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Research Article

Nanotherapeutic and stem cell therapeutic strategies in neurodegenerative diseases

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Abstract

In Neurodegenerative diseases the central or peripheral nerve systems gradually stop to perform proper functions. The treatments available are only help to relieve some physical or mental symptoms associated with these disorders. Due to its relatively extended duration, neurodegenerative disorders have become a major burden on families and society. Alzheimer´s disease, Parkinson´s disease (PD), and Huntington´s disease (HD) are examples of neurodegenerative disorders that are either incurable or extremely difficult to treat. Therefore, new therapies are sought in which autologous stem cells are used. Stem cell therapy produces positive outcomes through a variety of pathways, including the direct replacement of lost or injured cells, the production of neurotrophic and growth factors and the stimulation of endogenous stem cells. However, low rates of stem cells differentiation and survival prevent them from being used in more therapeutic settings. Numerous intriguing nanomaterials for biomedical applications have been made possible by the quick development of nanotechnology. These materials are already widely used in the treatment of neurodegenerative diseases and appear to be able to make up for some of the shortcomings in stem cell therapy. Thus, a viable therapeutic method to treat neurodegenerative disorders is the combination of stem cell therapy and nanotherapeutic technologies.

Keywords:
Neurodegenerative diseases, Autologous Stem cells, Nanotherapeutic technologies.

1. Introduction

Neurodegenerative diseases involve the progressive neuronal loss and degeneration, development of disease-specific misfolded proteins, and finally the cognitive and sensory impairment. These comprises of multiple system atrophy (MSA), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Parkinson's disease (PD), and Alzheimer?s disease [1]. The incidence of neurodegenerative diseases increases with age, and the incidence of sports-related traumatic brain injuries increases with time. Currently approved drugs for neurodegenerative diseases only temporarily reduce symptoms, but do not cure or slow the progression of the disease [2]. The lack of effective treatments causes a significant burden on society and large economic impacts. Regenerative cell therapy, sometimes referred to as stem cell therapy, has offered a great chance to investigate novel approaches that may be successful in treating neurodegenerative disorders over the past 20 years. This is because stem cells have the capacity to repair damaged nerve tissue by replacing damaged or lost cells with differentiated cells, providing a favorable environment that supports regeneration, or protecting existing healthy neurons and glial cells from additional damage. The possibilities of stem cell therapy for neurodegenerative diseases were first explored in the 1980s when PD patients were treated with fetal mesencephalic tissue transplantation. Today, stem cell therapy offers promising strategies for the treatment of almost all neurodegenerative disorders. These strategies include regeneration of neural tissue, stabilization of neuronal networks, provision of neurotrophic support, and mitigation of neurodegeneration at the levels of different neuronal circuits [3]. For these debilitating neurological diseases, nanotechnology has shown great promise in overcoming the challenges presented by conventional therapies and promises revolutionary breakthroughs in their treatment. Quantum dots, polymer nanoparticles, carbon nanotubes, gold nanoparticles, liposomes, micelles, and fullerenes are some examples of the many nanoscale materials that have been developed and used in everything from advanced diagnostics to the delivery of neurotherapeutic agents and the evaluation of treatment efficacy. These nanomaterials can overcome such barriers, target a specific cell or signaling pathway, respond to body stimuli, transport genes

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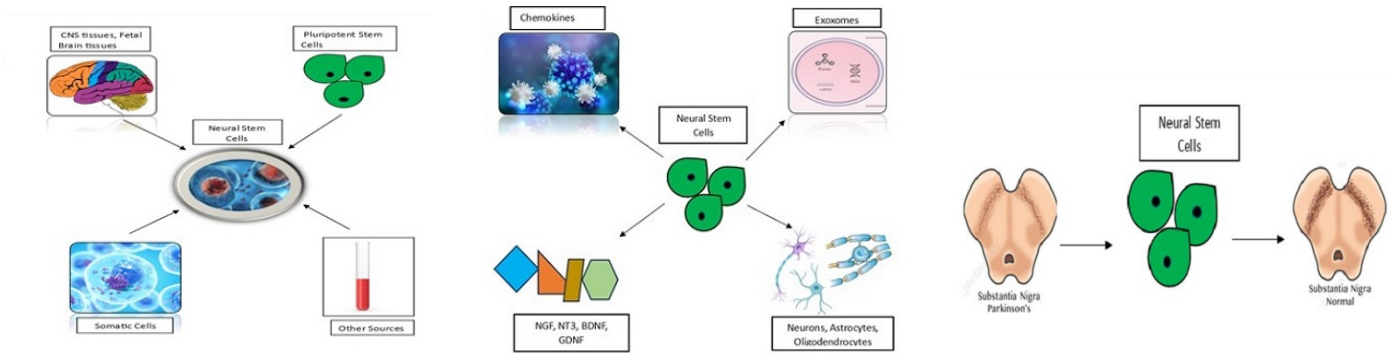
and promote nerve regeneration. Treatment of neurodegenerative diseases may become possible using effective drug delivery methods such as these frameworks. Medicines encapsulated in nanomaterials have been found to treat diseases better than bulk materials used in traditional therapies. Thus, combining stem cell and nanotherapeutic approaches can enhance the treatment of neurodegenerative disorders and produce better clinical outcomes .

