

Alzheimer's Disease and Stem Cell Therapy

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Abstract. Alzheimer's disease is a neurodegenerative disorder mainly caused by aggregation of neurofibrillary tangles and beta-amyloid plaques. As the most common cause of dementia, the population of AD patients has risen significantly in recent years. Due to the difficulty to diagnose AD at its early stage and the rapid development of the disease, AD is still an unsolved puzzle in the medical world. Though there are treatments for delaying symptoms of AD such as anti-amyloid therapy and medicine treatments that contain Cholinesterase inhibitors therapy, efficient therapies which treat AD fundamentally are yet to be discovered. The review paper will focus on one of the most promising therapies for AD, stem cell therapy. Compared to slowing down the disease, stem cell therapy can actually help the patients to grow brand-new neurons hence the treatment is pretty worthy to be studied. Stem cells are undifferentiated cells that are able to develop into new brain cells. There are four types of stem cell therapies for Alzheimer's Disease: Mesenchymal Stem Cells therapy, Neural Stem Cell therapy, Embryonic Stem Cell therapy, and Induced Pluripotent stem Cell therapy. Among all the stem cell therapies, induced pluripotent stem cells (iPSC) therapy has the most potential to work out due to the successful trials upon rodent animal models. Nevertheless, no stem cell therapy for AD succeeds in human trials so far. Besides, the likelihood of cancer and tumor should also be taken into consideration.

Keywords: Alzheimer's Disease, Sem cell, Therapy.

1. Introduction

Dementia is a severe chronic disorder that illustrates amnesia, behavioral disturbance, disorientation, progressive cognitive impairment, and functional decline. Alzheimer's disease is the most common pathology associated with dementia, a rising global health issue. AD is marked by continuous neurodegenerative pathology and it is the very first ailment of the loss of neurons and synapses [1]. The main cause of the disease is β amyloid plague formed by sticky amyloid beta which bond and stack up together outside of neurons. Beta-amyloid plaques interrupt signaling between neurons, leading to brain functions being diminished directly. Besides, beta-amyloid plague also activates kinase, the enzyme that transports the phosphate group to the tau protein to change its shape and tangle. According to the 2021 Alzheimer's disease facts and figures, AD became the sixth-leading cause of death in the States and the fifth-leading cause of death among Americans age 65 in 2019, with 121,499 deaths recorded. Between 2000 and 2019, the number of deaths from AD raised more than 145% [2]. AD is a gradually evolved disease. AD can be divided into three stages: Preclinical Alzheimer's disease which is the earliest stage of the disease, followed by Mild Cognitive Impairment due to Alzheimer's disease, and Dementia due to Alzheimer's disease. In Preclinical Alzheimer's disease stage, the disease can only be detected by assessable changes in biomarkers or limited cognitive tests. Brain imaging and microscopic changes in CSF (cerebrospinal fluid) are used for recognizing the biomarkers. Nevertheless, both biomarker and cognitive test methods are not mature enough to diagnose AD accurately at the early stage. Mild Cognitive Impairment is the second stage of AD. The first clinical changes can be observed at this stage, usually marked by slight alternations in memory as well as other cognitive abilities. The alternations which can be evaluated carefully at this stage in AD patients are conspicuous for the patients and their families. At the last stage of AD, more aspects of cognition and behavior of patients are afflicted, leading the patients' daily lives got affected more severely.

Although there are several applicable treatments for the disease, those therapies can only stabilize the early stage of Alzheimer's disease or temporarily improve symptoms of dementia. Among all the therapies for Alzheimer's disease, stem cell therapy has become one of the most potential treatments to succeed [3]. Stem cells are undifferentiated cells, meaning they don't have specific functions like the other cells. They are considered excellent materials for scientists to research treatments for pathologies due to their ability to develop into various cells. These newly differentiated cells can be used for replacing damaged or mutated cells caused by disease inside different organs in human bodies hence stem cells have great potential for researching new therapies. Adult stem cells, pluripotent stem cells, and induced pluripotent stem cells are the three types of stem cells. Pluripotent stem cells are stem cells that originated from embryos while adult stem cells are tissue-specific stem cells made from adult body cells. Induced pluripotent stem cells are somatic stem cells modified genetically by researchers. In recent AD research for stem cell therapy, embryonic stem cells (ESCs), mesenchymal stem cells (MSCs) which is a type of tissue-specific stem cells, brain-derived neural stem cells (NSCs), and induced pluripotent stem cells (iPSCs) are most frequently applied. Endogenous repair and exogenous cell therapy have also been applied in AD research.

