ALZHEIMER'S: HOW EMERGING GENE EDITING STRATEGIES COULD TRANSFORM TREATMENT

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Abstract

Despite decades of research and testing, Alzheimer's disease remains a progressive and currently terminal neurodegenerative disorder which affects over 55 million people across the world. It is a leading cause of mortality among the elderly without a full cure. Treatments for Alzheimer's primarily try to temporarily reduce amyloid-beta and tau accumulation in the brain, with these types of treatments being temporary. The effects of Alzheimer's, including neuroinflammation, memory loss, and metabolic stress, renders Alzheimer's disease one of the most prevalent neurodegenerative conditions to date. This paper aims to find theoretical methods and solutions to improve Alzheimer's treatment. Biomarkers, such as p-tau217, p-tau181, A-beta42/40 ratios, and neurofilament can also be used for early Alzheimer's detection. These biomarkers can enable earlier and more accurate detection of this disease, giving us the opportunity for earlier therapeutic intervention and treatment of Alzheimer's in patients.

Gene editing technologies have emerged as promising strategies to modify amyloid-beta and tau production to alleviate Alzheimer's. While CRISPR-Cas9 has seen success in reducing amyloid and tau production, several underused genetic tools, such as TALENs, Zinc Finger Nucleases, base and prime editors, and the newly developed seekRNA, offer unique advantages in precision or large scale DNA modification when dealing with mutations and diseases, especially with Alzheimer's. However, challenges such as side effects, size, and the blood brain barrier are still formidable obstacles; continued innovation in delivery systems, including engineered AAV capsids, lipid nanoparticles, and focused ultrasound, has the possibility to enable safe and effective deployment of these tools inside of the brain and central nervous system. Together, with a combination of these methods, these strategies offer a theoretical framework for future Alzheimer's modifying therapies that may one day move beyond symptom management.

Keywords

Alzheimer's; Gene Therapy; seekRNA; tau tangles; TALENs; amyloid-beta

Introduction

Alzheimer's disease is one of the most prevalent neurodegenerative disorders, affecting more than 55 million people worldwide and accounting for the majority of global dementia cases. As global life expectancy continues to rise, the prevalence of Alzheimer's is projected to proportionally increase, imposing a significant socioeconomic burden and pressure on patients, families, and healthcare systems. Despite decades of research, Alzheimer's currently remains incurable, and current therapies only offer temporary symptomatic relief rather than meaningful progress against the disease. This problem reflects the biological complexity of Alzheimer's, which involves far more than the accumulation of amyloid-beta plaques and tau tangles.

At the molecular level, Alzheimer's disrupts multiple interconnected systems within the brain. Protein aggregation impairs neuronal communication, while mitochondrial dysfunction reduces energy production and increases oxidative stress. Chronic neuroinflammation, driven by dysregulated microglia and astrocytes, accelerates neuronal death, causing neurodegeneracy. These overlapping mechanisms make it difficult for single target drugs to halt or reverse disease progression. Although recent advances in diagnostics, such as plasma p-tau217, p-tau181, A-beta42/40 ratios, and neurofilament, now allow earlier and more accurate detection, a single full cure at the moment is still lacking.

The emergence of gene editing technologies offers a new promising direction. While CRISPR-Cas9 is currently the most widely utilized gene editing tool in Alzheimer's research, a broader landscape of gene editing technology, including TALENs, Zinc Finger Nucleases, base and prime editors, and seekRNA, may provide safer or more precise approaches for targeting the proteins which cause Alzheimer's disease. Understanding these tools, their advantages, and their limitations, allows for the best pathway in the future in which we move beyond symptom management and toward true disease modification towards diseases such as Alzheimer's. This paper examines and proposes current and new untested biological foundations of Alzheimer's, evaluates current and emerging gene editing strategies, and explores the delivery challenges that must be overcome to translate these technologies into effective treatments

Methods

This paper is a theoretical review based on analysis of peer reviewed scientific literature related to Alzheimer's disease, diagnostic biomarkers, and emerging gene editing technologies. Research articles, clinical trial reports, and authoritative reviews were examined to evaluate mechanisms and effects of Alzheimer's disease. Additional sources were used to identify different gene editing technologies, such as TALENs, seekRNA, etc. Different technologies, while some have not been tested against Alzheimer's at the time of publication, were analyzed on their potential efficacy for fighting against Alzheimer's. Sources and references were gathered from databases such as the National Institutes of Health, Google Scholar, PubMed, and other scientific databases.

