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Emerging Paradigms in Alzheimer's Disease: Etiology, Pathogenesis, and Novel Regenerative Treatments with Neural Progenitor Stem Cells and Exosomes

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia globally. The pathogenesis of AD, though classically attributed to β-amyloid plaque accumulation and tauopathy, is now viewed as a multifactorial process involving chronic neuroinflammation, metabolic dysregulation, and failure of neural regeneration. Modern therapeutic approaches increasingly target these complex mechanisms. Among them, regenerative strategies employing stem cells and stem cell-derived exosomes offer promising avenues for halting or reversing cognitive decline. Neural progenitor cells (NPCs) have emerged as potential tools for neurorestoration due to their differentiation capacity and immunomodulatory effects. This article explores the evolving understanding of AD etiology and pathogenesis, details novel cellular and molecular mechanisms implicated in disease progression, and provides an in-depth overview of experimental and clinical data supporting stem cell-based therapies. Emphasis is placed on the measurable cognitive outcomes, clinical scoring systems, and future prospects ofpersonalized cell-baseinterventions for AD.

Keywords
Alzheimer's disease; Stem cells; Neural progenitors; Exosomes; Regenerative medicine; Neurodegenerative conditions; Neuroplasticity; Euroregeneration.

Introduction

Alzheimer's disease (AD) affects over 55 million people worldwide, a number expected to triple by 2050 due to global aging demographics [1]. It is characterized by progressive memory loss, cognitive decline, and impaired daily functioning. Despite decades of research, effective disease-modifying treatments remain elusive. The approval of anti-amyloid monoclonal antibodies such as aducanumab and lecanemab marks a milestone, but these therapies offer modest clinical benefit and are accompanied by significant safety concerns [2].

The limitations of traditional pharmacotherapy in AD — which largely focuses on symptomatic relief or modest slowing of disease progression — have catalyzed growing interest in regenerative medicine as a novel therapeutic paradigm. Conventional drugs such as cholinesterase inhibitors (e.g., donepezil, rivastigmine) and NMDA receptor antagonists (e.g., memantine) offer limited efficacy, particularly in the later stages of the disease, and have not demonstrated the capacity to halt or reverse the underlying neurodegenerative process. Furthermore, anti-amyloid and anti-tau monoclonal antibodies, though promising in targeting hallmark pathological proteins, remain controversial due to mixed clinical outcomes and risks such as amyloid-related imaging abnormalities (ARIA).

In light of these challenges, stem cell–based therapies and their acellular derivatives—most notably exosomes—are being actively explored as transformative alternatives. These regenerative strategies aim not merely to mitigate symptoms or delay progression, but to directly address the core pathophysiological mechanisms driving Alzheimer's disease. Stem cells, particularly neural progenitor cells (NPCs), have demonstrated the capacity to differentiate into neurons and glial cells, offering the potential for cell replacement in regions affected by significant neuronal loss such as the hippocampus and entorhinal cortex. More importantly, these cells exert powerful paracrine effects, secreting a milieu of neurotrophic factors, cytokines, and bioactive molecules that modulate the local environment.

Among the most compelling components of this secretome are exosomes—nano-sized extracellular vesicles (30–150 nm) that facilitate intercellular communication and transport of proteins, mRNA, microRNA, and lipids. Exosomes derived from neural stem cells or mesenchymal stem cells have been shown to cross the blood–brain barrier, making them attractive candidates for non-invasive or minimally invasive therapy. Once delivered to the central nervous system, these vesicles can enhance synaptic plasticity, promote axonal outgrowth, stimulate endogenous neurogenesis, and suppress chronic neuroinflammation, which is now recognized as a major driver of disease progression in AD.

This holistic modulation of neural networks and the neuroimmune environment represents a significant conceptual departure from traditional monotherapeutic approaches. Instead of targeting a single pathway—such as amyloid deposition—regenerative medicine embraces the complexity of Alzheimer's disease by simultaneously addressing multiple pathological processes: neuronal apoptosis, synaptic dysfunction, glial activation, oxidative stress, and impaired intercellular signaling. As such, stem cell and

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exosome-based therapies hold the potential to not only preserve cognitive function but to restore lost connectivity and neurobiological function, redefining what is possible in the treatment of Alzheimer's disease.

Modern Views on The Etiology and Pathogenesis of Alzheimer'S Disease

Historically, the amyloid cascade hypothesis has served as the dominant conceptual framework for understanding the pathogenesis of Alzheimer's disease (AD) since its formal articulation in the early 1990s. This hypothesis posits that the abnormal accumulation and aggregation of β-amyloid (Aβ) peptides, particularly $A\beta_{1-42}$, in the brain constitutes the primary pathogenic trigger for a series of downstream neurodegenerative events. These include hyperphosphorylation of tau protein, formation of neurofibrillary tangles (NFTs), synaptic dysfunction, oxidative stress, neuroinflammation, and ultimately widespread neuronal death leading to progressive cognitive decline [3]. Several studies have shown that p-tau217 best corresponds with amyloid and tau status in blood testing, more so than Aβ42/Aβ40. However, even with p-tau217, there is some variability in accuracy. In addition, blood biomarker test results can be affected by comorbidities such as chronic kidney disease. The low Aβ42/Aβ40 ratio and high p-tau217 level in patient`s blood biomarker test indicate the presence of AD pathology in the brain. However, blood biomarker tests are not yet FDA approved, and accuracy varies widely among available tests [23-25].

