Narrative Review Article

From Bench to Bedside: Evaluating CRISPR Strategies Reported Since 2020 for Correcting Alzheimer's Disease Pathology

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia worldwide. It is characterized by the accumulation of amyloid plaques and neurofibrillary tangles, often linked to pathogenic gene mutations. As no curative treatment is currently available, researchers are increasingly exploring CRISPR-based strategies, such as base editing, prime editing, and epigenetic editing, as potential therapeutic options. This review examines studies published since 2020 on the application of CRISPR technologies in the context of AD. The evidence highlights the considerable potential of gene editing for targeting AD-associated genes and alleviating disease-related pathology. However, all reported findings remain at the preclinical stage, as key barriers, particularly low editing efficiency and delivery challenges, in delivering CRISPR components to the brain.

Keywords: Alzheimer's Disease; CRISPR; gene editing; base editing; prime editing; epigenetic editing

INTRODUCTION

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disorder that impairs memory, reasoning, and the ability to carry out daily tasks. It is the most common cause of dementia, accounting for 60-80% of cases. Dementia is defined as a syndrome of cognitive decline that affects memory, language, and executive function. In 2022, there were approximately 32 million AD cases globally (1). Common symptoms of Alzheimer's include memory loss, challenges with planning or problem-solving, disorientation in time and place, changes in communication, mood and personality changes (2).

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There are two types of AD: sporadic AD (sAD) and familial AD (fAD). Sporadic AD is the most prevalent, accounting for approximately 75% of cases (3). It typically has a late onset, and its risk factors include lifestyle (sedentary behavior, dietary habits), metabolic disorders (diabetes, obesity) (4) and heart disease(5). A major genetic risk factor is the apolipoprotein E (APOE) gene, which has three main isoforms (ε2, ε3, and ε4), differing single amino acid substitutions at positions 112 and 158. The ε4 allele, identified in 40-65% of patients with sAD, carries a threefold increased risk of AD if present in an heterozygous manner, and of 12-fold if present in an homozygous manner (6). However, APOE ε4 is a risk factor rather than a direct cause, as not all carriers develop AD (7).

Familial AD, by contrast, represents 15-25% of cases (3) and is usually inherited in an autosomal dominant manner. It is linked to rare, high-penetrance mutations in APP, PSEN1, and PSEN2. Mutations in PSEN1, which include missense substitutions, insertions, and deletions, cause the most severe type of AD, sometimes

manifesting as early as 25 years old. In contrast, missense mutations in PSEN2, tend to cause AD with a later age of onset and incomplete penetrance. Both *PSEN1* or *PSEN2* mutations disrupt the function of the γ-secretase complex, an enzyme involved in the proteolysis of amyloid precursor protein (APP). APP cleavage can occur through two pathways: the non-amyloidogenic (α-secretase-dependent) pathway, which produces non-toxic fragments, and the amyloidogenic pathway (β- and γ-secretase-dependent) pathway, which generates amyloid-β (Aβ) peptides of different lengths: primarily Aβ40 (90%) and Aβ42 (10%) (8). Mutations in APP or presenilins alter the Aβ40/Aβ42 ratio, increasing the levels of Aβ42, which is prone to aggregation (7).

The earliest feature of AD is the accumulation of amyloid plaques and neurofibrillary tangles (NFTs). Amyloid plaques are extracellular aggregates of insoluble Aβ fibrils, especially in the hippocampus (responsible for memory), amygdala (responsible for emotion), and cerebral cortex (cognition and integration) (9). These deposits also trigger activation of astrocytes and microglia, causing further neuroinflammation and neuronal damage. The deposition of amyloid plaques also triggers tau pathology. Tau, a microtubule-associated protein that stabilizes axonal microtubules and regulates axonal transport (10), becomes abnormally hyperphosphorylated in AD, forming paired helical filaments (PHFs). PHFs then aggregate into neurofibrillary tangles (NFTs) within neuronal soma, axons, and dendrites, causing loss of cytoskeletal microtubules and tubulin-associated proteins (11). The combined accumulation of Aβ plaques and NFTs leads to synaptic dysfunction, progressive neuronal death and cognitive decline (11–13). In advanced stages, brain imaging shows marked cortical atrophy and neuronal death.