Results and Discussion

Background on Alzheimer's Disease

Alzheimer's disease still remains a significant challenge in our society today, with more than 55 million worldwide having dementia, the majority of whom have Alzheimer's disease (Gustavsson et al. 2022). Alzheimer's disease is a progressive neurodegenerative disorder of the brain which slowly destroys memory and thinking ability, and eventually leads to severe cognitive decline, in which people are unable to complete simple tasks (National Institute of Aging 2023). As global life expectancy increases, the number of individuals affected by Alzheimer's is expected to sharply rise in coming decades, making it important to find a solution or mitigator for Alzheimer's (Hao and Chen 2025).

Effects of Alzheimer's

Alzheimer's is caused by the abnormal buildup of proteins such as amyloid plaques and tau tangles (O'Brien and Wong 2011). These proteins damage neurons, disrupt communication, and cause shrinkage of the brain (Tyan et al. 2012). Alzheimer's causes mitochondrial dysfunction because the amyloid-beta and tau proteins impair neurons. This mitochondrial dysfunction impairs energy metabolism, increases oxidative stress, disrupts calcium homeostasis, and impairs mitochondrial transport (Wang et al. 2025).

Alzheimer's Detection

Alzheimer's detection is difficult, but there have been methods developed to try and predict if someone has Alzheimer's (National Institute on Aging 2024a). One such method involves monitoring the level of amyloid-beta plaques and tau tangles. By utilizing Positron Emission Tomography (PET) scans or cerebrospinal fluid (CSF) analysis, clinicians can measure the accumulation of these proteins inside of a patient (O'Brien and Wong 2011). This method utilizes the amyloid-beta plaques and tau tangles as biomarkers to measure if a person may have Alzheimer's. If they do show signs of having too much of either of these proteins, we can predict that a person may have Alzheimer's. Another method of detection we can use is the presence of the APOE-E4 allele. Unlike the neutral APOE-E3 allele or the neurological protective APOE-E2 variants, the E4 allele is associated with impaired amyloid-beta detection and clearance and heightened neuroinflammation (Bryant 2021). However, this method of detection can only work if the parents of the patient have passed down this allele, and considering that 14-15% of the population has the APOE-E4 allele, it is relatively common and can work well (Bryant 2021)

Current Treatment of Alzheimer's

While there are currently marketed treatments for Alzheimer's, they are not fixed treatments of Alzheimer's and mostly provide temporary relief by targeting symptoms (MDPI 2025; Liu et al. 2025). Most Alzheimer's treatments at the moment include drugs which remove amyloid-beta plaques; however, these are not permanent treatments and are instead temporary treatments which attack the symptoms (Alzheimer's Association 2019b). There are also drugs which address cognitive thinking and daily functioning, such as rivastigmine, galantamine, and benzgalantamine. However, these do not fix or mitigate Alzheimer's and are instead meant to help the brain function, overlooking the amyloid-beta plaques buildup entirely (Liu et al. 2025; National Institute on Aging 2023). Drugs and antibodies such as these only temporarily help, and can only help in earlier stages of Alzheimer's (Alzheimer's Association 2019b). The reason why there are currently no effective treatments for Alzheimer's is due to the complexity of the disease. Alzheimer's causes severe accumulation of amyloid-beta plaques and tau tangles, which disrupt the brain and start the massive apoptosis of neurons, leading to neurological decline over time and eventual death (O'Brien and Wong 2011). Alzheimer's disease also causes neurological inflammation, and due to Alzheimer's being present, microglia and astrocytes, cells which release chemicals to repair damage, into neurotoxic agents which actively drive for neurodegeneration and synapse loss, leading to severe neurological damage and eventual brain failure (Di Benedetto et al. 2022; Deng et al. 2023).