2. Stem cell therapy for parkinson disease

Parkinson's disease (PD) is the second most common neurological disease with a global prevalence of over 6 million for which there is yet no effective treatment available. It is predicted that during the next generation, the prevalence of Parkinson's disease would double. About 5% of those over 85 have Parkinson's disease (PD), as it is an age-related disorder. Alpha-synuclein (α-Syn) in the substantia nigra (SN) is the primary component of Lewy bodies (LBs), which are dopaminergic neurons that die in Parkinson's disease (PD). Because of the specific loss of dopaminergic neurons in the substantia nigra, Parkinson disease (PD) has long been regarded as one of the most promising disorders for cell replacement therapy. Over time, the idea of using stem cells to treat neurodegenerative disorders has changed, and it has recently advanced rapidly [4]. The most effective therapy for PD symptoms is dopamine replacement therapy (DRT). However, compensatory mechanisms for denervation alter and delay the relieving effect of DRT in a nonlinear way as the disease progresses. Additionally, surgical techniques such as deep brain stimulation and stereotactic ablations are used. However, in advanced Parkinson's disease patients, these methods only partially relieve the severe motor symptoms and DAergic desensitization that supports DRT. But neither surgical technique ends up being the main treatment. Early in the preclinical stage of research, scientists aimed to create a cell-based treatment using fetal ventral mesencephalon (fVM). Research on animals, which took place between 1977 and 1985, produced very positive outcomes using the 6-OHDA or MPTP lesion structure. either fetal tissue from humans or mice. The transplanted cells flourished in the damaged location, demonstrating the remarkable brain plasticity. Based on these findings, researchers have carried out a number of clinical experiments since 1987. The first trial involved a transplant carried out in Sweden, a nation that has an open stance regarding embryonic research. A wide range of open label trials and double-blind placebo-controlled trials conducted between 1987 and 2003 demonstrated that, generally, fVM transplantation was only slightly effective in relieving tremor in the majority of patients. But for a small percentage of patients, the procedure resulted failed to provide a quantifiable benefit. A wide variety of stem cells appears to be more promising and more probable to be created on a big scale when compared to fVM. More researchers are experimenting with stem cells in Parkinson's disease (PD) clinical trials, encouraged by evolving and improving technologies for cell derivation and differentiation. Benefits from stem cells include the ability to self-renew and their versatility in producing a wide range of tissues. So, they are suitable substitutes for impaired nonrenewable neurons, particularly in the treatment of Parkinson's disease. In classical biology, stem cells are classified as either adult stem cells or ESCs based on their state of development. Additionally, stem cells can be divided into totipotent, pluripotent, and unipotent groups based on their level of developmental potential. The three main types of stem cells utilized to treat Parkinson's disease are neural stem cells (NSCs), mesenchymal stem and iPSCs. Neural stem cells (NSCs) are present in some regions of the human brain and persist throughout life. are present in two distinct brain regions and are present in both developing embryonic brain and the adult nervous system during human life. (Figure 1a) Under the normal conditions CNS Possess the capacity to be self-renew and differentiate into neurons, astrocytes, or oligodendroglia are in charge of restoring brain function .One potential alternative treatment for Parkinson's disease is the regeneration of dopaminergic neurons from stem cells. NSCs are a crucial component of the central nervous system (CNS). Adult endogenous NSCs are abundant in the lateral wall of the subventricular zone and the sub granular region of the dentate gyrus. These cells play a significant role in the central nervous system (CNS), helping to maintain the cell pool of neural tissues. A few essential characteristics of these cells are self-renewal, proliferation, and multipotency. NSCs may replace the lost DAergic neurons in Parkinson's disease (PD) by differentiating into neurons, astrocytes, or oligodendrocytes. Furthermore, because NSCs may move close to the site of damage to boost neuroblasts and aid in tissue healing, they can support endogenous repair mechanisms. NSCs can limit T cell proliferation and secrete cytokines, chemokines, and chemokine receptors, among other immunomodulatory actions [5] (Figure 1b).

