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REVIEW ARTICLE

Therapeutic implication of CRISPR gene editing in Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with enormous societal impact and limited curative options. The emergence of CRISPR-based genome and epigenome editing has created a new therapeutic design space: correcting pathogenic variants in autosomal-dominant AD, reprogramming major risk alleles (notably APOE), and tuning genetically implicated microglial and neuronal pathways that drive disease initiation and progression. This review synthesizes the biological rationale, summarizes CRISPR modalities most relevant to CNS therapeutics (nucleases, base editors, prime editors, CRISPRi/a, and epigenome editors), and evaluates delivery, safety, biomarker strategy, and ethical governance required for translation. We conclude with a development roadmap emphasizing target selection grounded in human genetics, CNS-optimized delivery platforms, and rigorous genomic and functional safety analytics appropriate for preventive or disease-modifying interventions. This review synthesizes the therapeutic rationale for CRISPR in AD, surveys relevant editing technologies, highlights preclinical proof-of-concept directions (including APP terminus editing and APOE editing concepts), and outlines a translational roadmap emphasizing delivery engineering, safety analytics, patient stratification, and ethical governance.

Key words: Alzheimer's disease, CRISPR, target selection, CNS therapeutics

1. Introduction

Alzheimer's disease is the leading cause of dementia and constitutes a major and growing public health challenge in aging societies [1]. Dementia prevalence and related care needs are increasing worldwide, generating substantial personal, caregiver, and health-system burdens [1]. AD is defined biologically by the accumulation of amyloid- (A) pathology and tau pathology, alongside neurodegeneration and synaptic dysfunction [2, 3, 4]. Neuropathologically, AD progression is often staged by the anatomical spread of tau-related neurofibrillary changes, which correlates with clinical deterioration [5]. Contemporary frameworks emphasize that AD can be conceptualized and diagnosed using biomarkers reflecting amyloid, tau, and neurodegeneration, supporting earlier identification of at-risk individuals and enabling mechanism-based clinical trials [4].

Despite decades of therapeutic development, disease-modifying treatments have historically delivered limited clinical benefit, often targeting downstream pathology rather than upstream causes [3, 6]. Recent monoclonal antibodies against aggregated A—including lecanemab and donanemab—have demonstrated statistically sig-

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nificant slowing of decline in selected early-stage populations, but the magnitude of benefit is modest, and safety risks such as amyloid-related imaging abnormalities (ARIA) complicate deployment [7, 9, 10, 11, 12]. Cerebral amyloid angiopathy, frequently coexisting with AD, is also relevant to ARIA risk and therapeutic safety considerations [13]. These realities strengthen the rationale for approaches that intervene earlier and more causally, potentially by modifying genetic determinants of disease initiation, propagation, or resilience [14, 15].

Human genetics provides unusually strong causal anchors for AD target selection [14, 16, 17, 18]. Rare, highly penetrant variants in APP, PSEN1, and PSEN2 cause autosomal-dominant early-onset AD and establish a direct gene-to-pathology relationship through altered A production, processing, or aggregation [19, 20, 21, 22, 23]. In late-onset AD, polygenic risk implicates lipid metabolism, endosomal trafficking, and innate immunity, with APOE 4 as the most influential common risk allele [16, 24, 25, 26]. In parallel, rare coding variants in genes including TREM2 and other microglial-associated loci underscore the importance of microglial state transitions and immune-lipid signaling in disease risk and progression [27, 28, 29, 30, 31]. These genetic insights motivate strategies that either correct pathogenic sequence variants or modulate pathway activity toward protective states observed in human populations [14, 16, 17, 18].

CRISPR-based genome and epigenome editing offers a programmable means to achieve these goals at the level of DNA sequence or gene regulation [32, 33, 34, 35]. Unlike conventional small molecules or antibodies, CRISPR platforms can be designed to (i) correct a specific pathogenic nucleotide, (ii) convert a risk allele to a neutral or protective allele, (iii) disrupt a toxic gain-of-function mechanism, or (iv) durably tune gene expression programs in defined CNS cell types [32, 33, 34, 35, 36, 37]. At the same time, the brain imposes stringent translational constraints: delivery across or around the blood–brain barrier (BBB), cell-type specificity, immune responses to vectors and editors, and an especially high bar for genomic safety in long-lived neurons and in preventive settings [38, 39, 40, 41, 42, 43, 44, 45]. This review evaluates the therapeutic implications of CRISPR for AD by integrating (a) AD genetics and biology, (b) the relevant CRISPR technology landscape, (c) CNS delivery considerations, (d) safety and monitoring frameworks, and (e) ethical governance for interventions that may be permanent and administered early in life-course disease trajectories [4, 14, 38, 39, 40, 41, 42, 43, 44, 45].

2. Genetic architecture of AD and implications for editability

AD can be broadly divided into autosomal-dominant familial forms and the much more common sporadic late-onset form, each implying different "editability" assumptions [14, 16, 17, 18]. Autosomal-dominant AD provides the most straightforward therapeutic logic for gene correction because pathogenic variants in APP, PSEN1, and PSEN2 can be necessary and sufficient to cause disease with high penetrance [19, 20, 21, 22, 23]. APP mutations were among the earliest causal discoveries, with certain missense mutations segregating with familial AD and mechanistically influencing A generation or aggregation propensity [19, 22]. PSEN1 and PSEN2 encode presenilin proteins essential to -secretase, and many mutations shift cleavage preferences to increase longer, aggregation-prone A species [20, 21, 23]. These familial variants also reinforce the amyloid cascade hypothesis, which posits that A dysregulation initiates downstream tau pathology, synaptic failure, and neurodegeneration [22, 46]. From a therapeutic development perspective, familial AD offers clear genotype–phenotype links, the feasibility of identifying at-risk carriers, and interpretable molecular biomarkers (A species, amyloid/tau imaging) for pharmacodynamic monitoring [4, 7, 9, 10].