Gene Therapy & Biomarkers

Scientists have been doing extensive research on gene-editing technologies, such as CRISPR-Cas9 for preclinical Alzheimer's, and experimentation with Alzheimer's have shown promising results in reducing amyloid-beta plaques and tau proteins in animal models and human induced pluripotent stem cells (iPSCs) as biomarkers (Lu et al. 2021; Akbar et al. 2025). Additionally, scientists are successfully using CRISPR to edit and knock down genes associated with APP and PSEN1, and risk factors such as APOE-E4 alleles (Lu et al. 2021). While no human clinical trials have been conducted for CRISPR based on Alzheimer's, as of 2026, there have been other forms of gene therapy currently in phase 1 and phase 2 being tested in humans (He et al. 2025). For instance, researchers are investigating the usage of vectors to deliver protective genes directly to the central nervous system (He et al. 2025). While we are still in the early stages of determining long term efficacy and safety, these trials could show potential progress against Alzheimer's. Additionally, recent advances in biomarker research has made Alzheimer's detection more accurate and accessible. In addition to PET imaging and CSF analysis, clinicians are increasingly relying on alternative biomarkers which can detect Alzheimer's pathology with high sensitivity (Yim et al. 2025). Plasma phosphorylated tau proteins, such as p-tau217 and p-tau181, strongly correlate with tau accumulation in the brain and can be used to identify Alzheimer's even in its earliest stages (Yim et al. 2025). Other blood markers, including the A-beta42/40 ratio and neurofilament light chain (NfL), provide further detection of amyloid burden and neurodegeneracy (Borreli 2026). These tests are less invasive and significantly

cheaper than traditional methods, making them promising tools for screening and early diagnosis of Alzheimer's. (Lomte 2026).

TALENs

There are also other, less experimented tools we could use to help with Alzheimer's with their own benefits and drawbacks. While CRISPR-Cas9 is often recognized as the best and only tool to assist Alzheimer's, there are many other theoretical tools we could use to mitigate Alzheimer's. One of these tools is Transcription Activator-Like Effector Nucleases (TALENs). TALENs, while it may be more expensive and inconvenient, are incredibly precise compared to other gene-editing tools such as CRISPR-Cas9 (Gupta and Musunuru 2014). TALENs are proteins which are engineered to bind to specific DNA sequences with an exact match between amino acid repeats and nucleotides (Chandrasegaran 2017). The highly accurate makes them a particularly good tool for targeting the APP gene, or silencing the APOE-E4 allele, as TALENs are less likely to cause unintended consequences (Chandrasegaran 2017). Beyond editing nuclear DNA, TALENs has also shown precision in editing mitochondrial DNA, which is often dysfunctional in patients with Alzheimer's (Wang et al. 2025). With the usage of TALENs, in vitro studies suggest we could also restore mitochondrial function in neurons for patients with Alzheimer's, and prevent metabolic failure which precedes cell death (Wang et al. 2025). Although TALENs are more complex to manufacture and are more costly, they are generally the safer option, especially for patients with neurodegenerative diseases, such as Alzheimer's (Gupta and Musunuru 2014).

seekRNA

Another recently developed tool is seekRNA. Unlike CRISPR-Cas9, which creates potentially harmful breaks in the DNA, seekRNA, a newly discovered gene therapeutic tool discovered in 2024-2025, is a programmable system which can precisely insert, remove, or invert large sections of DNA with less errors than CRISPR (Siddiquee et al. 2024; University of Sydney 2024). For Alzheimer's research, this is a significant advancement. Rather than simply silencing a risky allele such as APOE-E4, seekRNA could be used to theoretically put in a new allele such as the APOE-E2 allele directly into the patient's genome with near perfect accuracy (Siddiquee et al. 2024). Furthermore, due to seekRNA being a stand-alone tool as it requires only a single small protein and short RNA strand, it is significantly easier to package into viral vectors for delivery across the blood brain barrier (BBB) (Siddiquee et al. 2024). However, it is still in the early stages of development and adaptation to human cells, and is still preclinical. (University of Sydney 2024). We could also use base editors and prime editors as another method to mitigate Alzheimer's. Base editors and prime editors are able to convert one nucleotide into another (Eid et al. 2018; Chen and Liu 2022). This is relevant for Alzheimer's research, as it offers a method to convert the risk factored APOE-E4 into the neutral APOE-E3 variant by just changing two nucleotides (Kantor et al. 2020). Prime editing, on the other hand, is capable of performing all twelve possible base to base conversions, as well as small insertions and deletions of the DNA (Chen and Liu 2022). Because prime editors do not rely on double stranded breaks of the DNA, they significantly reduce the risk of tissues being damaged, known as p53 mediated toxicity (Eid et al. 2018; Gudkov and Komarova 2010). As of 2026, these technologies are being refined and improved upon for better delivery with lipid nanoparticles, providing a clear pathway on how we can correct familial mutations in the APP or PSEN1 genes with safety (Fletcher 2024; Lee et al. 2025).