There is currently no available treatment for AD, however certain drugs, such as acetylcholinesterase inhibitors and memantine, are available to help manage the symptoms. Acetylcholinesterase inhibitors (donepezil, galanthamine and rivastigmine) are used to treat mild to moderate disease, enhancing cholinergic neurotransmission and improving cognitive function. Memantine, an NMDA receptor antagonist, is indicated for moderate to severe AD and can delay disease progression and reduce behavioral symptoms (14). Supportive interventions such as physical exercise (15), music therapy (16), cognitive stimulation, and counselling (17) can also contribute to maintaining function and quality of life. Despite these measures, AD remains incurable, imposing a significant personal and economic burden. In the US alone, the formal cost of care was estimated at $196 billion in 2020. This estimate is expected to rise to $1.4 trillion by 2050 (18).

Given the limitations of current therapies, innovative genetic approaches are under investigation. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPRs) were first identified in *Escherichia coli* in 1987 as short DNA repeats interspaced with unique sequences. Later studies revealed that CRISPR-associated (Cas) genes (Cas1-Cas4) provide adaptive immunity in prokaryotes against invading genetic elements. In 2007, CRISPR was demonstrated to function analogously to RNA interference in eukaryotes, using small RNAs and Cas proteins to target foreign genetic material. Cas9 has become a widely used endonuclease for precise genome editing (19). In addition to the Cas9 endonuclease, CRISPR technology uses a single guide RNA (sgRNA), a fusion of a combination of CRISPR RNA (crRNA) and trans-activating crRNA (tracrRNA). Guided by the sgRNA, Cas9 creates a double-strand break (DSB) in the target DNA region. The DSB is then repaired by endogenous DNA repair mechanisms (insertions, deletions, additions, or inversions) (20). This enables gene knockout, correction or replacement, making CRISPR-Cas9 a powerful tool for treating genetic disorders. In AD research, CRISPR has already shown promise; for example, correction of the *PSEN2* (PSEN2N141I) mutation led to the normalization of the Aβ40/Aβ42 ratio in experimental models (21).

Over the past five years, CRISPR technologies have advanced significantly, with the development of more precise editing systems such as base editing and prime editing. This narrative review explores the applications of CRISPR in Alzheimer's disease, with a focus on the potential of gene editing as a therapeutic approach in the context of Alzheimer's disease.

BASE EDITING

Base editing is a CRISPR-based genome editing approach that enables the precise conversion of single DNA bases without generating double-strand breaks. Base editors are engineered fusion proteins composed of three parts: a Cas9 nickase, a single-stranded DNA-specific deaminase, and additional regulatory domains such as uracil glycosylase inhibitor (UGI). The Cas9n, guided by a single-guide RNA (sgRNA), introduces a nick in the DNA sequence, and unwinds the double

helix, creating an R-loop, exposing a small section of single-stranded DNA. Within this region, the diagnosis catalyzes the modification of the base. There are two main types of base editors: cytosine base editors (CBEs) and adenine base editors (ABEs). In CBEs, the cytosine deaminase APOBEC1 converts cytosine to uracil, creating a U:G mismatch. Normally, the base excision repair pathway would remove the uracil, but this is prevented by the fused UGI. As a result, DNA repair processes convert the U:G mismatch into a T:A pair (22), achieving a C:G to T:A substitution. Continuous refinements to base editing have greatly improved efficiency and broadened its potential, with theoretical applications for correcting up to 60% of known pathogenic single-nucleotide variants (23).

In 2021, Guyon *et al.* applied base editing to introduce the protective A673T mutation into the APP gene, with the aim of preventing familial AD. The Icelandic APP mutation (A673T) reduces β-secretase cleavage of APP by 40%, and carriers of this variant show significantly lower accumulation of Aβ peptides in the brain (Figure 1) (24). To test this strategy, the researchers compared several Cas9/deaminase variants (SpCas9nVQR, SaCas9nKKH, SpCas9nEQR) to find the most efficient and precise one. The editors were first tested in HEK293T cells to determine the impact of the mutation on Aβ peptide production in both wild-type APP and the pathogenic V717I variant. Editing