Numerous preclinical investigations have demonstrated that many human NSC subtypes have the ability to move, survive, and multiply in particular brain regions following transplantation (Figure 1c). NSCs are involved in antiapoptotic, anti-inflammatory, and antioxidant brain repair processes.

The possibility that the transplanted human NSCs could be develop into functioning neurons and integrate into brain circuits is supported by immunohistochemical analyses. It has been shown through in vivo research that NSC transplantation is a successful PD treatment strategy. Compared to embryonic stem cells, MSCs have a number of benefits, such as a lesser immunological response, a decreased chance of tumor formation, and no ethical issues because they are adult stem cells with the ability to paracrine, immune control, and multidirectional differentiation. Since the identification of MSCs' immunomodulatory capabilities, further investigation has been conducted into the connection between inflammatory processes and MSCs. Evidence suggests that MSCs can use chemotaxis to migrate to the location of an inflammatory response. Once there, they can inhibit certain chemotaxis recruitment responses, which in turn lowers the inflammatory response in the damaged area and aids in tissue repair. Numerous autoimmune-related neurodegenerative and neuroinflammatory disorders, such as Parkinson's disease, Alzheimer's disease, multiple system atrophy, and amyotrophic lateral sclerosis, have been treated with



(a) Different Sources of Neural Stem Cells

(b) Immunomodulatory and paracrine effects of NSCs

(c) NSCs after transplantation, could migrate, survive, and proliferate in specific brain sites

Figure 1

MSC-based cell treatments. The different multi-target disease modifying therapies of therapies of MSCs modulates α-Syn in PD is shown in Table 1.

3. Nanotherapeutic and stem cells based strategies for alzheimer´s disease

Alzheimer Disease (AD) is the most common kind of dementia, affecting about 35 million individuals worldwide and exhibiting an upward trend. Unfortunately, no treatment strategies or preventative measures are now available for this progressive neurological condition. Since its first published description in 1907, tremendous progress has been made in understanding the molecular processes causing AD. Alzheimer's disease is characterized by the development of extracellular amyloid plaques, predominantly consisting of amyloid-β (Aβ), and intracellular neuro fibrillar tangles created by hyperphosphorylated tau proteins. These are both major clinical markers in the brains of AD patients. Clinical experiments aimed at treating Alzheimer's disease, including A production and aggregation, have had minimal effectiveness. AD is one of roughly 40 amyloidosis, defined by the abnormal deposition of endogenous proteins as amyloid fibrils. It remains a complicated central nervous system condition with no known treatment. The protective blood-brain and blood-cerebrospinal fluid barriers complicate the treatment of Alzheimer disease, limiting the efficacy of several therapeutic treatments. However, the developing science of nanomedicine provides a potential approach to Alzheimer's disease diagnostics and therapy. Recent advances in nanomedicine have allowed for successful medication delivery to the brain, surpassing earlier hurdles. However, challenges remain in translating these advances into viable clinical applications for Alzheimer's disease therapy [6]. In the larger context of central nervous system (CNS) illnesses, NDs such as Alzheimer's disease, Parkinson's disease, epilepsy, and others contribute considerably to worldwide morbidity and mortality. According to recent forecasts, 416 million people are affected by Alzheimer's disease, emphasizing the need for improved treatments. Despite the well-known neuronal features of Alzheimer's disease, existing therapies only give brief respite, and medications aimed at cognitive deficiencies encounter problems such as poor solubility, limited bioavailability, and hurdles along the drug delivery route. Nanotechnology-based platforms, such as polymeric NPs, dendrimers, and lipid-based NPs, provide potential alternatives for drug administration across the blood-brain barrier.

3.1. Nanotherapeutic Strategies

In recent years, nanotherapeutic techniques have emerged as viable options for diagnosing and treating Alzheimer´s disease (AD). This article investigates several nanomaterials and their uses in Alzheimer´s disease therapy, with an emphasis on medication transport, protein misfolding and aggregation, imaging, and diagnostic techniques. One of the most significant obstacles in AD therapy is the low permeability of substances via the BBB [7]. Nanomaterials act as efficient transporters for medications, genes, and cells, providing a solution to this problem. Functionalized targeting ligands, such as RGD peptides and transferrin, improve the targeting specificity of nanocarriers, enabling intelligent drug delivery systems. Furthermore, nanocarriers can provide regulated medication release by self-degradation or external stimulation, reducing drug dose while increasing effectiveness.