Zinc Finger Nucleases (ZFNs)

Another method of helping with Alzheimer's is the usage of Zinc Finger Nucleases (ZFNs). ZFNs are hybrid proteins which are engineered to recognize three base paired sequences of DNA, allowing for highly precision based targeting of Alzheimer linked genes, such as MAPT, the gene responsible for tau protein production (Cradick et al. 2011). A distinct advantage of ZFNs is their minimal size. They are significantly smaller than the Cas9 proteins used by CRISPR, and due to this, they can be more easily packaged into single Adeno-Associated Virus (AAV) vectors for delivery across the blood brain barrier (BBB) (Cradick et

al. 2011; Chandrasegaran 2017). Furthermore, ZFNs trigger a lower immune system response compared to CRISPR, as ZFNs have mostly human-like protein structures (Cradick et al. 2011). Clinical explorations using ZFNs to repress the expression of the tau gene have demonstrated that reducing the sheer volume of tau production is possible, and can actively help for the fight against Alzheimer's (Chandrasegaran 2017).

Gene Silencing

We can also use gene silencing approaches such as Antisense Oligonucleotides (ASOs) and Small Interfering RNA (siRNA), and while they are not permanent fixes, they can be temporary mitigators for Alzheimer's (Kantor et al. 2020). ASOs are short, synthetic strands of nucleotides which bind to specific messenger RNA (mRNA) sequences in an effort to prevent further translation of toxic proteins (Kantor et al. 2020). Similarly, siRNA uses the natural RNA interface (RNAi) of the body to intercept and destroy harmful mRNA before it can be translated into protein (Kantor et al. 2020). While these are considered as temporary fixes, they are still applicable in Alzheimer's research, and should not be overlooked.

Table 1: Comparative Analysis of Gene Editing and Silencing Platforms

Technology	**Primary Mechanism**	**Precision Level**	**Delivery Feasibility (Size)**	**Level of Evidence in AD**
CRISPR-Cas9	Double-strand DNA breaks	High	Challenging (Large Cas9 protein)	**Preclinical** (Animal/iPSC models)
TALENs	Protein-DNA binding repeats	Very High	Difficult (Bulky protein pairs)	**Preclinical / Theoretical**
ZFNs	Zinc-finger protein motifs	High	**Optimal** (Smallest nuclease)	**Preclinical**
Base/Prime Editors	Single-nucleotide conversion	Exceptional	Difficult (Very large complexes)	**Preclinical**
seekRNA	Site-specific integration	Exceptional	**High** (Small, stand-alone system)	**Theoretical / Discovery**

ASOs / siRNA	RNA interference/silencing	Moderate	High (Small synthetic strands)	**Clinical** (Phase 1/2 Trials)