Sporadic late-onset AD is polygenic and strongly influenced by age and co-morbidities, but genetics still points to tractable pathways [14, 16, 17, 18]. Large GWAS meta-analyses have identified risk loci implicating A processing, tau biology, lipid metabolism, endosomal trafficking, and immune signaling, highlighting convergent mechanisms rather than a single gene driver [14, 16, 17, 18]. APOE 4 remains the dominant common risk allele, with dose-dependent effects on risk and age at onset [24, 25]. APOE isoform state also influences A deposition, lipid transport, synaptic physiology, and glial immune responses, making it a compelling target for allele-state "reprogramming" strategies [26]. Protective human genetic states further illustrate potential therapeutic directions: APOE2 homozygosity is associated with exceptionally low likelihood of AD dementia, implying that shifting APOE biology toward a more protective isoform state could be clinically meaningful [47]. Importantly, immune and microglial genetics—particularly TREM2 and related loci—supports the hypothesis that microglial response programs can be protective or maladaptive depending on context, and that tuning these programs may alter disease trajectories [27, 28, 29, 30, 31, 48, 49, 50].

Translational "editability" depends on whether benefit requires precise nucleotide correction, allele-selective conversion, partial knockdown, or reversible expression tuning [36, 37]. Classical Cas9 nuclease editing relies on double-strand breaks (DSBs) repaired by non-homologous end joining (NHEJ) or homology-directed repair (HDR) [32, 33]. HDR is inefficient in post-mitotic neurons, limiting precise correction in the adult brain and increasing interest in DSB-free approaches [38, 39]. Base editors can install certain single-nucleotide transitions without DSBs, which is directly relevant for allele conversion concepts (e.g., APOE isoform-defining variants) and for correcting a subset of familial point mutations [34, 35]. Prime editing extends sequence flexibility, enabling all base substitutions and small insertions/deletions without requiring DSBs or donor templates, making it conceptually attractive for neuronal correction scenarios [35]. When the therapeutic intent is pathway modulation rather than sequence rewrite, CRISPR interference/activation (CRISPRi/a) and epigenome editing provide programmable regulation of gene expression without changing DNA sequence, potentially offering improved safety and reversibility profiles [36, 37, 51].

Cell-type specificity is central because many AD risk pathways are cell-contextual [26, 27, 28, 29, 30, 31]. APOE is predominantly expressed in astrocytes (and inducibly in microglia under certain conditions), whereas TREM2 is microglia-enriched, and APP processing is heavily neuronal but influenced by endosomal trafficking across cell types [26, 27, 28, 29, 30, 31, 48, 49, 50]. Therefore, therapeutic feasibility is not determined solely by gene choice but by whether a suitable delivery strategy can reach the relevant CNS cell population at adequate coverage and with acceptable safety [38, 39, 40, 41, 42, 43, 44]. These considerations motivate a precision-development paradigm: genetics defines compelling targets, but delivery engineering and CNS cell biology determine which targets can be safely and effectively edited in real-world patients [38, 39, 40, 41, 42, 43, 44].

3. CRISPR technology landscape relevant to CNS therapeutics

CRISPR-Cas systems were adapted from bacterial adaptive immunity into programmable genome-editing tools by pairing guide RNAs with Cas nucleases to target DNA sequences adjacent to PAM motifs [32, 33]. Early demonstrations established RNA-guided Cas9 editing in mammalian cells and enabled multiplexed genome engineering, inaugurating a platform era for functional genomics and therapeutic design [33, 52]. Subsequent advances have diversified CRISPR modalities to improve specificity, expand editable outcomes, and reduce genotoxicity—priorities that are particularly