Here some organic nanoparticles used in Alzheimer's drug delivery: Liposomes the small vesicular structures comprised of lipid bilayers, play a significant role in Alzheimer's drug delivery. Their unique self-assembling and amphiphilic properties have led to FDA approval, establishing their effectiveness as drug carriers. A major advantage is their versatility, enabling the encapsulation of both hydrophobic and hydrophilic compounds within their lipid layers. Polyethylene glycol (PEG)-coated liposomes have shown impressive abilities in evading the reticuloendothelial system (RES). This evasion is essential for ensuring prolonged circulation in the bloodstream, thereby increasing the likelihood of drug transport across the blood-brain barrier (BBB). PEGylation enhances the stealthiness of liposomes, preventing undesired clearance by the immune system and facilitating targeted delivery to the brain [8]. Alzheimer's

drug delivery has seen significant advancements with the introduction of glutathione-PEGylated liposomes. These liposomes utilize the unique properties of glutathione to efficiently navigate through the cellular environment, resulting in enhanced cellular uptake across the blood-brain barrier (BBB). This innovative approach not only overcomes the challenges associated with selective permeability but also facilitates the targeted delivery of therapeutic agents. Liposomal drug delivery has already demonstrated successful applications in Alzheimer's treatment. Specifically, tailored liposomal formulations have been utilized to effectively deliver therapeutic agents such as coenzyme Q and nerve growth factor (NGF). For instance, coenzyme Q has been successfully delivered using chitosan-conjugated polylactide-polyglycolide (PLGA) nanoparticles. The conjugation with chitosan enhances the interaction of liposomes with biological systems, ensuring efficient drug transport. This highlights the potential of organic nanoparticles, particularly liposomes, as carriers for crucial Alzheimer's therapeutics[8]. In another significant application, polysorbate 80-coated polybutyl cyanoacrylate (PBCA) liposomes have been employed for the delivery of NGF. The surface modulation with polysorbate 80 improves the ability of liposomes to traverse biological barriers, underscoring the versatility and adaptability of liposomal formulations for targeted drug transport. Polymeric nanoparticles (NPs), such as PLGA and PAMAM dendrimers, have emerged as adaptable instruments for personalized drug administration in the setting of Alzheimer's disease. Poly (lactic-co-glycolic acid) (PLGA) nanoparticles, when selectively functionalized with chitosan, demonstrate a novel strategy to Alzheimer's medication delivery. This alteration allows for efficient adsorption-mediated endocytosis across the blood-brain barrier (BBB). Chitosan, a natural polysaccharide, improves the interaction of PLGA NPs with cellular components, resulting in effective drug delivery. This technique demonstrates the versatility of polymeric nanoparticles in overcoming biological barriers for targeted medication delivery. Polyamidoamine (PAMAM) dendrimers with biocompatible hydroxyl groups offer a paradigm change in reducing invasiveness while increasing drug movement across the BBB. This breakthrough minimises damage to biological processes while efficiently conveying medicinal effects. While cationic amine group dendrimers have showed promise in drug delivery, worries about their possible toxicity have led researchers to investigate biocompatible alternatives. The search for safer dendrimeric structures demonstrates a dedication to improving medication carriers for Alzheimer's treatment. This emphasis on biocompatibility reflects continuous attempts to assure the safety and efficacy of polymeric nanoparticles in therapeutic settings. Carbon nanotubes (CNTs), known for their hydrophobic nature, are coated with chemical conjugates or hydrophilic biological molecules to improve their stability and functioning. Multi-walled carbon nanotubes functionalized with amine groups (MWCNTs-NH3+) offer an appealing method for crossing the BBB via transcytosis. This method produces good results in both in vitro and in vivo experiments, establishing carbon nanotubes as a feasible inorganic carrier for Alzheimer's medication delivery. Gold nanoparticles (AuNPs), especially when coupled with wheat germ agglutinin horseradish peroxidase (WGA-HRP), are effective at transporting medications over the BBB by intramuscular injection. This novel use of gold nanoparticles demonstrates their promise as efficient carriers for tailored medication delivery to particular brain areas. Inorganic nanoparticles, notably gold-based structures, provide alternate and promising approaches to circumventing BBB problems in Alzheimer's therapy[8].