Alzheimer's Disease remains an unsolved puzzle. Though biomarkers and cognitive tests are applied to recognize Alzheimer's disease at its early stage, AD can not be diagnosed at its preclinical stage so far since the methods are not accurate enough to become clinical criteria. Therefore, AD is usually unnoticeable until the later stages of AD when patients' memory and cognitive ability get affected. Besides, as mentioned earlier, there is no successful treatment that can help patients recover fundamentally these days. Although stem cell therapy for AD is relatively more promising than the other existing therapies, it is yet a mature and applicable treatment. Most stem cell therapy research for AD is based on transgenic animal trials and several animal trials worked successfully [4]. Nevertheless, Due to the biological distinctions between transgenic animals and humans, the research methods are all declined in human trials [5]. What's more, several safety concerns including tumor growth, metastasis, and overestimated the therapeutic potential of MSCs need to be taken into concern too [6].

The review paper focused on the iPSCs therapy while other stem cell therapies will also be covered briefly. The general definition, several sources of stem cells and the mechanism of stem cell differentiation will also be mentioned. Though stem cell therapies are relatively more potential to succeed in curing AD instinctively compared to the other treatments, several improvements need to be made. Besides, based on an article published on The U.S. Food and Drug Administration (FDA) website, there is no stem cell therapy for Alzheimer's Disease has been approved by FDA so far. The paper will end by summarizing the weaknesses of the current clinical trials on AD and the possible methods of improving the therapy.

2. The discovery of Alzheimer's disease

Alzheimer's disease is a severe neurological condition that damages neurons and results in dementia. Alzheimer's disease was recognized as the most common cause of dementia in 1976, identified by Neurologist Robert Katzman in his published editorial in Archives of Neurology. In 1984, the beta-amyloid protein was discovered to be the primary component of the brain plaques that cause Alzheimer's disease. Two years later, another major cause of AD, knotted Tau protein which forms the Neurofibrillary tangle was recognized as another key element of the cause of Alzheimer's disease. After figuring out the main factors leading to the disease, the first Alzheimer's drug trial, the tacrine clinical trials, was operated by NIA (National Institute on Aging) and Warner-Lambert Pharmaceutical Company with assistance from the Alzheimer's Association in 1987. As a cholinesterase inhibitor, Tacrine has the ability to raise the accessibility of acetylcholine in neurons [8]. Tacrine was the first drug treatment certificated by the FDA aiming at symptoms of Alzheimer's disease particularly. It works as an acetylcholinesterase inhibitor which increases the concentration of acetylcholine(ACh), a type of neurotransmitter released by nerve fibers. Almost a decade later than

that, the first transgenic mouse model which is used for developing Alzheimer-like brain disease treatments was proposed in 1995. Though there have been progressed in AD therapy research, the number of patients rose dramatically over time. The data from The Centers for Disease Control and Prevention (CDC) National Center for Health Statistics illustrates AD amounts to the sixth-leading cause of death in 2007. Then in 2012, an international research association introduces the first major clinical trial of drug treatment for people who inherited an autosomal dominant mutation to reduce the risk of AD. In 2021, aducanumab, the first medicine targeting the underlying biology of AD, was approved by FDA. Overall, although the treatment research of Alzheimer's disease has been developed over years, the appropriate therapy for AD is still an unmet need.