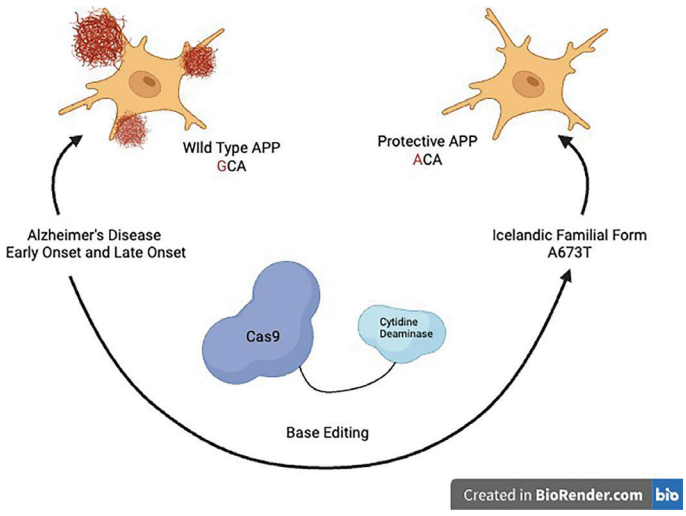

Figure 1. Schematic illustration of base editing introducing the protective A673T variant into the APP gene. The mutation reduces beta-secretase cleavage, lowering beta production and plaque formation.

efficiency was consistently higher in HEK293 cells than in SH-SY5Y cells, with successful introduction of the A673T mutation in up to 53% of HEK293T cells, which significantly reduced Aβ peptide accumulation. Among the tested variants, SpCas9nVQR showed the highest efficiency, with 98% and 70% greater deamination activity compared to SaCas9nKKH and SpCas9nEQR, respectively. These findings suggest that introducing the protective A673T mutation into neurons of patients with AD or pre-AD could be a promising therapeutic approach. In future work, Guyon *et al.* will aim to evaluate this strategy in AD mouse models (NL/F/G mice)(25), neurons carrying the V717I mutation, and iPSC-derived neurons from AD patients (22, 26, 27).

Apart from AD, base editing technology has also been explored in other dementias. Although the pathologies of dementia and AD differ, research on tau-targeted base editing provides important insights that could inform therapeutic strategies for AD. In 2024, Sung Gee *et al.* used base editing to correct tau mutations in mouse models expressing human MAPT-P301S gene. The tau protein, encoded by the microtubule-associated protein tau (MAPT) gene, located on chromosome 17, plays a critical role in stabilizing microtubules. Mutations in this gene, such as P301S are strongly linked to the development of frontotemporal dementia. Using an adenine base editor (NG-ABE8e), the researchers corrected the MAPT mutation, which reduced tauopathy and improved cognitive symptoms in mice. Specifically, the treatment lowered the levels of insoluble tau proteins, whose aggregation into neurofibrillary tangles contributes to cognitive decline. Behavioral tests, including the Morris water maze and passive avoidance test, showed that treated mice demonstrated improved spatial learning and contextual memory (28).

Despite these encouraging results, base editing is still relatively new technology, and further research is required to address safety and precision concerns. Key limitations include the introduction of bystander mutations, off-target DNA editing, and transcriptome-wide deamination. Since base editors have confined editing windows, nearby cytosines or adenines can be unintentionally modified, creating bystander) mutations. One solution being researched is engineering based editors with narrow editing windows. The off-target effects, where unintended DNA sites are modified, can have serious health implications, but can be reduced by using high-fidelity Cas9 variants. Further, transcriptome-wide RNA deamination can alter RNA

molecules in unpredictable ways, potentially leading to adverse effects (29). Future directions include testing these strategies in iPSC neurons and developing next-generation editors that can overcome current limitations.

PRIME EDITING

Prime editing was created to overcome the limitations of base editing, which is restricted to a narrow range of precise nucleotide substitutions (30). Like base editing, prime editing uses a Cas9n, but instead of relying on base determination it fuses the Cas9 enzyme to an engineered reverse transcriptase (RT). It also uses a modified sgRNA called a prime editing guide RNA (pegRNA). RT, an enzyme originally derived from retroviruses, is responsible for the synthesis of DNA from RNA, enabling it to integrate into the host's DNA (31).