The use of polymeric and inorganic nanoparticles represents a comprehensive approach to Alzheimer's medication delivery. These improvements, which range from modifying polymeric carriers for increased specificity to harnessing unique features of inorganic structures, highlight the changing landscape of nanotherapeutic techniques for tackling the intricacies of neurodegenerative illnesses. The blood-brain barrier (BBB) is a severe barrier to effective medication delivery to the brain, demanding novel nanotherapeutic approaches. Various ways have been taken to improve medication distribution across the BBB, resulting in a complex and dynamic environment in the search for successful Alzheimer's disease treatment. Lipophilic nanoparticles (NPs) serve an important role in improving medication delivery across the BBB. This is accomplished by endocytosis or lipophilic transcellular routes, which take advantage of the BBB's selective permeability. [18] The adsorptive characteristic of NPs towards blood capillaries provides long-term release, enhancing the chance of effective drug delivery. This technique emphasizes the need of designing nanocarriers to capitalize on lipophilic interactions for effective BBB penetration.

Liposomes, as flexible nanocarriers, may be efficiently functionalized and surface-modulated to improve medication delivery to the brain. Researchers use polyether, functional proteins, and cell-penetrating peptides (CPPs) to increase liposome interaction with the BBB. Polyethylene glycol (PEG) coating and glutathione-PEGylation appear as important strategies for improving cellular absorption and overcoming possible hurdles. [17] The capacity to change liposomal surfaces demonstrates the versatility of organic nanocarriers in crossing the BBB. Functionalized nanocarriers serve an important role in initiating receptor-mediated transcytosis and carrier protein-mediated transport of therapeutic candidates across the BBB. Cell-penetrating peptides (CPPs), such as SynB and Angiopeps, act as molecular facilitators in this process. These peptides allow small molecule medications to cross the BBB, bypassing its barriers. Recently, graphene quantum dots (GQDs) have been explored, which work as a carrier for the drug molecule and, due to their tiny size, may easily carry it into the brain. Specifically, ctGQDs were able to cross the BBB due to their tiny size and were helpful in lowering Alzheimer-like symptoms in animals. After successfully crossing the BBB, nanocarriers face the issue of targeted medication delivery inside the complex milieu of the brain. Various solutions have been used to overcome this challenge: Certain nanocarriers, such as phospholipid complexes, show a propensity for inflammatory areas in the brain. This focused method guarantees that drugs reach particular areas linked with Alzheimer's disease. The capacity of nanocarriers to selectively target inflammatory indicators demonstrates a sophisticated grasp of disease-specific microenvironments. Nanocarriers can be coated with neutral zwitterions to reduce the non-

targeted interactions and increase target specificity. This change adds a protective layer, reducing unwanted interactions and providing more regulated medication administration. The use of the zwitterionic coatings appears to be a potential approach for the optimizing nanocarrier behavior after the BBB crossing.

Modifying coronated nanocarriers further refines medication delivery to particular sites. Tailoring the surface characteristics of nanocarriers after protein corona creation enables precise targeting. This dynamic approach reflects continuing attempts to tailor nanotherapeutics to recognized interactions and limitations in the brain's complex milieu. Finally, nanotherapeutic treatments for Alzheimer's disease use a comprehensive strategy, using both organic and inorganic nanocarriers. From using liposomes and polymers to investigating the possibilities of carbon nanotubes and gold nanoparticles, each nanomaterial has various benefits in overcoming BBB barriers. Ongoing nanotherapeutics research not only addresses the obstacles of BBB penetration, but also seeks to improve post-BBB crossing behaviors, with the potential to revolutionize Alzheimer´s treatment. Nanotherapeutic techniques dynamic and developing character makes them critical actors in the search for more effective and focused remedies to neurodegenerative disorders.