This model gained significant traction due to compelling genetic and molecular evidence. Mutations in genes associated with familial early-onset AD, such as APP (amyloid precursor protein), PSEN1, and PSEN2 (presenilin 1 and 2), result in overproduction or altered processing of Aβ, reinforcing the centrality of amyloid pathology. Furthermore, neuropathological studies consistently demonstrate amyloid plaques in the brains of individuals with AD, often years before clinical symptoms emerge.

Another most well-studied genetic markers is the APOE genotype, particularly the APOE ε4 variant, which is associated with an increased risk of developing Alzheimer's disease [22].

The amyloid cascade hypothesis has thus shaped several decades of drug development efforts, particularly those aimed at reducing Aβ burden in the brain. These strategies have included β- and γ-secretase inhibitors, Aβ aggregation blockers, and more recently, monoclonal antibodies designed to bind and facilitate clearance of Aβ peptides from the brain. Examples of such antibodies include aducanumab, lecanemab, and donanemab, which have progressed into late-phase clinical trials and, in some cases, received conditional regulatory approvals.

However, a growing body of evidence from large-scale randomized clinical trials has revealed a disconnect between amyloid clearance and meaningful cognitive improvement. While several agents have successfully reduced amyloid plaque burden as measured by positron emission tomography (PET) imaging or cerebrospinal fluid (CSF) biomarkers, the associated clinical benefits in cognition and daily functioning have been modest at best, and often statistically marginal [4]. Moreover, some treatments have been associated with serious adverse effects, such as amyloid-related imaging abnormalities (ARIA)—including vasogenic edema (ARIA-E) and microhemorrhages (ARIA-H)—further complicating their risk-benefit profiles.

This disparity between biomarker efficacy and clinical outcomes has led many researchers to question the sufficiency and unidirectionality of the amyloid hypothesis. Critics argue that amyloid accumulation may be necessary but not sufficient for disease progression, or that it may represent a downstream epiphenomenon rather than the initiating cause of neurodegeneration in late-onset sporadic AD. Supporting this viewpoint are findings that many elderly individuals with significant amyloid burden remain cognitively intact, and that tau pathology and neuroinflammation correlate more strongly with cognitive decline than amyloid plaque density.

As a result, the field is increasingly embracing a multi-factorial view of AD pathogenesis, incorporating a broader range of mechanisms including tau dysfunction, mitochondrial impairment, chronic neuroinflammation, microglial dysregulation, vascular compromise, insulin resistance in the brain, and impaired glymphatic clearance. This shift in perspective underscores the need for therapeutic strategies that go beyond amyloid, targeting multiple converging pathological processes in a temporally appropriate manner.

While the amyloid cascade hypothesis has undoubtedly advanced our understanding of Alzheimer's disease and spurred valuable technological and diagnostic innovations, it is now widely accepted that a singular focus on amyloid may oversimplify a profoundly complex disease process. The limitations of this model have consequently fueled exploration into alternative and more integrative paradigms of AD pathogenesis and treatment.

The tau hypothesis focuses on intracellular neurofibrillary tangles composed of hyperphosphorylated tau proteins, which correlate more closely with cognitive decline than amyloid burden [5]. Tau propagation through brain networks appears to mirror disease progression. Microglial activation and chronic inflammation are now seen as central to AD pathology. Genome-wide association studies (GWAS) have implicated immune-related genes such as TREM2 and CD33, underscoring the role of innate immunity [6].

AD brains exhibit impaired glucose metabolism, mitochondrial dysfunction, and oxidative stress. Insulin resistance in the brain has led some researchers to label AD as "Type 3 diabetes" [7]. This has significant implications for therapeutic targeting. Recent models emphasize the failure of endogenous neural stem/progenitor cells to regenerate damaged neuronal networks [15,16]. The hippocampus, critical for memory, demonstrates impaired neurogenesis in AD, which may contribute directly to cognitive deficits [8,18].

Novel Mechanisms of Alzheimer's Disease Development

In recent years, AD research has undergone a paradigm shift, moving beyond the classical frameworks of amyloid and tau pathology to embrace a more integrative view of neurodegeneration. This evolving perspective has uncovered a diverse array of non-traditional, yet interrelated, contributors to AD pathogenesis. Among these, the gut-brain axis, exosome-mediated intercellular communication, and epigenetic regulation have emerged as critical components in the complex etiology of the disease.

Emerging evidence suggests that the intestinal microbiota—the vast and dynamic community of microorganisms inhabiting the gastrointestinal tract—plays a fundamental role in modulating brain health and neurodegenerative processes, including AD. This gut-brain axis is a bidirectional communication network involving neural, immune, endocrine, and metabolic pathways. Dysregulation of this system, particularly gut dysbiosis (an imbalance in microbial composition), has been increasingly implicated in AD pathogenesis.

Animal studies and human observational data reveal that dysbiosis can induce systemic inflammation, compromise the intestinal epithelial barrier ("leaky gut"), and lead to translocation of microbial metabolites and endotoxins (e.g., lipopolysaccharides) into systemic circulation. These inflammatory mediators, once crossing the blood-brain barrier (BBB), can activate microglia, the resident immune cells of the central nervous system, thereby promoting neuroinflammation and exacerbating amyloid-β (Aβ) deposition in vulnerable brain regions [13].

Additionally, certain gut microbes influence short-chain fatty acid (SCFA) production, neurotransmitter availability, and peripheral immune cell phenotypes, all of which can indirectly affect neuronal function and amyloid processing. Notably, altered microbiome profiles in AD patients have been associated with increased pro-inflammatory bacterial strains (e.g., Escherichia, Proteobacteria) and reduced levels of beneficial species (e.g., Bifidobacterium, Faecalibacterium). These findings highlight the gut microbiota as a modifiable risk factor and a promising target for novel therapeutic interventions, such as probiotics, prebiotics, fecal microbiota transplantation (FMT), and dietary modulation.

