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# POTENTIAL AND LIMITATIONS OF USING STEM CELLS TO CURE ALZHEIMER'S DISEASE: A Literature Review of Its Potential and Ethical Limitations in Translation to Human Trials

By Eleni Zivla

**ABSTRACT**— Alzheimer's disease has become one of the most significant, life-limiting illnesses of our time as a result of the rapid increase in the average life expectancy. To successfully develop a cure for this yet incurable disease, one must understand the pathology of Alzheimer's disease. As found in recent research studies, a brain that is diagnosed with Alzheimer's is characterized by the presence of extracellular amyloid plaques composed of the amyloid-beta (A $\beta$ ) peptide and intracellular neurofibrillary tangles composed of the microtubule-associated protein: tau. In this literature review, several stem cell therapies are being reviewed as a potential cure for Alzheimer's disease based on recent studies. Both iPSCs (Induced Pluripotent Stem Cells) and mesenchymal stem cells (MSCs) hold great potential, with the latter having progressed to human clinical trials. However, due to discrepancies in translation from animal to human studies, stem cell therapy remains under development. Ethically, the project raises serious questions about the morality of genetic engineering which limits the usage of stem cells in curing not only Alzheimer's disease but many other neurodegenerative diseases.

Keywords: Alzheimer's disease, iPSCs, Neuroscience, Stem Cells, Bioethics

## I. PATHOLOGY OF ALZHEIMER'S DISEASE

The "baby boomer" generation, which refers to people born between the end of World War II (1946) and the mid-1960s (1964), is quickly increasing the number of senior citizens as the average human lifespan has doubled in the last century due to the deceleration of late-life mortality rates.<sup>1,2</sup> This trend can be attributed to easier and quicker access to healthcare such as doctors, drugs, and vaccines. Since aging is the main risk factor for Alzheimer's, as the population continues to age without reproducing, the chance of Alzheimer's disease rises dramatically.<sup>3</sup> This places a considerable burden on not just those who are suffering from Alzheimer's but also their caretakers and family members.<sup>4</sup> It has been estimated that in 2022 approximately 6.46 million Americans over the age of 65 have clinical Alzheimer's disease with

a 95% confidence interval.<sup>5</sup> When the rest of the world is taken into account, the figures skyrocket – making Alzheimer's disease one of the most common mental illnesses worldwide.

To successfully develop a cure, the pathology of Alzheimer's disease must be fully understood and taken into consideration.<sup>6</sup> Although some medications have been introduced to the market to deal with memory and thinking impairment that occur in the early stages of Alzheimer's disease, there is presently no cure. Finding a cure for this disease, which is still incurable, is critical and could potentially change the lives of millions of people in the present and future. A panoramic view of the condition is presented in this literature review as well as an evaluation of a prospective treatment, its limitations, and the bioethical issues surrounding it which prevent its advancement to human trials.

The pathology of Alzheimer's disease is extremely varied; however, four main features have been recognized over the years. Tau, a microtubule-associated protein, becomes hyperphosphorylated, leading its microtubules to disintegrate and clump together to form neurofibrillary tangles (NFTs) – a characteristic feature seen in Alzheimer's disease patients' brains.<sup>7</sup> According to one study, NFTs are responsible for less than 17.5% (2.2-17.2%, mean 8.1%) of neuron loss in the CA1 region of the hippocampus observed in Alzheimer's disease.<sup>8</sup>  $\beta$ - and  $\gamma$ - secretase enzymes cleave the amyloid beta precursor protein (APP) which unavoidably leads to a collective increase of  $A\beta$  amyloid protein fragments that form the characteristic amyloid plaques found in Alzheimer's disease patients.<sup>3</sup> Findings have indicated that amyloid plaques are responsible for the advancement of Alzheimer's disease.<sup>9</sup> The presence of NFTs and amyloid plaques is required for the diagnosis of Alzheimer's disease.<sup>10</sup> The decrease in activated microglia in the brain, which produce cytokines such as tumor necrosis factor (TNF)-, interleukin (IL)-1, and nitric oxide (NO), which may promote or relieve

neuroinflammation, is a key feature of Alzheimer's disease.<sup>3,11</sup> The last major characteristic of Alzheimer's disease is mass neuronal and synaptic loss, which is the most closely linked to cognitive decline in the early stages of the disease.<sup>3</sup> Scientists have sought to reduce amyloid plaques by inhibiting the  $\beta$ - and  $\gamma$ - secretase enzymes using pharmaceutical techniques; however, when the methodology is translated into human clinical trials, various issues arise.<sup>3,12</sup>

