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EPIGENETIC THERAPY FOR ALZHEIMER'S DISEASE: CURRENT APPROACHES

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ABSTRACT

Alzheimer's disease remains the leading cause of dementia worldwide, and anti-amyloid antibodies, while a genuine milestone, have not closed the gap for most patients. Attention has therefore turned to a second layer of disease biology. The Alzheimer brain carries a reorganised epigenome: DNA methylation is redistributed across the cortex, repressive histone marks accumulate, acetylation at plasticity genes is lost, regulatory elements erode in a cell-type-specific manner, and the non-coding and epitranscriptomic machinery is perturbed. Because these marks are chemically reversible, they are druggable in a way the genome is not. This review surveys the resulting therapeutic strategies: histone deacetylase inhibitors, from pan-selective compounds to agents directed at HDAC2, HDAC3 and HDAC6; acetyltransferase activators and bromodomain inhibitors; sirtuin modulators and nicotinamide adenine dinucleotide precursors; inhibitors of the H3K9 methyltransferases EHMT1 and EHMT2; one-carbon metabolic interventions; programmable epigenome editors built on catalytically dead Cas9; and oligonucleotide and RNA-modification approaches. For each we weigh the mechanistic rationale against what has happened in patients. A consistent pattern emerges: compounds that rescue memory in transgenic mice have underperformed clinically for reasons that are systematic rather than idiosyncratic — inadequate isoform selectivity, poor blood–brain barrier penetration, dose-limiting toxicity, absent target-engagement biomarkers, and intervention at a disease stage that may be too late. We argue that progress now depends less on identifying new epigenetic targets than on solving these translational problems.

KEYWORDS: Alzheimer's disease; epigenetics; histone deacetylase inhibitors; DNA methylation; epigenome editing; histone methyltransferase; non-coding RNA; neurodegeneration.

1. INTRODUCTION

Alzheimer's disease (AD) is the single largest contributor to the global burden of dementia, and the arithmetic of population ageing is unforgiving. Estimates derived from the Global Burden of Disease programme indicate that roughly 57 million adults were living with dementia in 2019 and project that this figure will reach approximately 153 million by 2050, with the increase driven overwhelmingly by demographic change rather than by rising age-specific risk [1]. The clinical syndrome — progressive amnesia followed by broader cognitive and functional decline — rests on a pathology that is now described in considerable molecular detail: extracellular deposition of amyloid-β peptides, intraneuronal accumulation of hyperphosphorylated tau in neurofibrillary tangles, sustained glial activation, synaptic loss and neuronal death [2, 3].

Therapeutic progress against this pathology has been real but narrow. Monoclonal antibodies directed at aggregated amyloid-β, notably lecanemab and donanemab, have demonstrated statistically significant slowing of clinical decline in early symptomatic disease and have established that removal of a core pathological species can modify the trajectory of the illness [4, 5]. The benefit is nonetheless modest, the eligible population is restricted to early disease, amyloid-related imaging abnormalities impose a safety burden, and the infrastructure required places these agents out of reach for much of the world. The pipeline has accordingly broadened well beyond amyloid, with inflammation, metabolism, synaptic function and epigenetic regulation now accounting for a substantial share of agents in active clinical testing [6].

The case for the epigenetic layer is both genetic and biological. Common-variant studies have identified more than seventy loci associated with late-onset AD, yet these explain only part of the heritable risk and the great majority fall in non-coding regulatory regions whose activity is governed by chromatin state [7]. At the same time, roughly forty per cent of dementia cases worldwide are attributable to modifiable exposures — education, hypertension, hearing loss, smoking, obesity, physical inactivity, diabetes, social isolation, air pollution — which act over decades and are transduced into lasting transcriptional change largely through chromatin and DNA methylation [8]. Epigenetic mechanisms therefore sit at the interface where genetic susceptibility and environmental exposure converge on gene expression [9, 10].

What makes this layer therapeutically interesting is its chemistry. DNA methylation, histone acetylation and methylation, and RNA modification are installed, read and removed by enzymes amenable to small-molecule

intervention, and the marks are reversible in a way that sequence variation is not. The proposition that the transcriptional repression of the degenerating brain might be unlocked rather than merely prevented has animated a considerable body of work [11]. We first summarise the epigenetic alterations documented in the AD brain, including those resolved only recently at single-cell level, then consider each therapeutic class in turn, and finally address the obstacles separating preclinical promise from clinical benefit.