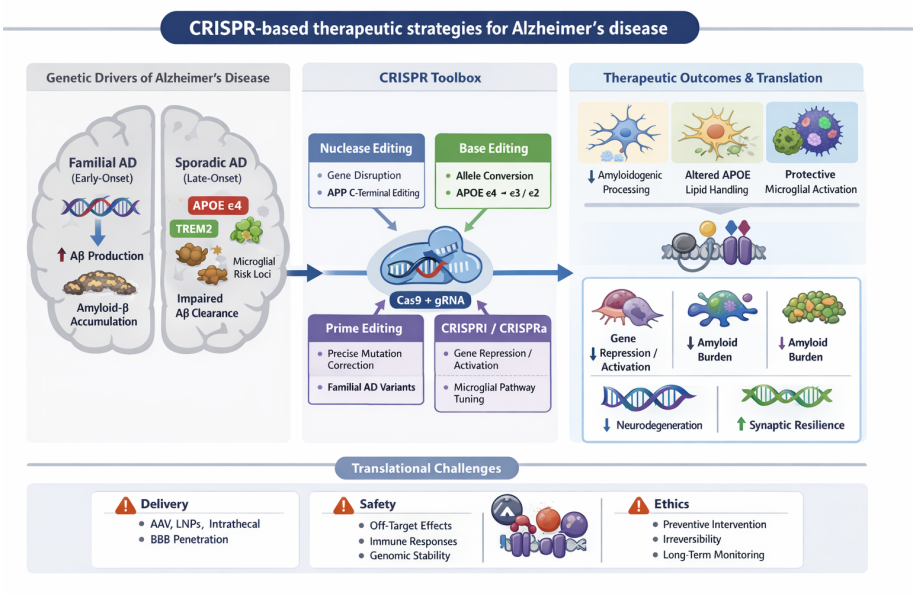

Figure 1. Mechanistic overview of CRISPR-based therapeutic strategies for Alzheimer's disease. Human genetics identifies causal mutations in autosomal-dominant AD (APP, PSEN1, PSEN2) and major risk pathways in sporadic AD (APOE, microglial immune-lipid signaling). CRISPR technologies—including nuclease editing, base and prime editing, CRISPRi/a, and epigenome editing—enable mutation correction, risk allele reprogramming, or pathway modulation in neurons and glial cells. These interventions aim to reduce amyloid- production and deposition, modulate neuroinflammation, and enhance neuronal resilience. Translation is constrained by CNS delivery, genomic and immunological safety, and ethical considerations, particularly for preventive applications.

acute for CNS applications [38, 39, 40, 41, 42, 43, 44, 45, 53].

3.1 Nuclease editing and specificity engineering

Canonical SpCas9 generates DSBs that are most commonly repaired by NHEJ, producing indels that can disrupt gene function [32, 33]. Nuclease editing is therefore most naturally suited to therapeutic concepts requiring gene disruption rather than precise correction, such as silencing a toxic gain-of-function mechanism or removing a pathogenic motif [38, 39]. However, DSBs can also induce large deletions and complex rearrangements at the on-target site, and they can elicit DNA damage responses with potential safety implications [40, 41]. In dividing cells, CRISPR-induced DSBs have been associated with p53-mediated responses, raising concerns about selection for p53 pathway abnormalities under certain conditions [40]. Although mature neurons are post-mitotic, glial populations can proliferate, and CNS injury or disease states can alter cell cycling and stress pathways, justifying conservative risk assessment [38, 39, 40, 41, 42, 43, 44, 45].

To mitigate off-target cleavage, multiple high-fidelity Cas9 variants have been engineered to reduce non-specific DNA interactions and thereby improve genome-wide specificity [54, 55]. Additional strategies such as paired nickases (double-nicking) can further enhance specificity by requiring two coordinated single-strand nicking events to generate an effective DSB [56]. Mechanistic work has also clarified proofreading-like behaviors that influence Cas9 targeting fidelity, informing editor selection and gRNA design [57]. For therapeutic development, these innovations provide a menu of nuclease architectures that can be matched to the acceptable risk profile and the intended duration of editor expression [38, 39, 40, 41, 42, 43, 44, 45].

3.2 Base editing

Base editors fuse a catalytically impaired Cas protein to a deaminase enzyme to enable direct base conversion within a defined "editing window," typically without generating DSBs [34, 58]. Cytosine base editors primarily mediate C→T (or G→A on the opposite strand) conversions, and adenine base editors mediate A→G (or T→C) conversions, enabling targeted transition mutations [34, 58]. This approach is particularly relevant to allele conversion concepts (such as modifying APOE isoform-defining variants) and to correcting a subset of familial point mutations that are compatible with available base editing chemistries and editable windows [26, 34, 58]. Base editing can also introduce bystander edits within the window and may generate unintended outcomes depending on sequence context, emphasizing the need for careful gRNA and editor engineering [34, 58]. For CNS use, the appeal of base editing lies in avoiding DSB-associated rearrangements, but comprehensive assessment of editing byproducts and off-target deamination remains essential [38, 39, 40, 41, 42, 43, 44, 45].

3.3 Prime editing

Prime editing couples a Cas nickase with a reverse transcriptase and uses a prime-editing guide RNA (pegRNA) that encodes the desired edit, enabling all base substitutions and small indels without DSBs or donor DNA templates [35]. Because prime editing can, in principle, execute precise edits in non-dividing cells, it is conceptually well-suited to neuronal correction challenges in the adult brain [35, 38, 39]. Prime editor payload size is large, creating practical delivery challenges for AAV vectors and motivating split-editor approaches or alternative delivery modalities [38, 39, 40, 41, 42, 43, 44]. Nevertheless, prime editing has been actively optimized in human stem cell systems for AD-relevant edits, including APOE-related allele engineering in iPSCs, supporting feasibility in human preclinical pipelines [59]. For therapeutic translation, prime editing's flexibility is balanced against delivery complexity and the need to minimize unintended byproducts or off-target effects across the genome [38, 39, 40, 41, 42, 43, 44, 45].

3.4 CRISPRi/a and epigenome editing

Catalytically dead Cas9 (dCas9) can be fused to transcriptional repressors or activators to achieve CRISPRi or CRISPRa—programmable downregulation or upregulation of

target genes without altering DNA sequence [36, 37]. This is attractive for AD when the therapeutic goal is to tune pathway activity (e.g., reducing harmful inflammation mediators or boosting protective programs) rather than permanently rewriting sequence [27, 28, 29, 30, 31, 36, 37]. Epigenome editors extend this concept by tethering enzymes that write or erase epigenetic marks, allowing locus-specific remodeling of chromatin states and potentially durable changes in gene expression [38, 60]. CRISPR-based transcriptional memory systems further demonstrate that epigenome editing can generate persistent gene silencing that is reversible under certain configurations, offering a design axis between transient pharmacology and permanent genome editing [51]. Reviews of epigenetic editing in neurological disease emphasize both the therapeutic promise and the need for careful long-term evaluation of neural circuit consequences [61].