3. Current therapies for Alzheimer's Disease

3.1. Cholinesterase inhibitors

One of the causes of Alzheimer's disease is the absence of cholinergic neurons located in the basal forebrain. In order to restore the cholinergic function of patients, cholinesterase inhibitors (ChEIs) are used to prevent the enzymes that dismantle acetylcholine, which is an essential neurotransmitter in the human body, as well as maintain acetylcholine to function properly at cholinergic synapses [9]. Since 1993, ChEIs play an important part in dealing with the symptoms and declining the progression of AD [10]. Tacrine was the first ChEIs drug approved by FDA. However, it became no longer available in 2013 because of its liver toxicity and multiple side effects including vomiting, nausea, diarrhea, clumsiness, and loss of appetites [11]. Donepezil, rivastigmine and galantamine are the three ChEIs recently certificated by FDA. All three of them can impede acetylcholinesterase breaking down acetylcholine while Rivastigmine is also able to inhibit butyrylcholinesterase apart from that [12]. Rivastigmine drug helps AD patients with increasing their cholinergic function. Nevertheless, the inhibitor usually takes a long period of time to see the result since it takes time for the enzyme to be activated. Besides Rivastigmine has several main side effects containing stomach pain, nausea and vomiting. If AD patients overtake the medicine, they also face symptoms such as chest pain, irregular breathing, and slow or irregular heartbeat. Donepezil treatment was certified for drug therapy of mild to moderate AD in 1996 [13]. In addition to these adverse effects, the medication has a risk of serious vomiting, low blood pressure, severe nausea, muscle weakness, bradycardia, and breathing difficulties [14]. Other side effects include sleeplessness, nausea, lack of appetite, diarrhea, muscle cramps, and muscle weakness. According to research on the drug efficacy of Galatamine published on Neurology, ChEIs users have a higher score of the Mini-Mental State Examination (MMSE) with a 27% lower risk of death compared to non-users among the patients who have severe Alzheimer's dementia [15]. Overall, although Cholinesterase inhibitors are helpful for slowing down the progression of AD, they do not change the symptoms of the disease conversely. What's more, ChEIs have multiple side effects and leads to severe symptoms under the condition of overdose, making some of the inhibitor drugs too dangerous for the patients to take. Besides, ChEIs are insufficient in efficacy due to their fast-acting mechanism [15].

3.2. Anti-amyloid therapy

β amyloid plague is one of the major causes of AD. It is formed by the accumulation of beta-amyloid, disrupting brain cells to function properly. Anti-amyloid therapy fights against the amyloid- β peptide in order to slow down the symptoms of AD. Immunotherapy is the most well-developed therapy among various anti-A β methods. It includes both active vaccines that trigger the immune system to make antibodies and passive immunization by the administration of exogenous monoclonal antibodies (mAbs). Active vaccines benefit AD patients by producing antibodies in long term with short-term medication administration. So far, CAD106 is the only vaccine that went through phase 3 trials and has been chosen for the Alzheimer Prevention Initiative APOE ϵ 4 homozygote study. Passive immunization, on the other hand, maintain consistent antibody titers as well as help control injurious events by stopping treatments. Nevertheless, the approach requires repeated drug intake and

larger cost compared to the previous method. Besides, mAbs trials are still unsolved puzzles due to the failures of the research though it provides researchers with essential information for future research [16].

Researchers often conclude the failure of anti-amyloid immunotherapy is due to the difficulty to set the trial before AD patients go into their later stages of the disease [17]. Before patients went into the dementia stage of AD, β amyloid have already piled up significantly hence the anti-amyloid therapy might be ineffectual. As mentioned before, Alzheimer's disease symptoms are unnoticeable until the Mild Cognitive Impairment and Dementia due to Alzheimer's disease stages which are the lateral phases of AD. On that account, it is difficult for the researchers to apply the method before the patients go into later stages of Alzheimer's dementia.

4. Stem Cells

Stem cells are undifferentiated cells that are capable of developing into various kinds of specific cells. Stem cells are either derived from the inner cell mass of embryos, located inside the blastocyst after zygotes go through the process of mitosis, or from somatic cells. Stem cells can be sorted into three types: embryonic stem cells (ESC), induced pluripotent stem cells (iPSC) and adult stem cells.

4.1. Embryonic stem cells (ESC)

Pluripotent stem cells, commonly referred to as embryonic stem cells, are stem cells derived from embryos. These stem cells are usually from surplus embryos donated by patients after their childbirth. Embryonic stem cells are pluripotent, meaning they are able to develop into diverse tissues in the body with the capacity of infinite self-renewal and differentiation [18]. They have the ability to differentiate into cells that are derived from 3 germ layers: endoderm, mesoderm, and ectoderm. The differentiation of stem cells is maintained by different proteins that instruct the cells to differentiate or inhibit the differentiation. Proteins Nanog, Oct4 and Sox2 are transcription factors that maintain ESC's pluripotency [19]. Nanog is in charge of suppressing ESC differentiation while Oct4 is responsible for inducing embryonic ectoderm differentiation along with SOX2 which helps adjust gene expression in fertilized [20].