2. The epigenetic landscape of the Alzheimer brain

2.1. DNA methylation

Early immunohistochemical and quantitative work reported a global reduction of 5-methylcytosine and of methylation-associated proteins in neurons of the entorhinal cortex and hippocampus in AD, with monozygotic twin pairs discordant for the disease showing divergent neuronal methylation [12, 13]. Early array-based studies in frontal cortex then described more complex, locus-specific patterns that did not reduce to global hypomethylation [14].

The field was reoriented by two independent epigenome-wide association studies published simultaneously in 2014. Lunnon and colleagues profiled multiple cortical regions and the cerebellum and identified robust, neuropathology-associated hypermethylation of the ankyrin 1 (ANK1) gene across cortex but not in cerebellum or blood [15]. De Jager and colleagues, drawing on more than seven hundred autopsy brains, independently implicated ANK1 together with BIN1, RHBDF2 and other loci, several showing concordant changes in transcript abundance [16]. Later work extended the signal to a 48-kilobase region spanning the HOXA cluster [17], and a cross-cortex meta-analysis consolidated these findings into differentially methylated positions and regions reproducible across cohorts [18]; a parallel prefrontal meta-analysis converged on many of the same loci and highlighted enrichment in immune processes [19].

A related question concerns 5-hydroxymethylcytosine, generated by the ten-eleven translocation enzymes as the first step of active demethylation. This mark is abundant in neurons and reduced in the hippocampus and entorhinal cortex in AD [13]. Because bisulphite chemistry cannot distinguish the two marks, much of the literature reports their sum; oxidative bisulphite analyses indicate that apparent hypermethylation at loci such as ANK1 partly reflects loss of hydroxymethylation [18]. The implication is not trivial, since removing methylation and restoring TET activity would address the same abnormality by opposite mechanisms.

Two caveats have proved important. First, much of the apparent disease-associated signal in bulk tissue is driven by shifts in cellular composition rather than by changes within a fixed cell population; deconvolution and sorted-nuclei analyses indicate that non-neuronal cell types contribute disproportionately to the cortical methylation signature of AD neuropathology [20]. Second, peripheral blood provides only a partial reflection of brain state, although consistent signals such as HOXB6 hypermethylation have been reported and remain of active interest for the development of accessible diagnostic and prognostic markers [21, 22].

2.2. Histone modifications and chromatin state

Chromatin profiling of post-mortem tissue has revealed that AD does not simply exaggerate the epigenetic changes of normal ageing but partly reverses and partly redirects them. Nativio and colleagues mapped several histone marks in lateral temporal lobe from young controls, aged controls and AD cases and found that the age-associated H3K4me3 and H4K16ac landscape is substantially reconfigured in disease, with loss of the age-dependent gain in H4K16 acetylation at many loci [23]. An integrated multi-omics extension of this work linked specific chromatin states to transcriptional dysregulation and nominated candidate regulators [24]. A histone acetylome-wide association study of entorhinal cortex identified widespread differences in H3K27 acetylation, enriched at loci implicated by genetic and methylomic studies, including the APP and MAPT regions [25]. In the murine CK-p25 model, immune and inflammatory gene enhancers are preferentially activated, a signature conserved with human AD risk loci [26]. Given that histone acetylation is a rate-limiting step in the consolidation of long-term memory [27], these data position the acetylation machinery as both a marker and a plausible effector of cognitive decline.

2.3. Cell-type resolution and epigenome erosion

The most consequential recent development has been the arrival of single-cell epigenomics, which has exposed the limits of everything that preceded it. Single-nucleus transcriptomic atlases first established that the response to AD pathology is profoundly cell-type-specific, that excitatory neuron subpopulations differ in vulnerability, and that cognitive resilience in the presence of pathology has its own molecular correlates [28, 29]. A multiregion dissection of 1.3 million cells across six anatomical regions subsequently identified selectively depleted neuronal subtypes, notably reelin-expressing populations of the entorhinal cortex and hippocampus, and showed that this vulnerability is coordinated across interconnected regions [30].