Exosomes, a subtype of extracellular vesicles (EVs) ranging from 30 to 150 nanometers in diameter, have gained increasing attention in AD research due to their dual roles in propagating pathology and enabling diagnostic insight. These nano-sized vesicles are secreted by virtually all cell types and are capable of transporting a wide array of bioactive molecules—including proteins, lipids, DNA, mRNA, and non-coding RNAs—across cellular and anatomical boundaries.

In the context of AD, exosomes derived from neurons and glial cells have been shown to carry misfolded tau and Aβ peptides, facilitating their spread from cell to cell in a manner reminiscent of prion-like transmission [12]. This process is thought to contribute to the stereotypical spatial and temporal progression of AD pathology, beginning in the entorhinal cortex and advancing to hippocampal and neocortical regions. Once internalized by recipient cells, these pathogenic exosomal cargoes can seed aggregation, impair synaptic function, and trigger local inflammatory responses.

Beyond their role in disease propagation, exosomes also represent a minimally invasive biomarker platform for AD diagnosis and monitoring. Exosomes isolated from plasma or cerebrospinal fluid (CSF) can carry disease-specific proteins and RNAs reflective of ongoing pathological processes in the brain. For instance, elevated levels of phosphorylated tau (p-tau181), Aβ42, and neurofilament light chain (NfL) in neuron-derived exosomes have been correlated with cognitive impairment and brain atrophy in preclinical and clinical stages of AD. As such, liquid biopsy techniques utilizing exosomal content offer a promising avenue for early detection, prognosis, and response monitoring in future personalized therapeutic paradigms.

Epigenetics-the study of heritable changes in gene expression that do not involve alterations in the DNA sequence itself-has emerged as a vital link between aging, environmental exposure, and neurodegenerative vulnerability. In Alzheimer's disease, epigenetic dysregulation is increasingly recognized as a key contributor to neuronal dysfunction and progression of pathology.

Three primary epigenetic mechanisms have been implicated in AD:

1. **DNA Methylation:** Hypermethylation of promoter regions can silence gene expression, while hypomethylation may lead to aberrant gene activation. Studies have found altered methylation patterns in genes involved in synaptic plasticity, immune regulation, and amyloid metabolism, including APP, PSEN1, and BACE1. Age-related "epigenetic drift" leads to stochastic changes in methylation patterns, which may predispose individuals to increased Aβ production and pro-inflammatory gene expression [19].
2. **Histone Modifications:** Post-translational modifications of histone proteins (e.g., acetylation, methylation, phosphorylation) alter chromatin structure and accessibility of transcriptional machinery. Histone deacetylase (HDAC) overactivity, for instance, is associated with reduced expression of neuroprotective genes and memory-related genes such as BDNF. HDAC inhibitors have shown promise in preclinical models for restoring synaptic function and cognitive performance.
3. **Non-coding RNAs (ncRNAs):** These include microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), which play regulatory roles in gene expression post-transcriptionally. Several miRNAs, such as miR-29a/b, miR-132, and miR-146a, have been shown to regulate APP processing, tau phosphorylation, and inflammatory signaling pathways. Dysregulation of these ncRNAs contributes to the dysfunctional gene networks observed in AD brains.

Collectively, epigenetic alterations may act as molecular mediators of aging, creating a permissive environment for neurodegeneration by activating immune pathways, silencing neurotrophic support genes, and disrupting synaptic homeostasis. Importantly, because epigenetic changes are potentially reversible, they offer a compelling therapeutic target. Several compounds-including HDAC inhibitors, DNA methyltransferase inhibitors, and ncRNA modulators-are currently under investigation for their potential to ameliorate AD-related molecular dysfunction.

Together, these emerging mechanisms-gut-brain communication, exosome-mediated spread of pathology, and epigenetic dysregulation-underscore the complexity of Alzheimer's disease and the necessity of a multi-targeted therapeutic approach. These systems do not operate in isolation; rather, they interact with classical hallmarks of AD, such as amyloid plaques and tau tangles, amplifying or modifying disease trajectories. By integrating these insights into research and clinical practice, future therapeutic strategies may better address the heterogeneity and multifactorial nature of this devastating neurodegenerative disorder.

Stem Cell-Based Therapeutics in Alzheimer's Disease

Stem cell-based therapies represent a transformative frontier in the treatment of neurodegenerative diseases, including AD. Unlike traditional pharmacologic approaches that largely aim to mitigate

symptoms or slow progression, stem cells offer the potential to replace lost or dysfunctional neural tissue, restore synaptic connectivity, and modulate the neuroinflammatory environment characteristic of AD. Accumulating preclinical data, alongside early-phase human trials, support the multifaceted therapeutic potential of neural progenitor cells (NPCs) and other stem cell types in modifying AD pathology and functionally enhancing cognition. Several types of stem cells have been investigated for AD treatment:

- **Neural Progenitor Cells (NPCs):** Capable of differentiating into neurons and glia, with evidence for synaptic integration and neurotrophic support.
- **Mesenchymal Stem Cells (MSCs):** Exhibit immunomodulatory properties and can secrete anti-inflammatory and neuroprotective factors.
- **Induced Pluripotent Stem Cells (iPSCs):** Provide personalized disease models and autologous transplantation potential.