Collectively, modern CRISPR platforms enable a spectrum of intervention types: nuclease-mediated disruption, base/prime editing for precise sequence change, and CRISPRi/a or epigenome editing for expression modulation [32, 33, 34, 35, 36, 37, 51]. In AD, where both monogenic causal mutations and complex risk architectures exist, this diversity increases therapeutic optionality but also heightens the requirement for rigorous delivery engineering and safety analytics matched to the CNS context [38, 39, 40, 41, 42, 43, 44, 45].

4. Therapeutic strategies for AD using CRISPR

CRISPR-based interventions in AD can be conceptualized into three therapeutic archetypes: (i) mutation correction or functional rewiring in autosomal-dominant AD, (ii) risk allele reprogramming (particularly APOE) for prevention or risk reduction, and (iii) pathway modulation in sporadic disease—especially microglial immune-lipid networks—aimed at disease modification in symptomatic stages [14, 16, 17, 18, 26, 27, 28, 29, 30, 31]. Each archetype implies different acceptable risk levels, patient selection approaches, and endpoints, which is critical because AD has a long preclinical phase and because permanent genomic modifications demand exceptional safety justification [4, 38, 39, 40, 41, 42, 43, 44, 45].

4.1 Familial AD: precise correction and functional rewiring of APP/PSEN biology

For autosomal-dominant AD, the most direct therapeutic hypothesis is to correct the causal variant in APP, PSEN1, or PSEN2 before substantial neuropathology accrues [19, 20, 21, 22, 23]. In practice, neuronal HDR inefficiency reduces feasibility for conventional "cut-and-repair" correction in the adult brain, elevating interest in prime editing or base editing approaches that can install precise edits without DSBs [35, 38, 39, 58]. Prime editing is particularly attractive because it can, in principle, revert diverse mutations—including transversions and small indels—without donor templates [35]. Base editing can address a subset of point mutations compatible with available conversion chemistries and editable windows [34, 58]. Familial AD mutation carriers can be identified genetically and monitored with biomarker trajectories aligned to amyloid and tau biology, supporting preventive trial designs with mechanistically interpretable readouts [4, 7, 9, 10].

Beyond literal variant correction, CRISPR can be used to "rewire" APP processing to reduce amyloidogenic A generation while preserving physiological APP functions [22]. A reported strategy has edited the APP C-terminus to remove an endocytic motif, reducing amyloid production in model contexts and illustrating a therapeutic logic of selectively altering pathogenic processing rather than eliminating APP entirely [62]. This approach is conceptually aligned with genetics suggesting that partial reductions in amyloidogenic processing—akin to protective states—may be sufficient to meaningfully alter risk while preserving normal protein functions [22, 46]. Nonetheless, any permanent modification in neurons requires stringent evaluation of network-level effects, given APP's roles in synaptic biology and neuronal health [3, 6].

A central translational challenge is timing: preventive editing in mutation carriers would likely need to occur years before symptoms to maximize benefit, which increases ethical demands because recipients may be asymptomatic and because long-term risks must be exceptionally low [4, 38, 39, 40, 41, 42, 43, 44]. Consequently, early clinical exploration—if pursued—would most plausibly begin in narrowly defined high-need populations, with robust biomarker endpoints and conservative dosing/delivery strategies to minimize genomic and immunological risk [38, 39, 40, 41, 42, 43, 44]. Unsupervised machine learning approaches have been shown to identify latent outcome-defined subgroups in complex clinical datasets, outperforming traditional risk indices and supporting the use of data-driven stratification strategies for precision therapeutic development [45].

4.2 APOE editing and allele-state reprogramming

APOE is a uniquely compelling target because 4 has a large effect size and because isoform state is defined by specific coding variants, making allele conversion theoretically addressable by base or prime editing [24, 25, 26, 34, 35, 58]. The dose-dependent risk conferred by 4 and the exceptionally low likelihood of AD dementia in 2 homozygotes together suggest that shifting APOE biology toward a more protective isoform state could be clinically meaningful [24, 47]. Mechanistically, APOE influences A deposition and clearance, lipid transport, synaptic function, and neuroimmune pathways—effects that are highly relevant to AD pathophysiology [26]. Prime editing optimization for APOE-related edits in human iPSCs has reinforced feasibility for precision allele engineering in human cellular systems used for preclinical validation [59].

However, therapeutic APOE editing must confront key biological and translational constraints. APOE is expressed predominantly by astrocytes and can be induced in microglia, so the most direct therapeutic logic targets glial compartments rather than neurons [26]. Cell-type restriction is crucial because systemic APOE modulation could alter peripheral lipid metabolism, implying that CNS-restricted delivery or highly specific regulatory control would be required for acceptable safety [26, 38, 39, 40, 41, 42, 43, 44]. Preventive editing for APOE 4 carriers also raises ethical questions because 4 is common, penetrance is incomplete, and modifiable risk factors meaningfully influence outcomes, complicating risk–benefit justification for permanent interventions [24, 26, 47, 83]. Therefore, APOE editing is best viewed as a long-horizon strategy contingent on major advances in CNS delivery, safety validation, and ethically robust frameworks for preventive genomic interventions [38, 39, 40, 41, 42, 43, 44, 45].