Chromatin accessibility mapping has added a regulatory dimension to this picture. Xiong and colleagues generated single-cell epigenomic profiles from hundreds of post-mortem samples, used them to fine-map AD risk variants to specific cell types and enhancers, and described a phenomenon they termed epigenome erosion: a progressive loss of the normal, cell-type-defining pattern of chromatin accessibility, with inappropriate opening of regions that should be closed [31]. A still larger effort profiling 3.5 million cells from 384 samples across six brain regions in 111 individuals extended this to disease progression, cataloguing more than a million

regulatory elements organised into regulatory modules and demonstrating region- and cell-type-specific erosion signatures that track with disease severity and, inversely, with cognitive resilience [32].

These findings cut in two directions. They provide the strongest evidence yet that epigenetic dysregulation in AD is not an epiphenomenon, since the eroding elements are the same ones that harbour fine-mapped genetic risk; but they also complicate any intervention acting uniformly on all cells. If the defect in microglia is inappropriate enhancer activation while the defect in neurons is loss of activity at plasticity genes, a systemically administered deacetylase inhibitor will push both populations in the same direction, and only one of them in the right one.

2.4. Non-coding RNA and RNA modification

A further regulatory layer operates after transcription. The antisense transcript BACE1-AS stabilises BACE1 messenger RNA, is elevated in AD brain, and drives a feed-forward loop that increases amyloid-β production [33]. Loss of the miR-29a/b-1 cluster in sporadic AD correlates with increased BACE1 expression, providing one of the earliest demonstrations that microRNA deficiency can contribute directly to amyloidogenesis [34]. More recently, the epitranscriptome has entered the picture. N6-methyladenosine (m6A) is the most abundant internal mRNA modification in the brain and regulates synaptic protein synthesis and memory consolidation. Expression of the methyltransferase METTL3 is altered in AD hippocampus, with accumulation of the protein in insoluble fractions correlating with insoluble tau [35]; functional work indicates that METTL3 reduction contributes to neurodegeneration through aberrant cell-cycle re-entry [36], while other studies report elevated m6A in transgenic models [37]. The direction of change is evidently context-dependent, and this inconsistency is itself informative about the maturity of the field. Table 1 summarises the principal epigenetic alterations described in AD and their functional consequences.

Table 1. Principal epigenetic alterations reported in Alzheimer's disease and their functional consequences.

Epigenetic layer	Alteration reported in AD	Representative loci or enzymes	Functional consequence
DNA methylation	Locus-specific hypermethylation across cortex; reduced global 5-mC in some neuronal populations	ANK1, BIN1, RHBDF2, HOXA cluster, SORL1	Altered transcript abundance of genes governing axonal integrity, endocytosis and immune signalling
DNA hydroxymethylation	Reduced 5-hmC in hippocampus and entorhinal cortex	TET1–TET3 activity	Impaired active demethylation; loss of transcriptional plasticity at neuronal genes
Histone acetylation	Loss of H4K16ac at age-regulated loci; redistributed H3K27ac	HDAC2, HDAC3, CBP/p300	Repression of synaptic plasticity and learning-associated transcriptional programmes
Histone acetylation (tubulin)	Reduced α-tubulin acetylation	HDAC6	Microtubule destabilisation, impaired axonal transport, tau accumulation
Histone methylation	Elevated repressive H3K9me2; altered H3K4me3 distribution	EHMT1 (GLP), EHMT2 (G9a)	Silencing of glutamate receptor and synaptic organisation genes
Chromatin accessibility	Cell-type-specific epigenome erosion; inappropriate opening of normally closed elements	>1 million regulatory elements; AD risk enhancers	Loss of cell identity programmes; de-repression of disease-associated glial states
Chromatin readers	Dysregulated bromodomain-dependent transcription	BRD2, BRD3, BRD4	Amplification of NF-κB-driven neuroinflammatory gene expression
NAD^+-dependent deacetylation	Reduced SIRT1 expression and activity	SIRT1, SIRT2, SIRT3	Loss of α-secretase activation; increased tau acetylation and

			phosphorylation
Non-coding RNA	Elevated BACE1-AS; depletion of miR-29a/b-1, miR-107, miR-206	BACE1-AS, miR-29 cluster	Increased β-secretase activity and amyloid-β generation; reduced BDNF signalling
RNA modification (m6A)	Altered METTL3 expression and subcellular distribution; perturbed m6A deposition	METTL3, FTO, YTHDF proteins	Disrupted local translation, synaptic protein synthesis and tau proteostasis