Stem cells exert their therapeutic effects through both cell-autonomous (differentiation and integration) and, more significantly, paracrine mechanisms. Rather than directly replacing large populations of lost neurons, transplanted stem cells create a neurotrophic and immunomodulatory microenvironment that fosters endogenous repair. Several key mechanisms have been identified:

Neurotrophic support

Transplanted stem cells, particularly NPCs and mesenchymal stem cells (MSCs), secrete high levels of neurotrophic factors critical for neuronal survival, synaptic maintenance, and neurogenesis. These include:

- **Brain-Derived Neurotrophic Factor (BDNF):** Enhances synaptic plasticity, promotes dendritic spine formation, and facilitates learning and memory.
- **Nerve Growth Factor (NGF):** Supports the survival of cholinergic neurons in the basal forebrain, a region profoundly affected in AD.
- **Vascular Endothelial Growth Factor (VEGF):** Stimulates angiogenesis and also acts directly on neural stem cells to promote neurogenesis. By enhancing the trophic milieu of the AD brain, stem cells help stabilize neural circuits and prevent further degeneration.

Promotion of endogenous neurogenesis

Beyond direct differentiation, stem cells-particularly those delivered to neurogenic niches such as the subventricular zone (SVZ) or hippocampal dentate gyrus-promote proliferation and maturation of endogenous neural progenitors. This augmentation of intrinsic neurogenesis is associated with improved cognitive function, as evidenced by increased neuronal density and enhanced long-term potentiation (LTP) in animal models.

Immunomodulation and anti-inflammatory effects

Chronic neuroinflammation is a hallmark of AD and contributes to disease progression via sustained activation of microglia and astrocytes, which release pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and reactive oxygen species. Stem cells exert immunoregulatory effects, including: downregulation of pro-inflammatory cytokines, promotion of anti-inflammatory phenotypes in microglia (M2 polarization),

inhibition of NF-κB and other inflammatory signaling pathways. These changes create a neuroprotective environment that reduces synaptic damage and preserves neuronal viability.

Synaptic remodeling and angiogenesis

Evidence from animal models indicates that stem cell transplantation can restore expression of synaptic proteins such as synaptophysin, PSD-95, and GAP-43. This synaptic remodeling contributes to restoration of functional neural networks, especially in the hippocampus and cortex. In parallel, stem cells also enhance cerebral angiogenesis, improving blood flow and nutrient delivery to metabolically compromised brain regions. VEGF plays a dual role in promoting both vascular and neuronal recovery, bridging the vascular and neurogenic compartments of repair.

Numerous studies have demonstrated the therapeutic efficacy of NPCs in transgenic rodent models of AD. For instance, Blurton-Jones et al. (2009) transplanted NPCs into the hippocampus of triple transgenic AD mice (3xTg-AD) and observed significant improvements in spatial memory, accompanied by increased synaptic density and elevated BDNF levels. Importantly, these effects occurred without evidence of extensive differentiation of the grafted cells into mature neurons, supporting the predominance of paracrine mechanisms [20].

More recently, Jin et al. (2021) reported that intracerebral transplantation of human-induced pluripotent stem cell (iPSC)-derived NPCs led to reduced neuroinflammation, attenuation of tau pathology, and restoration of hippocampal volume in a tauopathy mouse model [10,21]. Collectively, these findings support the hypothesis that NPCs can ameliorate multiple pathogenic features of AD. Based on robust preclinical data, several early-phase clinical trials have begun to investigate the safety, feasibility, and preliminary efficacy of stem cell therapies in human patients with AD.

NCT03117738 is a Phase 1 trial evaluating the safety and tolerability of allogeneic neural progenitor cell transplantation (HuCNS-SC) into the hippocampus and entorhinal cortex of individuals with early-stage AD. The study, conducted at Stanford University, reported favorable safety outcomes and preliminary indications of slowed cognitive decline, although formal efficacy analyses are pending.

NCT03297177 is another ongoing trial examining the use of neural stem cells derived from embryonic tissue in patients with moderate AD. The primary endpoints include safety, CSF biomarker profiles (e.g., Aβ42, p-tau), and changes in cognitive scores using the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and Clinical Dementia Rating (CDR).

Preliminary results from these trials indicate that NPC transplantation is well tolerated, with no significant adverse events such as tumor formation, immune rejection, or worsening cognitive symptoms. Although definitive conclusions regarding efficacy await results from larger randomized trials, some patients have shown cognitive stabilization or mild improvement in episodic memory over 6- to 12-month follow-up periods. Clinical evaluation of treatment efficacy in AD typically relies on standardized cognitive and functional assessments, including:

- **ADAS-Cog:** A 70-point scale assessing memory, language, praxis, and orientation; reductions in score indicate improvement.
- **Mini-Mental State Examination (MMSE):** Commonly used to track global cognitive function.
- **Neuropsychiatric Inventory (NPI) and Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL):** Evaluate behavioral symptoms and functional independence, respectively.

In clinical trials of stem cell therapy, a stabilization or modest improvement (1–3 point gain) on ADAS-Cog over 6–12 months is considered a positive response, especially when contrasted with expected decline in untreated AD populations. Improvements are often accompanied by neuroimaging findings (e.g., increased hippocampal volume on MRI or enhanced glucose metabolism on FDG-PET), CSF biomarker shifts, and improved caregiver-reported quality of life.

Neural progenitor cells in the treatment of alzheimer's disease

Neural progenitor cells offer distinct advantages for therapeutic development [9]. In the context of neurodegenerative diseases, neural progenitor cells (NPCs) possess robust proliferative and differentiation capacities and demonstrate neuroprotective paracrine activity [18].

