cognitive decline [48].
Multiple Sclerosis	Distinguished by the immune system attacking the myelin sheath, a protective covering that facilitates neural impulse movements, the degradation of the myelin sheath results in permanent nerve damage [49]

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With multiple sclerosis, the only drug medications for it allow for just a slowing down in progression similar to AD. A 2006 study indicated that the use of MSCs for MS was feasible in repairing the myelin sheath. It found that MSCs could influence NSCs to induce this repair, yet methods were not fully understood [53] A phase 1/2 study in 2018 was conducted that involved 20 subjects being exposed to umbilical cord mesenchymal stem cells (UCMSC). The result found an increase in higher function and seemed to show promise for MS symptom reversal. The study demonstrated that the participants enrolled had a reduction in symptoms and improved quality of life in events such as walking, bladder/bowel/sexual dysfunction, energy, fatigue, etc. Although the results of the study were promising it is important to note that this small sample size may be subject to some errors [14].

Parkinson's Disease is characterized by a degradation of dopamine pathways which leads to tremors. It is also the second most common neurodegenerative disorder after AD. The predominant use of stem cell therapy for PD is through the use of replacement therapy [16,17]. The primary utilization of iPSCs or human ESCs in order to replace dopaminergic neurons in order to restore the dopamine pathway and hopefully reverse the effects of PD. Two studies, 2014 and 2017, utilized human ESCs and found that stem cell *in vivo* transplantation was effective in restoring dopaminergic pathways in mouse models. The studies indicated an improvement in motor functions [51,52].

Finally, with Huntington's Disease, MSCs and NSCs can be used to replace damaged neural tissue in order to reverse the effects of HD [15]. MSCs can also be manipulated in HD to induce synaptogenesis and neurogenesis. A big part of HD is that it degrades medium-sized spiny projection neurons (MSNs), and by utilizing NSCs and MSCs scientists are able to replace them which can prevent further damage and reverse what has already occurred [15]. A 2018 mice study found that utilizing ESCs to differentiate into NSCs and then being transplanted into HD mice models has illustrated efficacy in the reduction of symptoms. It demonstrated an improvement in motor functions, cognitive impairment, and reversing synaptic alterations [56]. The most progressed stem cell therapy for HD is by the Brazilian company known as Cellavita. The therapy utilizes MSCs and the therapy is currently undergoing clinical trials, and the phase I trial has been completed with no results published, but an extension to phase 2/3 is being requested [54,55].

Conclusions

Research so far for stem cell therapy and AD pathology is highly promising. Although current human trial research illustrates some bottlenecks that need to be worked out through time. The struggle with translating the procedures and processes for mouse experiments to be applied to humans will most likely be the next phase of adapting stem cells. The strides in mice-related experiments reinforce the idea of promise for stem cell use in therapeutic means [5,21,23,24]. The already seen abilities in reversing and repairing AD with mice give hope to its potential as a means to be a cure to this disease. With the various stem cell types offering their own unique benefits and challenges, it is important to expand research in this field. The ability of iPSCs for 3D co-culture is very promising [7]. The use of MSCs seems to be the most promising for therapeutic potential as they have an abundance, are easier to handle and utilize, are multipotent, and can be used intravenously [4,24,25]. ESCs, while highly effective and promising, the difficulties in differentiation may pose some challenges, yet more research should be conducted. NSC transplantation seems to be feasible, and it seems effective [3,4]. In parallel, stem cells could possibly provide abilities and reversal of progression and repairing of damage in other neurodegenerative diseases. Possibly this technology could be applied to numerous diseases.

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