Limitations and Challenges of Gene Therapy

Although gene editing technology offers enormous therapeutic potential, each therapeutic method has its own important limitations. TALENs, while highly precise, are difficult to design and produce, and their large protein size complicates delivery into neurons (Chandrasegaran 2017). Zinc Finger Nucleases (ZFNs) require complex protein engineering and can produce side effects if zinc finger arrays bind to unintended sequences (Cradick et al. 2011). Base editors and prime editors avoid breaking DNA into double strands but remain bulky, making them challenging to vectors, and prime editing shows relatively low efficacy in post-mitotic cells such as neurons (Eid et al. 2018; Lee et al. 2025). seekRNA, despite its promise, remains in early development, with not much data available (Siddiquee et al. 2024). Even ASOs and siRNA, which are clinically validated, require constant dosing and struggle to cross the BBB without specialized delivery systems (Kantor et al. 2020; Nature Reviews Materials 2021). These limitations highlight the need for continued gene therapy before they can be used against Alzheimer's. The most formidable issue throughout all of genetic therapy for Alzheimer's is the Blood Brain Barrier (BBB) (Nature Reviews Materials 2021). The BBB is a highly selectively permeable layer for the borders of endothelial cells, which protect the brains from external toxins and pathogens (National Institute on Aging 2024b). While this barrier is essential for survival, it also recognizes therapeutic agents such as AAV Vectors, CRISPR-Cas9 and ASOs as foreign threats, blocking over 98% of all small molecule drugs and nearly all larger genetic tools from entering the central nervous system (Nature Reviews Materials 2021; Padridge 2025). To bypass this barrier, researchers in 2026 are experimenting with focused ultrasound (FUS) with the guidance of MRI to temporarily bypass this barrier and allow all of these gene therapies to take effect (UVA Health 2025). Overcoming the blood brain barrier remains one of the greatest challenges in Alzheimer's gene therapy, but several strategies are emerging. Engineered AAV capsids, such as AAV9 and PHP.eB, are being optimized to pass the BBB more efficiently and target neurons with high specificity (Kantor et al. 2020). Lipid nanoparticles (LNPs), which have been successful in certain mRNA vaccines, are being adapted to deliver gene editing components directly to the central nervous system (Nature Reviews Materials 2021). Researchers are also exploring receptor mediated transcytosis, where therapeutic molecules are attached to ligands which bind to receptors (Nature Reviews Materials 2021). Additionally, exosomes are being engineered as delivery vehicles for RNA and therapeutics which could be potential progress against Alzheimer’s (Nature Reviews Materials 2021). These approaches, combined with ultrasound, represent progress for bypassing the BBB and safely transporting gene editing technologies into the brain (UVA Health 2025). Additionally, most of these gene editing technologies are still in preclinical/discovery stages and have yet to be tested on humans. While Phase 1 and Phase 2 trials have begun for most technologies listed in this paper, the transition from testing upon animals into the central nervous system of humans requires further improvement of long term safety and more experimentation.

Future

Looking into the future, the future of Alzheimer's therapy will likely involve a combination of early detection of Alzheimer's with biomarkers, targeted gene editing with gene editing tools, and improved delivery systems (Yim et al. 2025; He et al. 2025). As blood based biomarkers enable earlier diagnosis, gene editing tools may be deployed before extensive neuronal loss occurs (Yim et al. 2025). This increases the likelihood of meaningful recovery and better treatment against Alzheimer’s (He et al. 2025). Continued refinement of delivery technologies, such as AAV engineering, nanoparticles, and focused ultrasound, will be essential for safe transportation of therapeutic molecules across the BBB (Kantor et al. 2020; UVA Health 2025).

Ultimately, the most promising path forward may involve integrating multiple approaches: correcting genetic risk factors such as APOE-E4, reducing amyloid and tau production, restoring mitochondrial function, and reducing neuroinflammation (Gupta and Musunuru 2014; Wang et al. 2025). While significant challenges remain, the progress of gene editing technologies provide a hopeful foundation for future Alzheimer's treatments which address the disease at its roots rather than treating symptoms (Chen and Liu 2022).

Conclusion

Alzheimer's disease remains one of the most complex and devastating neurodegenerative disorders, driven by the accumulation of amyloid-beta plaques and neurofibrillary tau tangles (O'Brien and Wong 2011). Alzheimer's can cause mitochondrial dysfunction, more stress on metabolism, chronic neuroinflammation, and even death (Wang et al. 2025; Di Benedetto et al. 2022). Although modern diagnostics, particularly plasma biomarkers such as p-tau217, p-tau181, A-beta42/40 ratios, and neurofilament light chain now allow earlier and more accurate detection, current treatments still offer only temporary symptomatic relief (Liu et al. 2025; Yim et al. 2025). The emergence of gene editing technologies provides a promising path towards addressing the roots of the disease rather than its effects (Lu et al. 2021). While CRISPR-Cas9 has dominated early research, other tools with their own benefits and limitations are discussed in this research paper (Gupta and Musunuru 2014; Siddiquee et al. 2024). Significant challenges also remain, particularly in achieving safe and efficient delivery across the blood brain barrier and ensuring long term safety in post-mitotic neurons (Nature Reviews Materials 2021). Continued innovation in delivery systems will be essential for translating these tools into viable therapies (Kantor et al. 2020). As diagnostic capabilities improve and gene technologies advance, a future in which Alzheimer's can be treated at its genetic and molecular origins becomes more plausible (He et al. 2025). The integration of early detection, targeted editing, and optimized delivery may ultimately shift Alzheimer's therapy from symptom management towards true disease modification (He et al. 2025).

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