Initially, the atrophy of the entorhinal cortex, the subiculum and CA1 hippocampal subregion and basal forebrain networks lead to verbal episodic memory deficits in Alzheimer's patients.<sup>13</sup> As a result, the temporal lobes deteriorate impacting the majority of cortical layers. Although stem cell therapy has appeared to be promising, there must be a focus on a specific subgroup of patients to be successful. This limits its use as a general approach in curing not only Alzheimer's disease but also many other neurodegenerative diseases such as Parkinson's and Huntington's disease.

It has been noted that adult hippocampal neurogenesis may help reverse the amnesia occurring in the early stages of Alzheimer's. One strategy that has been reported is to increase the levels of growth factors including brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), nerve growth factor (NGF), and vascular endothelial growth factor (VEGF), all of which are known to promote neurogenesis.<sup>3</sup> This process, however, is extremely challenging not only because the rate of neurogenesis in the hippocampus diminishes with age, but also because a patient with Alzheimer's loses a significant number of hippocampal neurons over a short period of time.<sup>14</sup> At the time of writing, endogenous neural regeneration techniques appear to be ineffective.

## II. STEM CELL THERAPY

In recent years, many scientists have concluded that the most promising approach in treating Alzheimer's disease is stem cell therapy. Embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), brain-derived neural stem cells (NSCs), and induced pluripotent stem cells (iPSCs) are the most widely utilized types of stem cells when conducting Alzheimer's disease research.<sup>3</sup> The selection of the proper cell source is a crucial step in the development of any stem cell therapy as each class of stem cells is appropriate for therapeutic restoration through different approaches.<sup>3</sup> The most suitable research tool to treat Alzheimer's disease at this time is iPSCs, which are produced by somatic cells with the capacity to proliferate.<sup>15</sup> Drug screening, treatment development, and disease modeling can all benefit from the application of iPSCs.<sup>16</sup>

Although some ESCs studies have shown promising results in restoring cognition in rodent models of brain injury, translation to clinical human trials has been limited due to the procedure's enhanced risk of tumor formation and growth.<sup>9</sup> When employing allogeneic donor cells for a stem cell transplant, many immunogenic issues arise making clinical translation of ESC-based therapies impractical.<sup>3</sup> The NAS Guidelines for Human Embryonic Stem Cell Research address ESCs research and recommend the establishment of embryonic stem cell research oversight committees (ESCROs) to assist in review of research design involving ESCs.<sup>18,19</sup>

At the time of writing, there is a heated debate in the United States about when human life begins as states are looking to restrict abortion.<sup>20</sup> As ESCs studies involve the destruction of human embryos there is an ethical debate about whether the embryos should be used in stem cell research, therefore restricting their usage and limiting their potential in scientific studies. Due to this controversy researchers have been looking for an alternative stem cell source that is more

ethically acceptable than ESCs.

NSCs have been observed to have paracrine effects which appear to be promising.<sup>21</sup> A considerable increase in neurogenesis and cognition, as well as a decrease in neuroinflammation, was reported in a rodent Alzheimer's disease model and an aged primate brain when NSCs were introduced.<sup>1</sup> It is hypothesized that this is caused by the paracrine abilities and direct neuronal differentiation of NSCs.<sup>22</sup> However, the exact mechanisms behind these changes are not completely understood and additional research is required.<sup>21</sup> The difficulty in producing non-neuronal glial cell types from stem cells limits the utilization of NSCs in research.<sup>23</sup>

MSCs are easier to study than the other two stem cell types mentioned above due to their ability to differentiate into multiple neural cell types. In studies involving rodent models MSCs, an increase in acetylcholine, BDNF, and NGF concentrations was observed which lead to improvement of cognitive function.<sup>24</sup> In rodent Alzheimer's disease models, it has been reported that MSCs appear to inhibit A $\beta$ - and tau-, thus reducing plaque formation and inducing neurogenesis. MSCs are capable of crossing the blood-brain barrier (BBB) and effectively migrate to areas with neural damage without triggering an immune response which ensures the safety of patients.<sup>25</sup> For this reason, MSCs are the only stem cells thus far that have actually progressed to human clinical trials.<sup>3,26</sup>