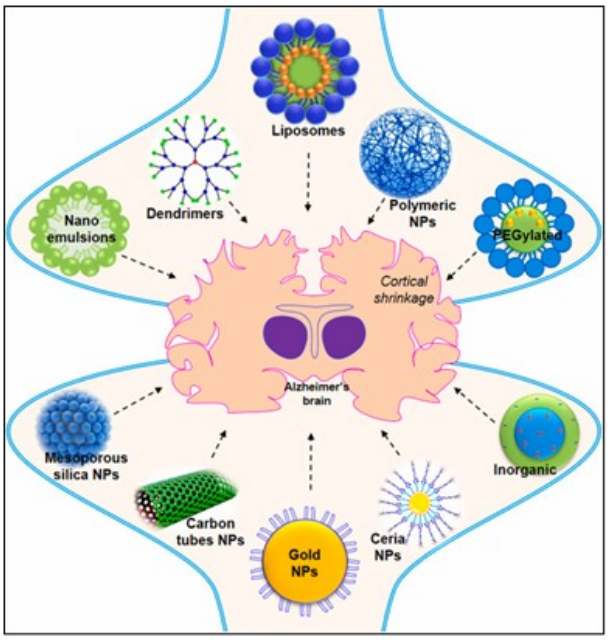


Figure 2: Various nanomaterials for treatment of Alzheimer´s Disease

3.2. *Stem cell based therapeutic strategies*

Alzheimer's disease (AD) is a major global health concern, characterized by gradual cognitive loss and memory impairment. Traditional therapies have frequently focused on symptom management, but recent advancements in stem cell research provide intriguing pathways for new therapeutic techniques. This paper investigates the many techniques utilizing neural stem cells (NSCs), multipotent stem cells (MSCs), pluripotent stem cells (PSCs), and the use of functional biomaterials in AD therapy [9].

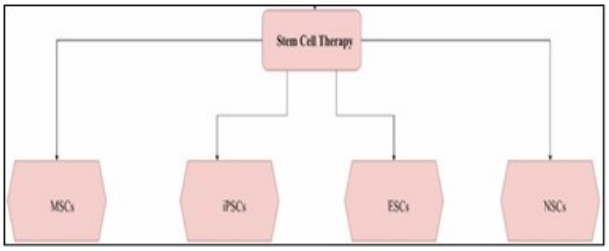


Figure 3: Different types of stem cells used for therapeutic purposes

3.2.1. *Neural stem cells*

The regenerative potential of NSCs has sparked interest in stem cell treatment for neurological illnesses such as Alzheimer's disease [10]. These self-renewing cells are critical for healing injured brain tissue. One strategy includes using endogenous NSCs found in the adult brain's hippocampus to trigger neurogenesis. Upregulation of growth hormones such as BDNF, IGF-1, NGF, and VEGF induces the patient's own NSCs to compensate for neurodegeneration. Despite its potential, but NSC transplantation has several hurdles, including ethical problems, safety concerns, and the need for standardization in clinic methods. Long-term culture may result in differentiation into glial cells, which reduces therapeutic efficacy. The variability of NSCs at various developmental stages complicates transplanting, emphasizing the necessity of purity, cell selection, and timing. To overcome these issues, continuing research is aimed at uncovering fundamental processes and devising innovative techniques. The use of bio scaffolds with NSC treatments shows potential. These scaffolds replicate the natural extracellular matrix (ECM) and provide an ideal environment for stem cell development, maturation, and transplantation. 2D and 3D hybrid inorganic nano scaffolds, such as those derived from MnO2 nanosheets, have variable biodegradation potential, which improves the efficacy of stem cell treatments. This novel strategy overcomes barriers to successful clinical stem cell therapy, encouraging a fresh viewpoint on the use of NSCs in AD treatment [9]

3.2.2. *Multipotent stem cells*

MSCs obtained from diverse tissues provide an appealing option in Alzheimer's disease therapy. MSCs isolated from bone marrow, adipose tissue, and peripheral blood are versatile and have a wide variety of potential uses. Notably, fetal MSCs have better properties, such as increased telomerase activity and pluripotency factors, making them useful for bone tissue engineering and other therapeutic techniques. Clinical research to assess the safety and effectiveness of several MSC types, including umbilical cord blood-derived MSCs and adipose-derived stromal vascular fraction cells, are under underway. These experiments shed light on MSCs' potential for treating Alzheimer's disease. For example, in a rat model of Alzheimer's disease,

combining bone marrow-derived MSCs with particular particles had a strong protective effect. The continuous investigation of numerous MSC types and their uses highlights the need for more research to understand the processes, migratory features, and tumorigenic potential of these cells. Bioprinting methods, which use both natural and synthetic bioink materials, provide new opportunities for cell-based therapeutics in neurodegenerative illnesses. Bioink materials such as fibrin, collagen, gellan gum, poly(caprolactone), and poly(ethyleneglycole) serve as a foundation for novel microfluidic and bio plotting technologies. These advances improve cell survival and open up new possibilities for optimizing stem cell therapy for Alzheimer's disease.