3. Targeting histone deacetylation

3.1. The rationale and the first generation of inhibitors

The therapeutic logic of histone deacetylase (HDAC) inhibition in AD derives from a specific and well-replicated observation: the cognitive impairment of the degenerating brain reflects an active transcriptional blockade rather than irreversible loss of plastic capacity. Guan and colleagues showed that neuronal overexpression of HDAC2, but not HDAC1, reduced dendritic spine density, synaptic number and plasticity and impaired learning, whereas HDAC2 deletion produced the converse phenotype [38]. Gräff and colleagues then demonstrated that HDAC2 accumulates in the CK-p25 neurodegeneration model and in human AD brain, that this accumulation represses a defined set of learning-associated genes, and that short-hairpin RNA-mediated knockdown of HDAC2 restores structural and synaptic plasticity and abolishes memory deficits [39]. Earlier work had already established that environmental enrichment and HDAC inhibition could recover apparently lost memories in the same model [40].

It is worth being precise about what these experiments show. In the CK-p25 model, memory was not merely improved but reinstated: animals recovered access to associations learned before the onset of neurodegeneration, which argues that the engram had been rendered inaccessible rather than erased [39]. In ageing and amyloid-bearing mice, the pan-inhibitor vorinostat restored a transcriptional signature overlapping substantially with the one lost during decline, indicating action on the relevant programme rather than non-specific stimulation of transcription [41]. Whether the same latitude exists in a human brain that has lost a large fraction of its synapses over two decades is the single largest extrapolation the field asks its readers to accept.

Pharmacological validation across chemically diverse compounds has been unusually consistent for preclinical neuroscience. Class I-selective inhibitors reversed contextual fear memory deficits in APP/PS1 mice without altering plaque burden [42], and sodium 4-phenylbutyrate ameliorated cognitive deficits, reduced tau phosphorylation and restored dendritic spine density in Tg2576 mice [43]. This convergence across models with different primary pathologies suggests that the target is the transcriptional consequence of neurodegeneration rather than any single upstream lesion.

3.2. Isoform-selective approaches

The principal liability of early compounds was promiscuity. Zinc-dependent HDACs comprise eleven isoforms with distinct subcellular localisations and substrate repertoires, and pan-inhibition produces the haematological, gastrointestinal and cardiac toxicities familiar from oncology practice, which severely constrain the chronic dosing that a neurodegenerative indication requires [44]. The field has therefore moved toward isoform-directed chemistry, and the pharmacological distinctions between isoforms turn out to be biologically meaningful rather than merely technical.

HDAC3 has emerged as a particularly attractive target. It is abundantly expressed in neurons, exerts negative control over long-term memory, and promotes neuroinflammation through transcriptional regulation of myeloid activation programmes. Janczura and colleagues showed that the selective HDAC3 inhibitor RGFP966 reduced amyloid-β and tau phosphorylation and improved spatial memory in 3xTg-AD mice [45]. Because HDAC3 inhibition can in principle be achieved without the broad class I blockade responsible for much of the toxicity of older agents, it offers one of the clearer routes to an acceptable therapeutic index.

HDAC6 occupies a different mechanistic niche: it is predominantly cytoplasmic and its principal substrates include α-tubulin and heat-shock protein 90 rather than histones. Its inhibition therefore targets the cytoskeletal and proteostatic arms of tau pathology directly. Genetic reduction of HDAC6 rescued memory and restored mitochondrial transport in APP/PS1 mice [46], and the selective inhibitor tubastatin A increased tubulin acetylation, lowered total tau and improved memory in a tauopathy model [47]. Because HDAC6 inhibition does not produce the global transcriptional disruption associated with class I blockade, its therapeutic index is expected to be considerably more favourable, and several brain-penetrant, orally bioavailable HDAC6 inhibitors have since been described.

Hybrid and multi-target molecules represent a further refinement. The dual HDAC–phosphodiesterase 5 inhibitor CM-414 rescued hippocampal synaptic impairment and cognitive deficits at doses below those required for either activity alone, exploiting convergence of the two pathways on CREB-dependent transcription and thereby widening the window between efficacy and epigenetic toxicity [48]. Targeted protein degradation offers an alternative route to isoform specificity that does not depend on exploiting the shallow structural

differences between catalytic pockets. Comprehensive accounts of this chemical landscape have been published recently [49, 50, 11].