Similar to the research conducted with base editing, prime editing has also been explored as a method of introducing the protective A673T Icelandic mutation into human cells (Figure 2) (32, 33). Initial attempts

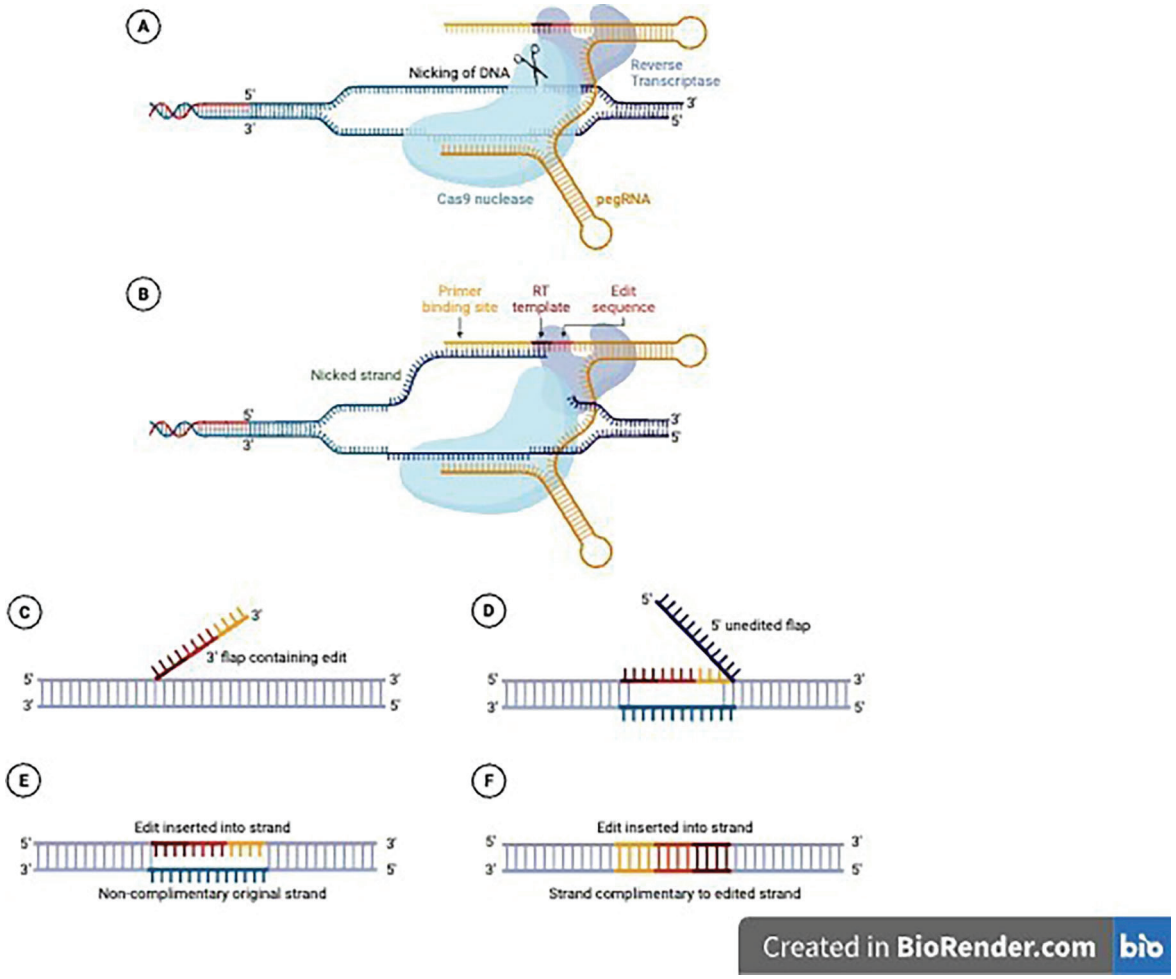

Figure 2. Prime Editing Mechanism. In prime editing, the pegRNA contains: i) a 20-nucleotide-long protospacer sequence that specifies the target sequence (i.e. directing the Cas9 enzyme to the correct target DNA sequence), ii) a primer binding site (PBS) and iii) an RT template (RTT) that encodes the desired edit. Once the pegRNA guides the Cas9 enzyme to the target sequence, it cuts the noncomplementary strand, three nucleotides upstream of the protospacer adjacent motif (PAM) sequence. The exposed 3' OH group anneals to the PBS. The RT then extends the nicked strand using the RTT, producing a 3' flap with the desired edit. The unedited 5' flap is removed by a 5' endonuclease (e.g. FEN1) or a 5' exonuclease (e.g. EXO1). DNA mismatch repair mechanisms are then triggered, either incorporating the desired modification or restoring the original sequence. If the original sequence is maintained, the Cas9n and pegRNA complex can bind to DNA again and start over.