### **III. INDUCED PLURIPOTENT STEM CELLS**

Since the derivation of iPSCs does not necessitate the destruction of embryos unlike ESCs, there are less ethical debates regarding their usage.<sup>20,27</sup> iPSC-derived neurons offer a profound new perspective on research involving dementia. iPSCs offer a limitless supply of human neurons that

are electrically active and imitate the cell type that has been observed to degenerate early in Alzheimer's disease.<sup>28</sup> iPSC-derived neurons are structurally and functionally mature and capable of forming electrophysiologically active synaptic networks which offers significant benefits when used in research.<sup>29,30</sup> For the first time, scientists have been able to model the disease in cells taken directly from patients using iPSCs.<sup>28,31</sup> The expeditious development of iPSCs technology encourages the application of iPSCs in the research of neurodegenerative diseases such as Alzheimer's as it eliminates the risk of the immune system rejecting the cells.

Although iPSCs carry enormous promise, their application in real-life conditions remains under development due to the inconsistencies in preclinical studies that prevent transitioning to human clinical trials. Both the scientific community and the general public are concerned about the usage of stem cells in humans, with the scientific community divided on the matter. Scientists need to develop a clear set of principles for genetic engineering involving stem cells to deal with both the medical opportunities and ethical dilemmas posed by using stem cells to cure Alzheimer's disease. These standards must be recognized internationally and followed by every research facility that uses stem cells of any kind. For brain disorders, where tissue from patients is beyond reach, iPSCs therapy offers the opportunity to study neural pathology as it develops in brain cells.

#### **IV. OBSTACLES IN USING STEM CELL THERAPY ON HUMAN SUBJECTS**

Stem cells may hold the secret to curing neurological diseases like Alzheimer's. Unfortunately, despite the superior technologies at our disposal, modeling via this approach remains difficult as inconsistencies in preclinical research have prevented several promising stem cell therapies from progressing to human clinical trials. Some claim there is evidence for the safety and efficacy of

stem cell-based therapies in animal models, which have provided the foundations to support the approval of several human clinical trials. Although rodents and mice are physiologically and genetically close to humans and have been favored in disease modeling, scientists must be mindful when designing and developing experiments involving stem cells due to their complex nature.<sup>32,33</sup>

Researchers often disagree over the precise limits of stem cells therapy debating whether the clinical studies should involve humans or only animal subjects. Preclinical studies suggest that stem cells have the potential for the treatment of Alzheimer's disease; however, this area is notable for the poor translation between animal studies and human trials. Indeed, researchers have effectively treated Alzheimer's in transgenic mouse models in more than 50 different ways.<sup>3,34</sup> However, the fact that transgenic models are based on genetic Alzheimer's disease in a genetically homogeneous population – while the vast majority of human Alzheimer's disease occurs in a genetically heterogeneous population – is one of the main reasons for the failure of translation between animal and human experiments.<sup>3</sup> Because the effect of iPSCs in humans is unpredictable, the translational process is challenging in the absence of reliable animal models.<sup>18</sup> Although iPSCs could serve as a promising avenue for disease modeling, the molecular principles for this technique, particularly in human cells, still remain poorly understood due to donor-to-donor variability and intercellular heterogeneity.<sup>31</sup>

Every researcher that works with human and animal subjects is obligated to follow a strict set of ethical guidelines. When human subjects are involved the Belmont report written by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research must be followed.<sup>35,36</sup> Respect for persons, justice and beneficence are the three main ethical values emphasized in the Belmont Report. Respect for people is the right of competent

individuals to make reliable judgments about their own lives, whereas justice is the fair distribution of benefits from research.<sup>36</sup> The Belmont Report also condenses beneficence to maximizing the benefits while limiting the risks and not causing harm.