4.3 Microglial and immune pathway editing

Genetics and functional studies converge on microglia as central players in late-onset AD, with TREM2 emerging as a key receptor influencing microglial responses to lipid and amyloid environments [27, 28, 29, 30, 31, 48, 49, 50]. Rare TREM2 variants substantially increase AD risk, supporting the hypothesis that restoring or enhancing TREM2 signaling—or modulating downstream pathways—could be therapeutic in genetically defined subsets [30, 31]. More broadly, immune-lipid pathway genes implicated by GWAS suggest a network architecture where shifting microglial states may influence plaque compaction, synaptic pruning, inflammatory cascades, and neurodegenerative propagation [27, 28, 29, 30, 31, 48, 49, 50]. CRISPR can support this domain in two complementary ways: (i) mechanistic target validation through isogenic human cell models and perturbation screens, and (ii) even-

tual therapeutic editing for variant correction or pathway tuning in vivo [14, 16, 36, 37, 63].

Because microglial responses can be protective or harmful depending on disease stage, interventions that enable graded or reversible tuning may be preferable to permanent sequence changes [48, 49, 50]. CRISPRi/a and epigenome editors are therefore attractive modalities for microglial pathway modulation, providing a potential means to dampen maladaptive inflammatory programs or boost protective phagocytic and lipid-handling programs without permanent genome alteration [36, 37, 51]. Translation would still require delivery systems capable of reaching microglia at sufficient coverage in the adult human brain and would require biomarkers that reflect microglial state changes alongside clinical outcomes [38, 39, 40, 41, 42, 43, 44, 45].

4.4 Resilience engineering and combinatorial logic

AD progression correlates with synaptic dysfunction and network failure, suggesting that enhancing resilience pathways could complement pathology-targeting approaches [2, 3, 6]. CRISPRa could, in principle, boost protective genes, while CRISPRi could reduce expression of drivers of toxic protein production or maladaptive inflammation [36, 37]. Genome-scale CRISPRi/a screening frameworks can identify functional modifiers and druggable nodes, providing a discovery engine that is directly relevant to building multi-target therapeutic hypotheses for a complex disorder like AD [63]. Epigenetic editing reviews in neurological disorders emphasize the opportunity to reprogram gene networks but also highlight uncertainties about long-term circuit consequences, reinforcing the need for careful translational gating [61].

Overall, CRISPR's therapeutic implication in AD is best framed as a portfolio: near-term utility in target discovery and mechanistic validation; mid-term plausibility in genetically defined high-need subtypes; and longer-term potential for risk allele reprogramming and pathway tuning if delivery and safety hurdles are resolved to a standard appropriate for preventive CNS interventions [38, 39, 40, 41, 42, 43, 44, 45].

5. Delivery to the CNS and cell-type specificity

The dominant translational barrier for CRISPR therapeutics in AD is delivery: achieving sufficient editor exposure in relevant CNS cell populations while minimizing systemic exposure, immune activation, and off-target effects [38, 39, 40, 41, 42, 43, 44, 45]. The BBB limits entry of large biologics and gene therapy vectors, and AD-relevant targets span neurons, astrocytes, and microglia distributed across widespread cortical and subcortical regions [2, 3, 4, 26, 27, 28, 29, 30, 31]. Therefore, delivery is not only a pharmacokinetic problem but a systems-engineering problem integrating route of administration, vector or carrier design, payload constraints, and cell-type specificity [38, 39, 40, 41, 42, 43, 44, 45, 64, 65, 66, 67, 68, 69].

5.1 Viral vectors

Adeno-associated virus (AAV) is widely used for CNS gene delivery due to relatively favorable safety, diverse serotypes, and the potential for long-term expression in non-dividing cells [64, 65]. AAV9 and related vectors have shown CNS transduction after intrathecal administration in nonhuman primates, supporting translational relevance of CSF-based delivery routes [66]. Reviews emphasize that therapeutic AAV delivery to the nervous system is increasingly clinically real, yet human dosing can be constrained by pre-existing immunity, inflammatory toxicities, and organ-specific risks such as liver injury at high systemic doses [65, 67]. For CRISPR, durable AAV expression can be advantageous for CRISPRi/a constructs that rely on sustained dCas9-mediated regulation, but it can be undesirable for nuclease editors because prolonged expression may increase cumulative off-target risk [36, 37, 38, 39, 40, 41, 42, 43, 44, 45].

AAV also imposes a stringent packaging limit (approximately 4.7 kb), which is challenging for large editors such as SpCas9-based base editors and especially prime editors [35, 38, 39, 40, 41, 42, 43, 44, 45]. Dual-AAV split-intein strategies can reconstitute large proteins in vivo, but these approaches can reduce efficiency and complicate manufacturing and regulatory evaluation [38, 39, 40, 41, 42, 43, 44, 45, 67]. Consequently, editor choice often becomes a delivery-driven decision in CNS programs: smaller Cas orthologs, split-editor designs, or non-viral systems may be required depending on therapeutic goals [38, 39, 40, 41, 42, 43, 44, 45, 52, 70].

5.2 Non-viral delivery

Lipid nanoparticles (LNPs) have achieved broad clinical success for nucleic acid delivery and are attractive for gene editing because they can deliver Cas mRNA and gRNA (or potentially RNPs) with transient expression, which may reduce off-target and immunogenicity risks relative to persistent viral expression [68, 69]. Reviews of LNP-based gene therapy emphasize that formulation chemistry can tune biodistribution and intracellular trafficking, affecting endosomal escape and functional delivery outcomes [68, 69]. However, many LNPs preferentially accumulate in liver after systemic delivery, making CNS targeting challenging without specialized formulations, targeting ligands, or alternative administration routes [68, 69]. Intrathecal or intracisternal delivery could provide higher CNS exposure while limiting systemic distribution, but each route introduces procedural considerations and distinct biodistribution profiles [38, 39, 40, 41, 42, 43, 44, 45, 66, 68, 69].