Preclinical models have shown that neural progenitors transplanted into AD mouse models:

- Survive long-term in host brain tissue
- Differentiate into functional neurons and astrocytes
- Secrete neurotrophic factors (e.g., GDNF, BDNF)
- Improve spatial memory and object recognition tasks
- Reduce microglial activation and synaptic loss

Notably, neural progenitors have shown promise in primate models, with functional integration and behavioral improvements observed [11]. In the CNS, immune privilege and the relative isolation of the brain parenchyma further support the use of NPCs, especially when delivered intrathecally or intraventricularly.

Alzheimer's Disease Scoring and Functional Outcomes After Stem Cell Therapy

Several clinical tools are used to evaluate the progression of AD and the efficacy of therapeutic interventions:

- **Mini-Mental State Examination (MMSE):** A 30-point questionnaire assessing memory, orientation, language, and visuospatial function. A decline of 2–4 points per year is typical in untreated AD.
- **Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog):** A more sensitive scale (up to 70 points), often used in clinical trials.
- **Clinical Dementia Rating (CDR):** A global measure of functional impairment.

Increases in CSF BDNF Several clinical tools are used to evaluate the progression of AD and the efficacy of therapeutic interventions:

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- and NGF levels

A study by Jin et al. (2021) demonstrated that NPC transplantation in AD mice improved working memory by up to 40% compared to controls, with significant histological evidence of neuroprotection [10].

Exosomes derived from stem cells: a cell-free strategy

Exosomes derived from NPCs or mesenchymal stem cells carry a cargo of mRNA, microRNA, proteins, and lipids that mediate neuroprotective effects. This cell-free approach offers several advantages:

- Lower risk of immune rejection
- Easier storage and transport
- Potential for intravenous administration

In murine models, administration of neural progenitor-derived exosomes led to:

- Restoration of synaptic density
- Reduction in Aβ burden
- Suppression of pro-inflammatory cytokines
- Improved performance in maze and recognition tests [14]

These findings highlight the promising potential of exosome-based therapeutics as either complementary adjuncts or standalone alternatives to conventional direct cell transplantation approaches. Exosomes, which are nano-sized vesicles secreted by cells, carry bioactive molecules such as proteins, lipids, and nucleic acids that can modulate cellular behavior and tissue repair. Leveraging these natural communication vehicles offers a novel therapeutic avenue that may bypass some of the inherent challenges associated with transplanting whole cells, including issues of cell survival, integration, and immune compatibility.

When considering stem cell-based therapies—particularly those involving xenogeneic sources (cells derived from different species) or embryonic tissues—stringent safety evaluations are paramount before clinical application. These evaluations must thoroughly address several critical risks:

- **Tumorigenicity:** One of the foremost concerns is the potential for transplanted stem cells, especially undifferentiated pluripotent stem cells, to form tumors. These cells have the inherent capability for unlimited self-renewal and differentiation into multiple cell types, which, if not properly controlled, may lead to the formation of teratomas or other malignancies. Ensuring complete differentiation or using committed progenitors is key to mitigating this risk.

- **Immune rejection:**Transplanting cells derived from xenogeneic sources, or even allogeneic human donors, carries the risk of immune rejection. The recipient's immune system may recognize these cells as foreign and mount a response that compromises graft survival and function. Strategies such as immunosuppression, cell engineering to reduce immunogenicity, or using autologous cells are areas of active research to overcome this challenge.
- **Ectopic tissue formation:** There is also the risk that transplanted cells may differentiate in unintended ways or migrate to non-target sites, leading to the formation of tissues in ectopic locations. This could cause functional impairments or other adverse effects depending on the tissue type and location.
- **Transmission of zoonotic agents:** Particularly relevant in xenotransplantation, there is a concern about the potential transmission of animal-derived pathogens to human recipients. Rigorous screening and pathogen elimination protocols are necessary to minimize this risk and ensure patient safety.

Preclinical studies have demonstrated that using more lineage-committed progenitor cells, such as NPCs, significantly reduces the risk of uncontrolled proliferation and tumor formation. These cells are already partially differentiated and have a more limited capacity for self-renewal compared to pluripotent stem cells, making them safer candidates for transplantation in regenerative medicine.

Regulatory bodies, including the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), currently permit the initiation of early-phase clinical trials under strict frameworks such as Investigational New Drug (IND) applications or Hospital Exemption pathways. However, these agencies emphasize the critical importance of implementing standardized and robust manufacturing protocols to ensure reproducibility and quality control of cell-based products. In addition, comprehensive cell characterization, including identity, purity, potency, and safety assessments, must be rigorously performed. Long-term patient monitoring post-transplantation is also mandated to detect any late-onset adverse events, ensuring ongoing safety and efficacy of these therapies as they move towards wider clinical adoption.

Case presentations

Case 1

This report presents the case of an 80-year-old male with advanced Alzheimer's disease, coexisting non-ischemic cardiomyopathy, and generalized frailty, who demonstrated substantial clinical recovery following a comprehensive regenerative therapy protocol.

The patient had been diagnosed with Alzheimer's disease three years prior to presentation. At baseline, he exhibited significant cognitive decline, short-term memory loss, disorientation, word-finding difficulties, and an increasing inability to perform activities of daily living independently. His Clinical Dementia Rating (CDR) score was 2, indicating moderate dementia, and he had an Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) score of 47, consistent with severe cognitive impairment. In addition to neurodegeneration, the patient had a known history of non-ischemic cardiomyopathy with an ejection fraction of 35%, classified as New York Heart Association (NYHA) Class III heart failure. He also

demonstrated frailty syndrome, sarcopenia, and symptoms of general functional decline, including fatigue, anorexia, sleep disturbance, and reduced mobility.