3.2.3. Pluripotent stem cells and innovative biomaterials

The pluripotent stem cells, which include embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), have a unique potential for treating Alzheimer's disease. ESCs, produced from the blastocyst's inner cell mass, have well-regulated pluripotency, allowing them to differentiate into a variety of cell types. The ethical, safety, and regulatory issues of using pluripotent stem cells to treat Alzheimer's disease must be carefully considered. Ongoing research and developments in stem cell technology, however, offer hope for creating novel medicines that address the underlying causes of Alzheimer's disease, possibly opening the door for later, more potent therapies. These cells can also be used to simulate the disease in culture dishes, which enables researchers to watch pathological processes and test possible treatments in a safe setting.

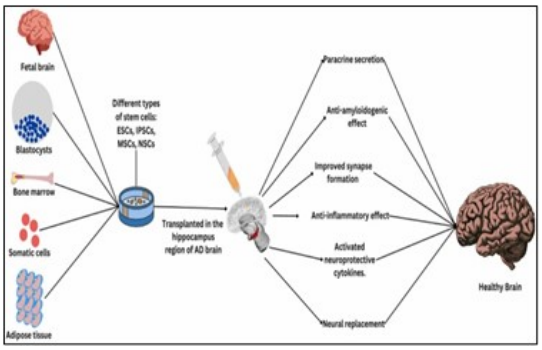


Figure 4: Injection of various types of stem cells being injected in the hippocampus area of brain and their benefits in clinical studies

Preclinical studies have shown that ESCs may successfully differentiate into cholinergic and GABAergic neuronal groups in AD models, leading to better memory impairment. However, the use of human ESCs has been linked to concerns about cancer development due to their strong proliferative capacity. To resolve ethical and safety concerns, researchers have resorted to iPSCs. iPSCs generated from mouse skin fibroblasts, treated with embryonic stem cell proteins, can develop into glial cells and decrease A? plaques in transgenic AD mice models. Specific inducers such as Wnt, Fgf-8, BMP, Hedgehog, Notch, and retinoic acid are required for PSC development, including ESC and iPSC. The regulation of miRNAs and essential transcription factors has been investigated for inducing somatic cell trans differentiation into neural stem cells and functioning neurons. The efficacy of stem cell treatments is determined not only by the features of the stem cells, but also by the techniques used to transfer them into host tissues. Innovative biomaterials have an important role in improving stem cell transplantation and encouraging therapeutic outcomes. Polymer-based materials have been created to aid in the nonenzymatic temperature-induced detachment of stem cells, assuring their gentle release for future uses. For example, homo polymeric coatings have been shown to allow the moderate thermally driven enzymatic-free selective release of undifferentiated iPSCs while leaving spontaneously developed cells attached to the surface. This technology purifies iPSCs quickly, inexpensively, and without the use of antibodies, which is critical for preserving maximum purity and homogeneity [10].

Bio scaffolds intended to replicate the natural extracellular matrix (ECM) provide a platform for increasing the efficacy of stem cell treatments. 2D and 3D hybrid inorganic nano scaffolds using materials like MnO2 nanosheets provide variable biodegradation capability. These nano scaffolds promote stem cell differentiation, maturation, and transplantation by activating focal adhesion pathways and laminin binding. The adoption of such unique materials creates new opportunities for overcoming difficulties in clinical stem cell treatment, resulting in better outcomes [9].

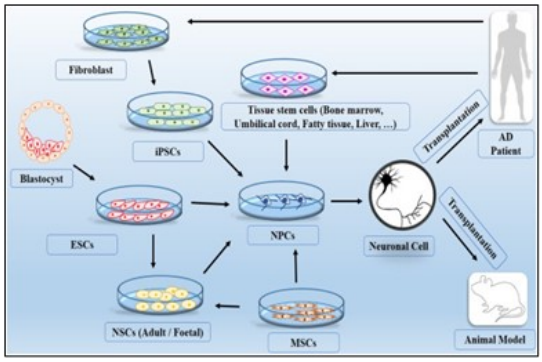


Figure 5: Various types of stem cells used in treatment of Alzheimer's Disease

3.2.4. Evaluating stem cell therapies in Clinical Trials

While stem cell-based therapy options for Alzheimer's disease are promising, moving these breakthroughs from preclinical investigations to clinical trials presents additional obstacles. Although most Alzheimer's disease cases are sporadic, transgenic animal models have mostly focused on familial AD. Despite failures, current clinical trials have evaluated the safety and effectiveness of several stem cell types in phase I trials. For example, a phase I experiment assessed the efficacy of human umbilical cord blood-derived MSCs delivered intracranially. Another experiment looked at the safety and efficacy of ASTOSTEM (autologous adipose tissue-derived mesenchymal stem cells) in 60 people and found that it improved their condition after delivery. Other trials, such as those using ischemia-tolerant human

bone marrow-derived MSCs, adipose-derived stromal vascular fraction cells, and umbilical cord blood-derived MSCs, are now in phase I/II