5.3 Routes of administration and coverage in a distributed disease

Potential CNS delivery routes include intracerebral injection, intrathecal/intracisternal administration, and systemic intravenous delivery [38, 39, 40, 41, 42, 43, 44, 45, 66, 68, 69]. Intracerebral delivery can provide high local concentration but is invasive and region-limited, which may be insufficient for a disorder with widespread cortical and hippocampal pathology [2, 3, 4, 5]. CSF-based routes can provide broader CNS exposure and are increasingly used clinically for certain gene therapy approaches, although cell-type transduction patterns vary by vector and species [66, 67]. Systemic delivery is least invasive but faces BBB constraints and risks peripheral exposure, which is particularly problematic for targets like APOE with important peripheral functions [26, 38, 39, 40, 41, 42, 43, 44, 45].

5.4 Cell-type specificity and regulatory control

Cell-type specificity is essential because editing the same gene in different CNS cell types may yield divergent outcomes and safety profiles [26, 27, 28, 29, 30, 31]. Promoter and enhancer choices can bias expression toward neurons, astrocytes, or microglia, but activity can vary by species, developmental stage, and disease state, requiring careful validation in human-relevant systems [38, 39, 40, 41, 42, 43, 44, 45]. Restricting editor expression can reduce immune exposure and off-target risk while increasing therapeutic index, especially for nuclease or base editors [38, 39, 40, 41, 42, 43, 44, 45]. Therefore, delivery development for AD must incorporate biodistribution mapping, single-cell resolution assessment of transduction/editing, and robust modeling of how partial coverage translates into biomarker and clinical effects in a network disease [2, 3, 4, 38, 39, 40, 41, 42, 43, 44, 45].

In summary, delivery is the rate-limiting step that will largely

determine which CRISPR strategies can realistically be tested and eventually deployed for AD, and it must be solved in a manner compatible with the extraordinary safety expectations for CNS gene editing [38, 39, 40, 41, 42, 43, 44, 45].

6. Safety, precision, and long-term monitoring

Safety is the defining constraint for CRISPR therapeutics in AD because edits may be permanent, target long-lived cells, and be administered in older individuals or even presymptomatically [38, 39, 40, 41, 42, 43, 44, 45]. Safety evaluation must address off-target editing, on-target genotoxicity, immunogenicity of editors and vectors, and unintended biological consequences of target modulation [38, 39, 40, 41, 42, 43, 44, 45, 71, 72, 73, 74, 75]. Given AD's long natural history and the prospect of preventive interventions, acceptable residual risk may be lower than for many other therapeutic areas [4, 38, 39, 40, 41, 42, 43, 44, 45].

6.1 Off-target editing and mapping methods

Off-target cleavage or editing can introduce mutations at unintended genomic sites, potentially causing toxicity or dysregulated gene expression [38, 39, 40, 41, 42, 43, 44, 45]. Editor specificity depends on gRNA sequence, chromatin context, and the duration and level of editor exposure, making both design and delivery critical levers [38, 39, 40, 41, 42, 43, 44, 45, 54, 55]. Multiple empirical methods have been developed to map off-target activity genome-wide, supporting guide selection and preclinical de-risking. GUIDE-seq enables genome-wide profiling of DSBs in cells by capturing integration of oligonucleotide tags at break sites [76]. CIRCLE-seq provides a highly sensitive in vitro approach for identifying candidate off-target cleavage sites [77]. DISCOVER-seq uses recruitment of DNA repair factors to detect nuclease activity in a context-dependent manner, improving relevance to specific cell types and delivery conditions [78]. For CNS programs, these tools should be applied in human-relevant neuronal and glial models, and ideally combined with unbiased sequencing strategies post-delivery to capture context-specific risks [38, 39, 40, 41, 42, 43, 44, 45, 59, 64].

6.2 On-target genotoxicity and genome integrity risks

Even perfectly on-target DSBs can yield adverse outcomes, including large deletions, chromosomal rearrangements, and activation of DNA damage signaling [40, 41]. These findings have helped motivate DSB-free modalities such as base editors and prime editors, although these approaches still require rigorous evaluation for unintended edits, indels, and sequence byproducts [34, 35, 38, 39, 40, 41, 42, 43, 44, 45, 58]. The observation that CRISPR-Cas9 can induce p53-mediated DNA damage responses in certain settings also underscores the need for careful cell-context assessment and for avoiding selection pressures that could favor abnormal clones in proliferative compartments [40]. Although mature neurons do not divide, glial cells can proliferate, and long-term monitoring should incorporate surveillance for clonal expansions where biologically plausible [38, 39, 40, 41, 42, 43, 44, 45].

6.3 Immunogenicity

Immune responses can arise against AAV capsids and against Cas proteins derived from common bacterial species, affecting both efficacy and safety [71, 72, 73, 74, 75]. Human studies have identified pre-existing adaptive immunity to Cas9 proteins, including Cas9-reactive T cells, which can complicate in vivo gene editing and raise the risk of inflammatory adverse events [71]. Immune responses to AAV in clinical trials are well documented and can limit re-dosing and contribute to toxicity at higher exposures [73]. In AD—where neuroinflammation is already a key disease feature—additional immune activation in the CNS could plausibly exacerbate pathology, making immunological safety particularly important [48]. Therefore, clinical translation may require immune screening, immunomodulatory regimens, alternative Cas orthologs, or transient delivery approaches that reduce antigen exposure [38, 39, 40, 41, 42, 43, 44, 45, 71, 72, 73, 74, 75].