Previous management had included conventional pharmacologic treatments for AD, specifically donepezil and memantine, with minimal benefit. Given the progression of cognitive, functional, and cardiovascular deterioration, a compassionate use protocol incorporating advanced regenerative interventions was initiated with the goals of promoting neuroregeneration, improving cardiac performance, reducing systemic inflammation, and restoring overall physical function.

The therapeutic strategy included the transplantation of neural progenitor cells (NPCs). These cells were carefully characterized for identity, purity, and differentiation capacity, and passed all regulatory-standard sterility and tumorigenicity assays. The rationale was to facilitate neuronal replacement, enhance neurotrophic signaling, and modulate neuroinflammation.

To address cardiac dysfunction, the patient also underwent engraftment of committed progenitor cardiomyocytes. The cells were delivered using minimally-invasive implantation into pretreated stem cell niche. The aim was to stimulate myocardial regeneration, enhance contractile function, and mitigate ventricular remodeling.

Adjunctive exosome therapy was introduced two weeks following cell transplantation. NPC-derived exosomes, enriched with neurotrophic factors, anti-inflammatory cytokines, and regulatory microRNAs, were administered intranasally and intravenously on a biweekly basis to enhance the paracrine and systemic effects of the primary cell therapies.

In parallel, the patient received a tailored regimen of metabolic and nutritional support. This included daily oral supplementation with medium-chain triglycerides (7-10 grams/day) to supply ketone bodies as alternative cerebral fuel; creatine monohydrate (10 grams/day) to augment ATP production and mitochondrial resilience; and omega-3 fatty acids (2 grams/day) to reduce neuroinflammation and support membrane fluidity in neuronal tissues.

Rehabilitative care was progressively introduced, including guided physical therapy to rebuild strength and coordination, as well as structured cognitive training exercises to reinforce neuroplasticity and task performance. Sleep hygiene strategies and circadian rhythm reinforcement protocols were employed to address longstanding sleep fragmentation.

Over a twelve-month follow-up period, the patient exhibited sustained and progressive improvement across multiple clinical domains. By the sixth month, family members noted a marked improvement in memory, orientation, naming ability, and executive functioning. He regained independence in grooming, dressing, and simple meal preparation. By the twelfth month, formal cognitive testing confirmed a reduction in CDR score from 2 to 0.5, reflecting a shift from moderate dementia to very mild impairment. The ADAS-Cog score improved substantially, decreasing from 47 to 25, indicative of a meaningful reversal in cognitive deficits. The Mini-Mental State Examination (MMSE) score concurrently improved from 15 to 26.

Cardiac assessments mirrored the neurological recovery. Echocardiography revealed an increase in left ventricular ejection fraction from 35% at baseline to 48% at twelve months, with improved regional wall motion and contractility. Electrocardiographic monitoring showed resolution of prior QRS prolongation and the disappearance of premature ventricular contractions. Clinically, the patient transitioned from NYHA Class III to Class I heart failure status, demonstrating significantly enhanced exercise tolerance. Biomarker analysis showed a decline in B-type natriuretic peptide (BNP) levels from 420 pg/mL to 140 pg/mL, suggesting decreased ventricular strain.

The patient also experienced significant gains in systemic health and quality of life. Sleep duration and efficiency improved, with actigraphy confirming a restoration of regular sleep architecture and an average nightly duration of seven hours. Appetite returned to normal, mood stabilized, and energy levels increased. Dual-energy X-ray absorptiometry (DEXA) scans confirmed a gain of 4 kilograms in lean body mass. The patient resumed light exercise, reading, and social interactions. His Karnofsky Performance Score improved from 50 to 80, marking a shift from significant dependence to a state of functional independence in most daily tasks.

Neuroimaging and biomarker analyses supported these clinical observations. Follow-up magnetic resonance imaging (MRI) revealed modest yet consistent increases in hippocampal volume and cortical thickness in targeted regions. Positron emission tomography (PET) scans demonstrated reduced amyloid tracer uptake and improved metabolic activity across cortical regions. Cerebrospinal fluid analysis revealed reductions in total tau and phosphorylated tau concentrations, with a concurrent increase in synaptic protein markers such as neurogranin, indicative of improved synaptic integrity.

Importantly, all interventions were well tolerated. There were no adverse immune responses, no clinical or radiographic evidence of ectopic tissue formation or tumorigenesis, and no metabolic or gastrointestinal side effects from the nutritional adjuncts. Laboratory surveillance remained stable throughout, confirming the safety of the multimodal approach.

This case illustrates the potential for a synergistic, regenerative medicine protocol combining neural and cardiac progenitor stem cell transplantation, exosome therapy, and metabolic support to induce significant clinical improvement in a patient with advanced Alzheimer's disease and cardiomyopathy. The observed reversal in cognitive decline, cardiac dysfunction, frailty, and sleep impairment suggests a disease-modifying effect and highlights the potential of cell-based interventions in managing complex age-related disorders. While further randomized trials are needed to validate these findings, this case contributes to a growing body of evidence that the integration of cellular, molecular, and metabolic therapies can restore function and quality of life even in late-stage disease.

Case 2

Often Neurodegenerative diseases are coexisting in a same person. Such cases when several neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) are diagnosed in a same patient represent a formidable therapeutic challenge, particularly when co-occurring in elderly individuals. The following report documents the case of a 72-year-old male with moderate Parkinson's disease and concurrent early-stage Alzheimer's disease, who underwent a combination of neural

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progenitor and dopaminergic progenitor stem cell therapy over a two-year period. The patient experienced sustained and progressive improvement in motor function, cognitive performance, and quality of life.