4.2. Induced pluripotent stem cells (iPSC)

Similar to embryonic stem cells, induced Pluripotent stem cells, also known as iPS, are also able to develop into several kinds of stem cells. They are genetically reprogrammed somatic cells by researchers which serve the same function as Pluripotent stem cells. iPS technique is the key for regenerative medicine, it helps patients to repair impaired tissue using their own stem cells. iPSC provides patients with new organs and prevents them from immune rejection complications since the stem cells are from their own bodies. In 2006, Kazutoshi Takahashi and Shinya Yamanaka proved that iPSC, the reprogrammed somatic stem cells, can be made from mouse embryonic fibroblasts (MEF) and adult mouse tail-tip fibroblasts by retrovirus-mediated gene Oct3/4, Sox2, c-Myc, and Klf4 under ES cell culture conditions [21].

4.3. Adult stem cells (ASC)

Adult stem cells, which is also known as tissue-specific stem cells, are stem cells inside different organs which function as new replacement cells when existing cells wear out and die. Different from pluripotent stem cells, stem cells can only differentiate into one particular kind of cell or multiple types of cells from one specific tissue. Adult stem cells can be taken from all 3 germ layers and placenta. Impaired organs are able to be repaired by adult stem cell transplantation outside of human bodies.

5. Stem Cells mechanism

5.1. Asymmetric segregation of cellular determinants

Embryonic stem cells (zygote) go through a process called Asymmetric protein segregation as it differentiates into different specific-function cells. Transcription factors clustered around the bottom of the zygote along with other mRNA precursors to activate certain genes and determine the specific types of cells that the daughter cells will develop into. Mex-5, MEX-6 and PIE-1 are three CCH-Zn finger proteins within the segregating transcription proteins [22]. PIE-1 is a determinant that splits into cells called posterior P1 cells, which express genes specific to the germline while suppressing transcription in general [23]. Contrary, MEX-5's ectopic expression represses the expression of germline proteins, as well as MEX-6 [24].

5.2. Obligate asymmetric replication

Obligate asymmetric replication is a mechanism that maintains the quantity of stem cells. During the process, stem cells divide into two daughter cells. One of them is exactly the same as the original stem cells while the other daughter cell has the ability to differentiate. As the daughter cell further differentiates, the other cell replace the original stem cell. The process of obligate asymmetric replication is shown in figure 1 [25].

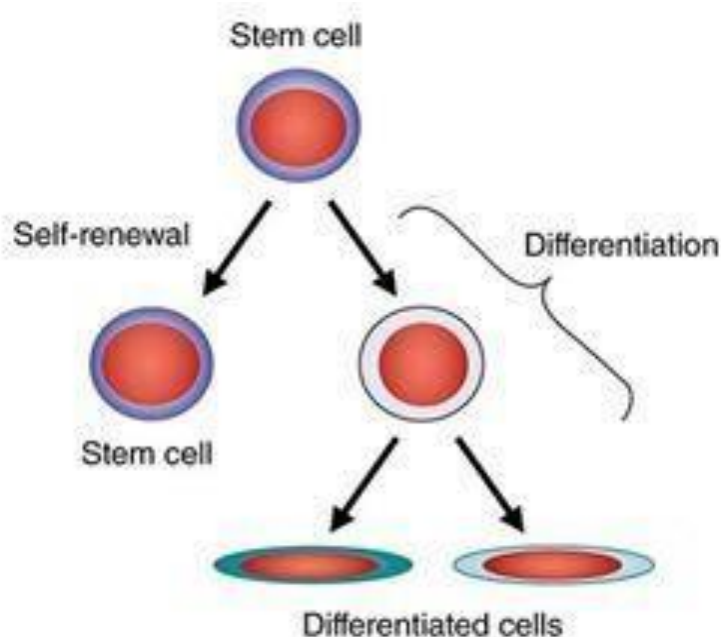


Fig 1. The original stem cell divides into two daughter cell through self-renewal and differentiation.

5.3. Stochastic differentiation

Stochastic differentiation is another stem cell mechanism that involves one stem cell divided into two differentiable daughter cells. As the absence of the original stem cell is recognized by another stem cell, the stem cell goes through mitosis, dividing into identical cells in order to replace the original stem cell. Based on research on the pluripotency of hematopoietic stem cells, stochastic differentiation is crucial for maintaining the number of stem cells in the body [26]. The research was done based on B cells, an ideal model for researchers to study differentiation since the complicated processes in a distinctive manner can be observed when B cells correspond to the stimuli along with identified transcription factors and enzymes. When the original stem cells are divided into two daughter cells, through asymmetrically distributed components and receptors, B cells pick up on environmental signals sent by antigen and T cells, which may then be used to control how the daughter cells differentiate.