Significant ethical issues must also be considered when conducting Alzheimer's disease research, as discussed throughout this literature review. These issues, if not addressed carefully, could become major obstacles preventing research. The main ethical question to consider is whether large groups of human subjects must be recruited for a single experiment. These are lengthy investigations that will almost certainly result in the death of the subjects.<sup>37</sup> As research participants' cognitive abilities deteriorate due to Alzheimer's disease, researchers must seek informed consent after receiving approval from the research facility's respective institutional review board (IRB).<sup>38</sup> Participants in early phase I clinical trials should be competent enough to give consent in order to progress to the next phase.<sup>37</sup>

Clinical studies employing stem cells should adhere to stringent ethical criteria and researchers must ensure that participants are fully aware of the study's major aspects and the risk-benefit ratio.<sup>20,39</sup> Informed consent relies on autonomy, which must be respected in research. This means that participants are free to leave the study at any time. Because subjects must be studied continuously and consistently until the study is completed, if participants choose to leave, it can hinder the research progress. To maintain the public's trust in the scientific community, research involving human beings must be handled with utmost care and responsibility towards the subjects.

## V. THE FUTURE OF STEM CELLS

Stem cell therapy, like any other scientific breakthrough, must be closely monitored and studied until experts deem it safe and commercially viable. Even after stem cell therapy becomes widely available hopefully in the near future, there will be many skeptics, as demonstrated by the COVID-19 pandemic, which resulted in an exponential rise in science skepticism.<sup>40</sup> Although there are major ethical and practical challenges that stem cell therapy must face before it can be used to treat neurodegenerative diseases such as Alzheimer's, scientists are hopeful about its potential.<sup>41</sup> Several concerns and challenges including long-term safety, the optimum cell source, and the transportation mechanism to the target cells have been highlighted across literature and should be addressed and discussed moving forward.<sup>3</sup> There are great advancements happening every day in the field of stem cells, and some stem-cell based therapies are already utilized to treat diseases. Unrelated donors' hematopoietic stem cells (HSCs) were successfully transplanted into leukemia patients, for the first time 42 years ago and this therapy has subsequently saved millions of lives since then.<sup>42,43</sup>

Although the outcomes of research which employs various types of stem cells have been inconsistent, they are encouraging, and stem cell therapy may be utilized to treat a variety of neurodegenerative diseases in the near future.<sup>44</sup> While stem cell therapy may not yet be able to stop or reverse the mass neuronal loss, it may be able to temporarily protect the remaining healthy nerve cells allowing them to maintain physiological function and increase survival rate.<sup>31,45</sup> Because of the nature and variety of stem cells, developing strategies that can be used for a wide range of stem cells may be difficult, as some are more challenging to proliferate and differentiate than others.<sup>41</sup>

## VI. CONCLUSION

Summarizing the information studied, it can be declared that iPSCs technology offers a new method of studying the human brain and its pathologies with exciting implications for basic research. Although this technology has great potential in terms of developing a cure, one cannot help but have reservations about it as there is currently no evidence that guarantees its efficacy on human subjects. The transition from animal to human trials is difficult due to a lack of reliable evidence from human studies. Undoubtedly, to find an effective treatment, human subjects should be used in this kind of research instead of animals. According to recent studies, researchers have successfully treated Alzheimer's disease in transgenic mouse models but none of these methods appeared to give effective enough results for the experiments to be translated into human trials.<sup>3,46</sup> While there are ethical guidelines in place for human and animal research, such as the Belmont report, there are no strict principles in place for genetic engineering, which raises fundamental concerns about its morality.

Despite these issues, MSCs-based studies have been the most consistent and are the only ones that have advanced to human clinical trials.<sup>3</sup> It is important in the future that researchers not only take into consideration the immense differences between rodents and humans but also attempt to employ efficient transitional models to close the gap between the two.<sup>1</sup> There is hope in linking stem cells and Alzheimer's disease as stem cells could potentially induce regeneration of neurons and synapses, prevent activation of inflammation which causes neuron destruction, promote activation of anti-inflammatory cells, and increase degradation of accumulations of proteins.<sup>3</sup>

With the rapidly advancing technology, scientists are optimistic that they will find a cure for Alzheimer's in the future. The mechanisms behind stem cells are poorly understood and a

cautious approach is recommended by scientists as it could potentially reduce patient morbidity and mortality rates.<sup>47</sup> Before considering commercializing this technology, more research with human subjects is essential, but the ethical concerns surrounding stem cells become a difficult obstacle to overcome thus limiting its potential.<sup>18,48</sup>

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