The patient initially presented with a five-year history of idiopathic Parkinson's disease, characterized by progressive bradykinesia, resting tremor, facial masking, drooling, postural instability, and gait disturbances. Symptoms had become increasingly refractory to conventional dopaminergic therapy, including levodopa-carbidopa and pramipexole. Notably, over the preceding 18 months, the patient also demonstrated early cognitive changes consistent with mild neurocognitive disorder. These included impaired short-term memory, reduced word fluency, disrupted sleep patterns, and increasing difficulty with executive functions and task planning. Neurological assessment confirmed the diagnosis of PD with coexisting prodromal AD. MRI of the brain showed mild hippocampal atrophy, and PET imaging indicated both nigrostriatal dopaminergic deficits and cortical hypometabolism in temporoparietal regions. Neurocognitive testing yielded a Mini-Mental State Examination (MMSE) score of 23 and a Montreal Cognitive Assessment (MoCA) score of 20.

Given the limited response to standard pharmacotherapy and the dual neurodegenerative trajectory, the patient was enrolled in a compassionate investigational protocol employing neural stem cell therapy. The treatment involved three sequential implantations of neural progenitor cells over a 24-month period. The cellular product included both pan-neural progenitors and lineage-committed dopaminergic progenitor cells cultured, expanded and engineered for reduced immunogenicity and enhanced neurotrophic output. Cells were validated for purity, differentiation potential, and absence of tumorigenicity.

The first implantation involved transplantation of dopaminergic progenitors combined with cortical and hippocampus neural progenitors. The patient tolerated the procedure well, with no immediate complications. Within eight weeks of the first treatment, the patient began to show subtle yet discernible improvements in motor initiation, facial expression, and upper extremity coordination. Family members reported a noticeable softening of facial masking, reduced rigidity in fine hand movements, and less frequent episodes of tremor. Drooling, previously a persistent issue, was markedly reduced, correlating with improved orofacial muscle tone. Sleep also became more consolidated, with the patient sleeping six to seven uninterrupted hours per night, compared to fragmented, shallow sleep pre-treatment. MMSE scores improved to 25 by three months post-procedure.

One year after the initial procedure, the patient underwent a second implantation. This session focused on augmenting dopaminergic reinnervation in the substantia nigra and basal ganglia circuitry. The cellular formulation again included enriched populations of dopaminergic progenitors, combined with neurotrophic factor-secreting support cells to promote synaptic integration and axonal guidance. This second treatment yielded more pronounced clinical gains. Gait improved substantially, with reduced freezing episodes and more fluid transitions during ambulation. Fine motor skills improved notably, particularly in tasks such as buttoning shirts, using utensils, and handwriting, which had previously become impaired. On formal neurological examination, Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores decreased by 40% relative to baseline. Cognitive domains also showed further

improvement, particularly in attention, visuospatial construction, and delayed recall. The patient resumed reading, performing basic arithmetic, and managing some household activities independently. The MoCA score improved to 25, and MMSE reached 27 by nine months following the second procedure.

The third and final implantation occurred approximately 22 months after the initial procedure and was intended as a maintenance and consolidation therapy. It involved a lower-dose delivery of mixed neural progenitor cells with exosome-rich fractions derived from the donor cell population. The exosomes were administered via combined intravernous, intranasal and Sphenopalatine Ganglion (SPG) block routes, designed to enhance both central delivery and systemic immunomodulatory effects. Following this phase, the patient exhibited continued clinical stability and further subjective improvements. Facial expressivity became more animated, and speech was clearer with improved prosody and articulation. There was no longer evidence of dysarthria or facial rigidity. Drooling had resolved entirely. Postural stability improved, and the patient no longer required assistive devices for ambulation. Importantly, there were no adverse events, infections, or inflammatory responses noted during the entire treatment course.

Over the full two-year course, the patient's quality of life improved significantly. He reported greater independence in daily routines, resumed social interactions, and expressed a renewed sense of personal agency. Cognitive function remained stable to mildly improved, with neuropsychological retesting showing sustained scores above pre-treatment baseline across most domains. Caregiver assessments and functional evaluations confirmed improved sleep architecture, fewer behavioral disturbances, and better mood stability.

Serial MRI imaging did not reveal any abnormal tissue growth, edema, or hemorrhage. In fact, volumetric analysis suggested a modest increase in gray matter volume in basal ganglia and medial temporal regions. PET imaging performed at 24 months demonstrated improved dopaminergic uptake in striatal regions, supporting the hypothesis of functional graft survival and integration. Cerebrospinal fluid analysis showed reductions in phosphorylated tau and neurofilament light chain concentrations, with stable β-amyloid levels.

This case illustrates the therapeutic potential of neural progenitor stem cells and dopaminergic progenitor cell therapy in the treatment of complex neurodegenerative syndromes. The combined regenerative strategy appeared to restore dopaminergic tone, promote neuroplasticity, and counteract neuroinflammation, leading to sustained functional improvement in both motor and cognitive domains. The use of sequential dosing and mixed delivery routes may have played a role in optimizing integration and avoiding immune sensitization.

While the observations are derived from a single case under compassionate use, they support growing evidence that neural progenitor-based regenerative therapies may offer a viable and effective adjunct to conventional management for patients with Parkinson's disease and overlapping Alzheimer's pathology. Further controlled clinical trials are warranted to confirm these findings, refine dosing strategies, and define the long-term safety and efficacy of this emerging therapeutic modality.