6. Stem cells therapy in Alzheimer's disease

6.1. Neural Stem Cells therapy

The neural stem cell is a type of pluripotent stem cell that has great potential of becoming a successful treatment of Alzheimer's disease due to its capacity for differentiation into new neurons: astrocytes and oligodendrocytes. NSCs reside in specific niches including the subventricular zone (SVZ) that is located along the ependymal cell layer and subgranular zone (SGZ), the dentate gyrus of the hippocampus [27]. Loss and impairment of neurons are two main causes of Alzheimer's disease. Based on experimental research done on transgenic mice, survival, migration, and differentiation were observed on the NSCs transplanted transgenic models after the damaged neurons ablated [28]. Other researches based on transgenic animal models also prove that neural stem cell transplantation therapy illustrates substantial migration, significant engraftment, and even long-term survival [29].

6.2. Mesenchymal stem cells therapy

Mesenchymal stem cells (MSCs) are adult stem cells that can be obtained from multiple body tissues including bone marrow, adipose tissue, etc. MSCs therapy is also generally researched trials with 125 MSCs clinical trials have been registered to treat neurodegenerative diseases due to their antiapoptotic, paracrine, and multidirectional ability to differentiate. One of the essential causes of AD IS neuroinflammation, as well as aggregation of amyloid beta and neurofibrillary tangles. MSCs therapy was proven that it helps improve cognitive damage by decreasing and even getting rid of amyloid beta deposition inside the AD transgenic animals [30]. The same study showed that the AD patients' physical function and neuron functionality were improved after the MSCs transplantation. The transplantation also helped maintain and remodel the axons inside patients' neurons. Though MSCs is a relatively efficient therapy for AD, there is a risk that mesenchymal stem cell therapy can develop unwanted tissues and the growth and metastasis of tumor [31].

6.3. Embryonic Stem cells therapy

Embryonic stem cells are located in the bottom of the zygote as it went through the blastocyst stage. They are multipotent stem cells that can be derived into any type of specific cells hence they are ideal for researching stem cell therapy. Mouse embryonic stem cells are crucial for researching pluripotency as well as stem cell-based therapy due to their significant self-renewal capacity. Shows that human ESC transplantation might help repair cognitive damage since the stem cells are able to live and derive along neuronal lineages [32].

One of the reasons the development of ESCs therapy has been slowed down due the ethical dilemma involving whether is moral to destruct human embryos [33]. Besides, safety issues such as three-layered tumors and teratomas should also be taken into concern.

6.4. Induced pluripotent stem cells (iPSC) therapy

iPSCs therapy is considered a promising treatment of neurodegenerative diseases. iPSCs are genetically reprogrammed tissue-specified stem cells which have the same capacity as pluripotent stem cells. The reprogramming technique was first proven by Takahashi and Yamanaka in 2006 and it became widely used for researching cell transplantation therapy as well as disease modeling and drug screening [13]. As mentioned before, transcription factors determine a cell's pluripotency directly. iPSCs therapy introduces extra transcription factors, including c-Myc, Sox2, Oct3/4, and Klf4 to somatic stem cells [13]. Cultivation inside pluripotent stem cells was used to grow Embryoid bodies (EB) which is a common medium used to produce specific cell lineages of pluripotent stem cells [34]. After that, iPSCs can develop into a new differentiated cell such as motor neuron. The study also illustrates that iPSC can be produced from adult HDF (Human Dermal Fibroblasts), as well as other somatic cells such as human fibroblast-like synoviocytes (HFLS). What's more, the modified somatic cells turned out to show the same morphology and growth as ESC, as well as some cell marker genes as the researchers expected. Another study in an aged triple transgenic mouse model

which shows similar severe brain damage as AD patients display that neural precursors derived from iPSCs are able to improve AD patients' memory, as well as synaptic and pathological abnormalities [35]. A study done by Yahata and Asai illustrates that operative γ - and β -secretases are associated with the production of A β . the researchers also proved that the iPSCs technique can also be used for drug screening and AD patient-specific iPS cell research [36]. How iPSCs can be produced is shown in figure 2 [37]. Experimental research on human AP mice shows that transplantation of neuronal precursors of cholinergic neuron phenotype developed from iPS cells survived successfully in PDAPP mouse hippo campus and its spatial memory dysfunction got enhanced [38]. As materials mentioned above, iPSCs therapy has more potential to become a successful stem cell therapy compared to the other stem cell therapies since there are more successful researches. Besides, iPSCs therapy faces less ethical debate since it does not destruct embryos in comparison with ESCs therapy.