involving PE2 only achieved modest efficiencies (<6.4%), prompting the use of PE3, which induced an additional nick to aid editing. This led to an increase in the frequency of A673T mutation to almost 10%, while keeping the formation of indels low (0.06-0.89%). Further optimization involving pegRNAs that simultaneously introduce A673T and eliminate the PAM sequence both increased efficiency and ensured edit conservation upon repeated treatments. With a 10-week timeframe, these optimizations increased A673T editing frequencies to almost 70%, again while generating low indels. This study shows how prime editing could be used to targ*et al*zheimer's-related mutations, such as A673T, especially with repeated treatment (33). While prime editing allows highly precise nucleotide conversion, achieving sufficient levels of editing remains a challenge. In a recent study by Rottner *et al*., the authors optimized and developed a prime-editing strategy to introduce the APOE protein into human cells with an efficiency of 28-42%. However, despite using the same pegRNA binding site, when attempting to correct the APOE4 to 3, the editing efficiency was less than 1%. The low correction efficiency observed when converting e4 to e3 highlights an important challenge for the therapeutic translation of prime editing (34).

Delivery remains one of the main challenges for CRISPR-based therapies, including prime editing. The brain poses particular obstacles due to the blood-brain-barrier and the heightened sensitivity of neural tissue to immune activation and inflammation, all of which can reduce editing efficiency and safety (35). Compared to base editing, prime editing is associated with fewer off-target mutations in human cells, but it also has distinct limitations. For example, prime editing can still occasionally introduce small insertions at the target site, and DNA mismatch repair pathways can interfere with editing efficiency. To overcome these barriers, researchers are developing new delivery systems, including engineered new adeno-associated virus (AAV)-vectors that enhance prime editor expression, stabilize pegRNAs, and modulate DNA repair pathways, thereby improving precision and efficiency (36).

EPIGENETIC EDITING

Epigenetic editing modifies the epigenome to control gene expression without changing the DNA sequence. Artificial transcriptional activators, such as the fusion of DNA-binding domain and a transcriptional activation domain, allow us to precisely regulate the expression of certain genes. A typical tool for gene regulation encodes components consisting of a targeting domain that binds to a specific genome, fused with an effector domain. catalytically inactivated Cas9 (dCas9), which is a CRISPR/Cas9 mutant that when fused with effector domains, can be used for DNA methylation, gene expression modulation, and epigenetic regulation (37). Thus, it is unable to cut DNA, but it retains strong binding activity programmed by the co-expressed sgRNA molecule (38). In a 2022 study, Hanseul Park *et al*. attempted to use epigenetic editing to methylate the APP promoter to reduce APP mRNA expression and, therefore, avoid AD-related neuronal cell death. They used dCas9 fused with Dnmt3a, a DNA methyltransferase that methylates CpG dinucleotides, to suppress APP in primary neurons in the APP knock-in (APP-KI) mouse model in vivo. They found that APP expressions in dCas9-Dnmt3a treated cells was significantly decreased. They also validated the decrease in the Aβ42/Aβ40 ratio, suggesting that APP methylation via dCas9-Dnmt3a can alleviate neuronal deficits in neurons of patients with AD (37).

Epigenetic editing was also tested on 5xFAD mouse models with five familial AD disease mutations (APP K670N/M671L, V717I, I716V, and PS1). Cathepsin D (Ctsd) is an intracellular aspartyl protease whose levels increase with elevated Aβ expression in AD, helping to mitigate Aβ accumulation. In a recent study, Moonsu Park *et al*. used a dCas9-Tet1-mediated DNA demethylation system to upregulate Ctsd expression in primary neurons and the mouse brain in vivo. Results showed a significant increase in Ctsd expression, leading to a decreased Aβ42/Aβ40 ratio in both in vitro and in vivo models of AD. Additionally, the treatment showed an improvement in cognitive function and memory in 5xFAD mice (39).

Epigenetic editing holds great promise in treating AD, however, there are a number of issues that still need to be addressed before clinical application. For instance, clinical trials integrating viral vectors with CRISPR/Cas9 technology can lead to random insertional mutagenesis. To target this issue, non-viral vectors need to be developed for efficient delivery of the CRISPR/Cas9 components. Another limitation is that the injection of viruses for delivery of dCas9 holds back the efficiency and safety of gene editing. The dCas9 delivery systems need to be improved to accelerate the widespread use of epigenetic editing (37).