4. Collective use of nanotherapeutic and stem cell based strategies for treating alzheimer´s disease and various other neurodegenerative disorders

Nanomaterials' dimensional features have a substantial impact on their physical, chemical, and biological properties. Nanomaterials are classified as zero dimensional (0D), one dimensional (1D), and two-dimensional (2D) structures. Nanoparticles and other zero dimensional nanomaterials are ideal for use as bioactive supplements, nanocarriers, or cell labels in stem cell treatment. On the other hand, one-dimensional (1D) or two dimensional (2D) nanomaterials, such as nanotubes, nanowires, graphene, and polymer membranes, have the potential to serve as 2D/3D nano scaffolds for stem cell differentiation. In the context to Alzheimer's disease, the combination of nanotherapeutic techniques with stem cell therapy offers a viable path to better treatment outcomes. While each strategy has advantages and limits in tackling the intricacies of Alzheimer's, their combination may provide complimentary benefits, increasing treatment success. The incorporation of stem cell therapy with nanotherapeutic methods has enormous promise for improving Alzheimer's disease treatment. When combined with stem cell therapy, zero-dimensional nanomaterials can act as useful supplements, transporters, and labelling agents. Simultaneously, the investigation of one-dimensional and two-dimensional nanomaterials, as well as their composites, as 2D/3D nano scaffolds shows potential for boosting stem cell development in the setting of Alzheimer's disease. In conclusion, the combination of nanotherapeutic techniques with stem cell treatment appears as a synergistic strategy with enormous potential for addressing the intricacies of Alzheimer's disease. This combination provides a holistic strategy that leverages nanoparticles' unique features and stem cells' regenerative capacity to improve treatment results.

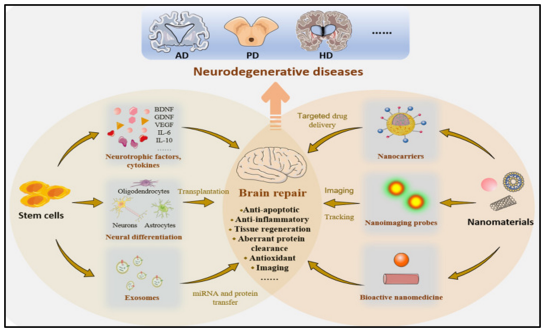


Figure 6: Schematic diagram showing use o stem cells therapy in collaboration with the nanotherapeutic strategies

5. Future perspectives

Despite advancements in clinical studies, stem cell treatments for Alzheimer's disease remain in their early phases. Several hurdles must be overcome in order to optimise these medicines for effective clinical use. These issues include the need for more studies to better understand the action mechanisms, migratory features, and tumorigenic potential of stem cells in the setting of AD. Unravelling the complexity is critical to developing focused and successful treatment methods. To ensure the safety and efficacy of stem cell treatments, processes for cell isolation, propagation, and transplantation must be standardized. To determine the safety profile of these medicines, their tumorigenic potential and physiological changes must be extensively evaluated. The inadequate and poor development of immature induced pluripotent stem cells (iPSCs) into somatic cells presents a difficulty [10]. Spontaneous differentiation into undesirable somatic cell types must be managed in order to improve the predictability and reliability of these treatments. The use of novel biomaterials, such as bio scaffolds and polymer-based materials, demands careful optimization. Balancing the requirement for effective stem cell distribution with regulated release while minimizing possible side effects is critical [11]. As clinical trials move to later stages, the design and quality of experimental research become more important. [24] Addressing experimental design concerns and providing rigorous procedures will be critical in assessing the protective benefits of stem cells in AD therapy. To summarize, the route towards using stem cells to treat Alzheimer's disease entails overcoming various difficulties. While continuing clinical trials give useful insights, collaboration among academics, physicians, and regulatory authorities is critical for navigating the complicated terrain of stem cell-based treatment options.

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