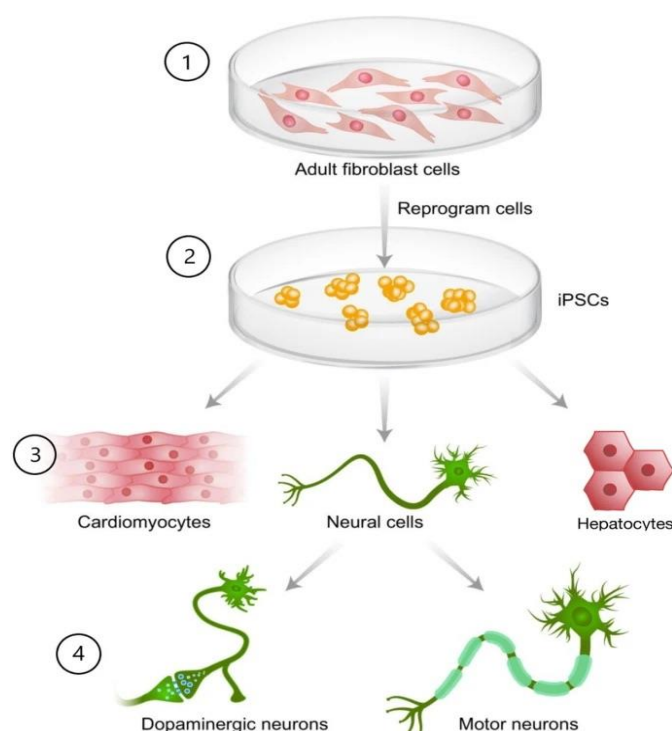


Fig 2. The figure shows how adult fibroblast cells developed into induced pluripotent stem cell through being introduced by transcription factors (Oct3/4, Klf4, c-Myc, and Sox2). Along with a certain differentiation medium, the reprogrammed pluripotent stem cells has the ability to grow into diverse cell type of body.

7. Future direction

As discussed in the article, studies show that stem cell therapies have great potential in treating AD disease and other neurodegenerative pathologies, as well as other diseases which require tissue transplantations. However, stem cell therapies for AD are yet a mature and applicable treatment since they have not been approved by FDA (The U.S. Food and Drug Administration) yet [39]. What's more, though some of the clinical trials worked successfully upon animal models, no stem cell therapy research succeeds in human trials so far. The different results in human and animal model research trials for AD might be due to the biological distinctions between transgenic animals and humans [5]. To address the issue, large animal models are suggested to be utilized since their physiological parameters such as immune system properties are more similar to the humans', compared to rodent animal models. Besides, large animals also have more various categories and bigger quantities of stem cells. Apart from the distinction between transgenic animal models and humans, the risks of the growth and metastasis of tumors should also be taken into concern [40]. Apart from that, Alzheimer's disease faces specific challenges since various kinds of brain cells are affected in several brain regions.

8. Conclusion

Alzheimer's disease is a serious neurological condition that slowly impairs patients' cognitive ability and memory while also accelerating their demise. AD patients are usually treated with medicines such as Tacrine and Donepezil that include Cholinesterase inhibitors in order to restore patients' cholinergic function. However, the current medical therapies are not able to heal the disease fundamentally, not to mention the risks of quite a few side effects. Due to stem cells' ability to differentiate into brain cells, it is regarded as an ideal material to treat AD since the cause of the disease is basically damaged brain cells. Among the stem cell therapies for AD, iPSC therapy, which was first introduced by Takahashi and Yamanaka in 2006 [13], is the stem cell therapy that is most likely to succeed based on several successful trials on transparent rodent animals. Nevertheless, stem cell therapy of AD is yet to succeed in human trials because of the structural distinction between humans and rodent animals. It is a treatment of modifying adult stem cells into a new stem cell that has the same capacities as embryonic stem cells without destructing embryos. Although the therapy illustrates a promising future for efficient treatments for Alzheimer's Disease, there are some problems needed to be solved further. Large animals such as domestic animals are suggested to replace rodent animals in stem cell therapy trials. Besides, more researches need to be done in order to lower the risk of cancer as well as tumor.

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