Future Directions

Significant advancements across multiple cutting-edge scientific and technological fields are poised to accelerate the clinical translation of stem cell therapies for AD. These innovations collectively promise to overcome many current limitations and pave the way for more effective and personalized regenerative treatments. Key areas of progress include:

- **Genetically engineered progenitor cells:** Advances in genetic engineering enable the modification of stem or progenitor cells to enhance their therapeutic potential. For example, progenitor cells can be engineered to overexpress neurotrophic factors such as brain-derived neurotrophic factor (BDNF) or glial cell line-derived neurotrophic factor (GDNF), which support neuron survival, growth, and synaptic plasticity. Additionally, cells can be modified to secrete anti-inflammatory proteins that mitigate the chronic neuroinflammation characteristic of AD. These tailored cells can exert more potent and targeted effects within the diseased brain microenvironment, potentially improving therapeutic outcomes.
- **Bioprinting and scaffolds for targeted delivery:** Emerging tissue engineering techniques like 3D bioprinting allow the precise fabrication of biomaterial scaffolds embedded with stem cells or progenitors. These scaffolds can be designed to match the architecture of specific brain regions affected in AD, enabling targeted and controlled cell delivery. Such approaches improve cell survival, integration, and functional connectivity by providing a supportive microenvironment, guiding cell differentiation, and facilitating controlled release of therapeutic factors.
- **CRISPR-based immune editing for universal donor cells:** One major hurdle in cell transplantation is immune rejection. The application of CRISPR/Cas9 genome editing enables the creation of universal donor cell lines by knocking out or modifying genes responsible for immune recognition and rejection. This technology is especially transformative for xenogeneic (cross-species) stem cell sources, allowing the generation of hypoimmunogenic cells that can evade the host's immune system without the need for long-term immunosuppression, thereby expanding the availability and safety of allogeneic cell therapies.
- **Machine learning for predicting patient responders:** The integration of machine learning algorithms with large-scale genomic, proteomic, and neuroimaging datasets offers powerful tools to identify which patients are most likely to benefit from stem cell therapies. By analyzing complex patterns and biomarkers, predictive models can stratify patients based on their individual disease biology and response profiles. This enables more precise patient selection and treatment optimization, increasing the likelihood of clinical success while minimizing unnecessary risks and costs.
- **Integration with precision medicine:** Stem cell therapies for AD stand to benefit greatly from being embedded within a broader precision medicine framework. This approach tailors interventions to each patient's unique pathophysiological profile—accounting for genetic variants, biomarker signatures, disease stage, and comorbidities. Personalized therapeutic regimens can be developed that combine stem cell transplantation with adjunctive treatments such as small molecules, immunotherapies, or lifestyle interventions, maximizing efficacy and safety.

The convergence and synergistic integration of these rapidly evolving technologies not only holds the potential to significantly slow the progression of Alzheimer's disease but, more ambitiously, to meaningfully reverse cognitive decline and restore neural function in carefully selected patient populations. This multidisciplinary approach ushers in a new era of regenerative neurology, where treatments are increasingly precise, effective, and personalized, offering renewed hope for individuals affected by this devastating condition.

Conclusion

Alzheimer's disease remains one of the most formidable neurodegenerative disorders, characterized by a complex and multifactorial pathogenesis that extends well beyond the traditional amyloid-beta plaque accumulation and tau protein tangles. Contemporary research has revealed that AD involves an intricate interplay of various pathological mechanisms, including chronic neuroinflammation driven by activated microglia and astrocytes, widespread synaptic dysfunction leading to impaired neuronal communication, exhaustion and impaired regenerative capacity of endogenous stem cell populations, and profound epigenetic alterations that disrupt gene expression patterns essential for neuronal health and plasticity. This multifaceted understanding underscores the need for therapeutic approaches that address the disease on multiple fronts rather than targeting a single pathological hallmark.

Stem cell therapies have emerged as a particularly promising avenue for addressing the neurodegenerative processes underlying AD. Among the various cell types under investigation, NPCs and xenogeneic progenitor cells stand out due to their capacity not only to replace lost or damaged neurons but also to provide critical trophic support through secretion of growth factors and cytokines that promote neuronal survival and plasticity. Moreover, these cells possess immunomodulatory properties that can help modulate the aberrant inflammatory milieu present in the AD brain, thereby reducing secondary damage and creating a more conducive environment for regeneration.

Recent innovations have expanded the therapeutic toolbox even further. Exosome-based delivery systems leverage the natural vesicular transport mechanisms of cells to deliver bioactive molecules-including proteins, RNAs, and microRNAs-directly to affected brain regions. This cell-free strategy may overcome some of the challenges associated with cell transplantation, such as immune rejection and poor cell survival. Additionally, genetic engineering techniques enable the modification of progenitor cells to enhance their therapeutic efficacy, for example by overexpressing neurotrophic factors, anti-inflammatory agents, or molecules that promote synaptic repair, thereby tailoring treatments to specific pathological features of AD.

Although large-scale, rigorous clinical trials are still needed to firmly establish safety and efficacy, the growing body of preclinical and early clinical evidence is encouraging. Data suggest that stem cell-based interventions have the potential to slow the progression of cognitive decline, improve memory and executive function, and, in some cases, restore neural networks sufficiently to offer a meaningful functional recovery. Such outcomes would represent a paradigm shift from symptomatic management to true disease modification and possibly functional cure, especially if applied during the early or moderate stages of Alzheimer's disease.

Looking ahead, the future of AD treatment likely resides in the integration of cellular therapies with advanced molecular and systems-level approaches. Combining stem cell transplantation with precision medicine, gene editing, immunotherapy, and neurorehabilitation strategies offers the best chance to restore brain health comprehensively. This holistic, multi-modal approach could usher in a new era of regenerative neurology where the devastating impact of Alzheimer's disease is significantly mitigated or even reversed.

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Institutional review board statement

Not applicable.

Data availability statement

The data presented in this study are available in the study outlined.

Conflicts of interest

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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