CONCLUSION

Alzheimer's disease remains a widespread neurodegenerative disorder that impairs cognitive function. Despite its significant medical challenges and substantial economic burden on healthcare systems, there is still no curative treatment available. Current therapies, such as acetylcholinesterase inhibitors and memantine, can alleviate symptoms but do not halt disease progression. However, the rapid advancement of CRISPR-based technologies, particularly base editing, prime editing, and epigenetic editing, has opened new possibilities for therapeutic intervention. Base editing has been applied to reduce amyloid-beta accumulation in human cells and to correct tau-related dysfunction in animal models, showing promising results. Prime editing offers broader editing capabilities, although achieving high efficiency remains challenging. Meanwhile, epigenetic editing enables regulation of gene expression without altering the DNA sequence, presenting potential for reversible modulation of disease-associated genes.

Although base, prime, and epigenetic editing share the same CRISPR-guided targeting system, they differ substantially in their mechanism, efficiency, and risk of off-target effects. Base editing is generally the most efficient, achieving nucleotide conversion of up to an average of 80% in vitro (24). But it is limited to specific transition mutations and can cause bystander edits. Prime editing offers higher versatility, since it's capable of small insertions, deletions, and all 12 possible base substitutions, but its efficiency remains low (35% efficiency) (34). It is also, technically, more complex due to the design of the pegRNA and RT requirements. Epigenetic editing, by contrast, does not alter the DNA sequence, but instead, modulates gene expression, offering a potentially safer approach. However, its gene regulatory effects may be transient, and the long-term stability of epigenetic modifications remains unknown. In terms of delivery, all three approaches face major challenges in crossing the blood barrier with viral bacteria (AAV and lentivirus) showing the highest transduction efficiency but raising concerns about immunogenicity and limited cargo capacity. Non-viral systems, such as lipid nanoparticles or exosomes, are promising, but require optimisation. Off-target effects remain a concern across all systems, although high fidelity Cas variants an improved guide design have significantly reduced unwanted edits. Each method presents a trade-off between efficiency, flexibility, and safety, which need to be balanced when developing therapeutic strategies for AD.

Several translational barriers. Key requirements include the development of safe and efficient delivery vectors capable of targeting neuronal cells across the blood brain barrier, minimizing activation of the immune system, and ensuring the long-term expression of editing components. Dual-AAV systems and engineered nanoparticles are currently the most promising options for central nervous system delivery. Additionally, strategies to achieve region-specific targeting, such as neuron-selective promoters, are essential to avoid off-target editing in non-neuronal tissues. Ethical considerations are also key as somatic gene editing for neurodegenerative disorders must ensure a minimal risk of germ editing and maintain transparency regarding patient consent, long-term follow-up, and data-sharing. Addressing these translational and ethical factors will be essential for advancing CRISPR-based approaches towards human trials in AD.

These experiments showed great editing efficiency, and a decline in cognitive symptoms, respectively. However, some limitations, such as bystander mutations, off-target editing, and transcriptome-wide mutations, call for more research and engineering of newer base editing versions. Prime editing is associated with more precise base substitutions, and while it has been used to induce new mutations into human cells, researchers are still trying to find a solution to mitigate the technology's poor editing efficiency and delivery challenges. Lastly, epigenetic editing manages to control gene expression without having to modify the DNA sequence. It has been tested on mouse models, with the results showing a decreased Aβ42/Aβ40 ratio. While this technology holds great promise in AD treatment, it is still relatively new and needs to be tested on clinical trials. Delivery is a problem, as well, as it holds back the technique's efficiency potential and raises safety concerns. Nevertheless, in the future, these technologies can be revolutionary in the field of healthcare, and treating diseases, such as AD. To bring them into clinical use, more research needs to be conducted particularly on the delivery challenges and the treatment's efficiency.

In conclusion, while all three CRISPR-based strategies remain in the pre-clinical stage, continued improvement could transform the treatment landscape for Alzheimer's disease. Future work should prioritize reducing off-target effects, delivery optimization, and assessment of long-term efficacy and safety in human-relevant models to bring this technology from bench to bedside.

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CONFLICT OF INTEREST

The author(s) declares that there are no conflicts of interest related to this work.

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