6.4 Long-term follow-up and regulatory expectations

Gene therapy regulatory frameworks emphasize long-term follow-up to detect delayed adverse effects, durable expression consequences, and rare events that may emerge years after administration [79]. For CNS editing in AD, long-term surveillance should include clinical endpoints, imaging, biomarker monitoring (amyloid/tau/neurodegeneration), immune profiling, and molecular analyses aimed at verifying editing durability and absence of concerning genomic events [4, 38, 39, 40, 41, 42, 43, 44, 45, 79]. Because AD trials increasingly incorporate biomarker-defined staging and progression metrics, CRISPR programs can align safety monitoring with established biomarker infrastructures while adding genomic-specific surveillance requirements [4]. Ultimately, CRISPR safety assessment in AD must be proportionate to the intended population: preventive interventions in asymptomatic individuals demand a substantially higher confidence threshold than treatments for rapidly fatal diseases [38, 39, 40, 41, 42, 43, 44, 45]. Recent advances in semi-supervised deep learning, including GAN-based architectures with hybrid regularization and evolutionary hyperparameter tuning, demonstrate how leveraging large unlabeled datasets alongside limited annotations can enhance predictive accuracy in biomedical decision-making [79].

7. Translational development pathway

A credible development pathway for CRISPR therapeutics in AD must integrate genetics-based target choice, human-relevant validation models, CNS delivery feasibility, and clinical trial designs anchored in biomarkers and meaningful functional outcomes [4, 14, 16, 38, 39, 40, 41, 42, 43, 44, 45]. The complexity and heterogeneity of AD make translational discipline especially important: many biologically plausible interventions fail when moved from animal models to humans due to differences in aging biology, microglial programs, and disease staging [2, 3, 4, 48, 49, 50, 80].

7.1 Preclinical models and human relevance

Mouse models have been invaluable for amyloid and tau biology but often fail to recapitulate the full spectrum of late-onset AD mechanisms, particularly human-specific immune genetics and microglial states [2, 3, 4, 48, 49, 50]. Human iPSC-derived neurons, astrocytes, and microglia provide complementary systems for validating genetic targets, testing allele-specific editing, and assessing cell-type-specific functional consequences in human genetic backgrounds [59, 80]. For example, human iPSC-derived brain cell types have been used to show that APOE4 can drive widespread molecular and cellular changes relevant to AD phenotypes, supporting the value of human cellular platforms for mechanistic evaluation [80]. These isogenic systems also enable direct comparison of APOE isoforms or TREM2 variants under controlled conditions, improving interpretability of editing outcomes [26, 30, 59, 80]. Nonetheless, iPSC-derived models can be developmentally immature and may not fully capture aging-related epigenetic and metabolic contexts, motivating the use of complementary organoid, chimeric, or aged animal approaches where appropriate [80].

7.2 Patient stratification and indication selection

Clinical translation is most straightforward for autosomal-dominant AD because mutation carriers can be identified, enrolled early, and monitored with biomarker trajectories that reflect disease biology [4, 19, 20, 21, 22, 23]. In sporadic AD, genetic and biomarker stratification can enrich for individuals whose disease biology matches the intervention mechanism, improving the probability of detecting meaningful effects [4, 14, 16]. APOE genotype is an obvious stratifier for allele-focused interventions and also influences amyloid deposition and therapeutic response profiles, including ARIA risk in anti-amyloid antibody programs [11, 12, 24, 25, 26]. For microglial pathway modulation, enrichment by rare variants (e.g., TREM2) or by immune-related biomarker signatures could align treatment mechanism with patient biology, although operationalization remains an evolving field [27, 28, 29, 30, 31, 48, 49, 50].

7.3 Endpoints and biomarkers for gene editing trials

Modern AD drug development increasingly relies on biomarkers to demonstrate target engagement and disease modification, including amyloid PET, tau PET, CSF/plasma A species, and phosphorylated tau and neurodegeneration markers [4, 7, 9, 10]. Gene editing trials must add endpoints that quantify editing efficiency, biodistribution, immune response, and molecular durability [38, 39, 40, 41, 42, 43, 44, 45, 79]. Because direct CNS tissue sampling is limited, programs may need to rely on a combination of CSF biomarkers, imaging, peripheral immune assays, and (where feasible) surrogate sampling strategies informed by delivery route and vector biodistribution [38, 39, 40, 41, 42, 43, 44, 45]. Early-phase studies may prioritize robust biomarker shifts consistent with the target mechanism, acknowledging that cognitive outcomes may require longer time horizons and larger sample sizes, particularly in early disease stages [4, 7, 9, 10].

7.4 Manufacturing, quality systems, and regulatory readiness

CRISPR therapeutics require GMP-grade components and validated assays for identity, potency, off-target risk, and safety, with manufacturing scalability and lot consistency critical for clinical progression [38, 39, 40, 41, 42, 43, 44, 45, 79]. Regulatory guidance for gene therapies emphasizes long-term follow-up and comprehensive preclinical toxicology, and CNS gene editing will likely face heightened scrutiny given irreversibility and the vulnerability of neural tissue [79]. Therefore, translational success in AD will depend as much on delivery manufacturability, quality control, and safety analytics as on target biology [38, 39, 40, 41, 42, 43, 44, 45, 79].

In sum, the translational pathway suggests staged progress: first in mechanistic and discovery applications, then in tightly defined genetic indications with strong biomarker readouts, and only later—if delivery and safety milestones are met—in broader risk-reduction or pathway-tuning applications for late-onset AD [38, 39, 40, 41, 42, 43, 44, 45, 79].

8. Ethical, societal, and governance considerations

Ethical analysis is central to CRISPR therapeutics in AD because interventions may be administered presymptomatically, may be permanent, and may interact with sensitive domains such as genetic risk disclosure, cognition, and autonomy [4, 38, 39, 40, 41, 42, 43, 44, 45, 81, 82, 83]. While somatic editing is generally viewed as ethically more acceptable than germline editing, CNS somatic editing still raises distinctive concerns due to the brain's role in identity and the long-term uncertainties of altering neural cell genomes or epigenomes [81, 82, 83].

8.1 Somatic versus germline boundaries

International governance frameworks emphasize that clinical germline editing is scientifically and ethically unacceptable at present, whereas somatic editing can be ethically permissible under strict oversight when addressing serious disease and when risk–benefit balance is favorable [81, 82]. AD interventions should remain strictly somatic, particularly because late-onset risk reduction does not justify germline modification and because societal risks of heritable editing are profound [81, 82, 83]. Clear regulatory and institutional safeguards are needed to prevent any erosion of boundaries between somatic therapeutic programs and reproductive applications [81, 82, 83].

8.2 Informed consent in a cognitively vulnerable disease continuum

Informed consent is complex in AD because candidates may have cognitive impairment, and preventive trials involve individuals who are clinically normal but psychologically and socially affected by knowledge of genetic risk [4, 83]. For autosomal-dominant AD, individuals may voluntarily undergo predictive testing and participate in prevention trials, but permanent gene editing heightens the need for transparent communication regarding uncertainty, irreversibility, and long-term monitoring obligations [4, 38, 39, 40, 41, 42, 43, 44, 45]. For APOE-focused prevention, ethical complexity increases because APOE 4 is common, penetrance is incomplete, and non-genetic risk modification (vascular health, education, lifestyle) materially influences outcomes, making it difficult to justify irreversible interventions absent extraordinary safety and effectiveness evidence [24, 26, 47, 83].

8.3 Justice, access, and societal impact

Gene editing therapies are likely to be expensive and infrastructure-intensive, raising concerns about equitable access and the potential widening of disparities in dementia outcomes [83]. Because AD prevalence is high, population-scale preventive editing is neither ethically appropriate nor practically feasible in the foreseeable future, increasing the importance of fair prioritization and careful avoidance of genetic stigmatization [1, 83]. Governance should also ensure that enthusiasm for genetic interventions does not divert attention from public health measures, caregiving systems, and modifiable risk factor interventions that have broad societal impact [1, 83].

8.4 Data stewardship and long-term obligations

Recipients of gene editing therapies may require long-term surveillance, which raises privacy and data governance issues and obligates sponsors and health systems to maintain durable monitoring infrastructures [79, 83]. Given the length of AD trajectories, responsible translation should include clear plans for longitudinal follow-up, adverse event reporting, and patient support, potentially extending over decades [79, 83]. Ethical readiness must therefore be treated as co-equal to technical readiness when considering CRISPR-based interventions in AD, especially for preventive applications [81, 82, 83, 79].

9. Conclusions and future directions

CRISPR-based therapeutics have meaningful potential implications for Alzheimer's disease because AD genetics identifies both

causal mutations (APP, PSEN1, PSEN2) and high-impact risk alleles and pathways (APOE, microglial immune-lipid networks) that are conceptually amenable to genome or epigenome intervention [14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31]. The expansion of the CRISPR toolkit—nucleases, base editors, prime editors, CRISPRi/a, and epigenome editors—enables multiple therapeutic styles, from permanent sequence correction to durable gene-expression reprogramming [32, 33, 34, 35, 36, 37, 51, 61]. For familial AD, precise correction or functional rewiring of APP processing offers a direct causal strategy, while for late-onset AD, APOE isoform reprogramming and microglial pathway tuning represent compelling but higher-complexity concepts [24, 25, 26, 30, 31, 59, 62].

Translation, however, is dominated by delivery and safety [38, 39, 40, 41, 42, 43, 44, 45]. CNS delivery must overcome BBB constraints, achieve sufficient coverage in distributed brain regions, and restrict editor exposure to intended cell types and durations [38, 39, 40, 41, 42, 43, 44, 45, 64, 65, 66, 67, 68, 69]. Safety assurance must address off-target edits, on-target genotoxicity, immune responses, and long-term neurobiological effects, supported by genome-wide off-target mapping methods and long-term follow-up aligned to gene therapy regulatory expectations [40, 41, 71, 72, 73, 74, 75, 76, 77, 78, 79]. These constraints imply that early clinical exploration—if pursued—will most plausibly focus on narrowly defined genetic indications or on interventions with strong biomarker alignment and conservative risk profiles [4, 38, 39, 40, 41, 42, 43, 44, 45].

Future progress will likely depend on convergent innovation: CNS-tropic and cell-type-targeted delivery vectors, smaller or more efficiently split editors, improved off-target prediction and detection, and clinical trial designs anchored in biomarker-defined early disease states [4, 38, 39, 40, 41, 42, 43, 44, 45, 64, 65, 66, 67, 68, 69, 76, 77, 78]. Equally important, ethical governance must remain proactive, particularly regarding preventive use, risk communication, and equitable access [81, 82, 83]. If these advances coalesce, CRISPR may evolve from a powerful discovery engine in AD biology into a credible therapeutic platform—initially for rare genetic forms and eventually for broader precision interventions in late-onset AD [38, 39, 40, 41, 42, 43, 44, 45].

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Conflict of interest

The authors declare no conflict of interest regarding the publication of this paper.

Ethical approval

Not applicable

Availability of data and material

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Consent for publication

Not applicable.

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