4. Writers, readers and NAD$^+$-dependent deacetylases

If removing acetyl groups is harmful, adding them should help, and this logic has been pursued through the acetyltransferases. Viral delivery of CREB-binding protein to the hippocampus of 3xTg-AD mice increased brain-derived neurotrophic factor and improved learning without altering amyloid or tau pathology [51], a dissociation that is itself informative: cognitive benefit need not pass through plaque clearance. Small-molecule activators of CBP/p300 promote adult neurogenesis and extend memory duration in mice [52]. Activator chemistry nonetheless remains far less mature than inhibitor chemistry, and no acetyltransferase activator has advanced to clinical testing in AD.

The sirtuins, class III NAD$^+$-dependent deacetylases, have attracted sustained interest because they couple cellular energetics to chromatin state, a link of obvious relevance to a disease in which cerebral glucose hypometabolism precedes symptoms by years. SIRT1 expression and activity decline in AD cortex in parallel with tau accumulation [53], and SIRT1 suppresses amyloid-β generation by activating transcription of the α-secretase ADAM10 [54]. These observations motivated clinical evaluation of resveratrol, a polyphenolic SIRT1 activator. A 52-week randomised, placebo-controlled phase 2 trial in 119 patients with mild-to-moderate AD showed the compound to be safe and CNS-penetrant and to attenuate decline in cerebrospinal fluid amyloid-β40 and activities of daily living, although it was underpowered for efficacy and no effect was seen on cognitive scales [55]. Analyses of the same cohort indicated modulation of central immune responses [56], consistent with the broad anti-inflammatory profile of the compound but not specific to sirtuin activation.

Nicotinamide, an NAD$^+$ precursor that inhibits sirtuins at high concentrations, restored cognition and selectively reduced Thr231-phosphorylated tau in 3xTg-AD mice [57]. The translation is instructive. A randomised phase 2a trial gave 3,000 mg daily for 48 weeks to participants with mild cognitive impairment or mild AD dementia and biomarker-confirmed pathology; the intervention was safe but did not reduce cerebrospinal fluid phosphorylated tau-231, the primary endpoint [58]. Post hoc pharmacokinetic analysis identified the probable reason: plasma nicotinamide rose more than a hundredfold, yet cerebrospinal fluid concentrations were below the limit of quantitation in most participants because of extensive methylation to 1-methyl-nicotinamide, and among the minority with measurable central exposure phosphorylated tau-231 fell substantially [59]. This is a failure of delivery rather than of mechanism.

Acetyl-lysine readers constitute the third element of this system. Bromodomain and extraterminal (BET) proteins couple histone acetylation to transcriptional elongation and are required for induction of immediate-early and inflammatory genes. BRD4 activates neuronal transcription, and acute BET inhibition impairs memory formation in healthy mice [60], which complicates any straightforward therapeutic proposition. Nevertheless, the BET inhibitor JQ1 reduced neuroinflammation and tau phosphorylation at Ser396 in the 3xTg model [61] and improved brain plasticity in wild-type and APP mice [62]. Whether the anti-inflammatory benefit can be separated from the cognitive liability — by targeting individual family members, or by restricting exposure to microglia — remains open, and the cell-type-resolved chromatin data should now make it tractable.

5. Histone methylation as a therapeutic target

Repressive histone methylation offers a mechanistically distinct entry point. Zheng and colleagues reported that H3K9 dimethylation and its catalysing enzymes EHMT1 and EHMT2 are markedly elevated in the prefrontal cortex of aged familial AD model mice and, importantly, in post-mortem prefrontal cortex from patients with AD. Brief treatment with the selective EHMT1/2 inhibitors BIX01294 or UNC0642 restored glutamatergic transmission, reversed the transcriptional repression of synaptic organisation genes, and rescued recognition and spatial memory; notably, the benefit persisted for days after a short dosing course, which suggests that intermittent rather than continuous exposure might suffice [63].

Independent work in the 5XFAD model found that UNC0642 restored cognition, reduced H3K9me2, shifted the balance of DNA methylation toward hydroxymethylation, and lowered oxidative stress, neuroinflammation and plaque burden [64]. Convergence of two laboratories using different models and chemistry is encouraging, and elevated H3K9me2 in human tissue supplies the target validation many preclinical programmes lack. The principal caution is that EHMT1 and EHMT2 are broadly expressed developmental regulators whose heterozygous loss in humans causes Kleefstra syndrome, so chronic systemic inhibition would require careful characterisation. No EHMT inhibitor has yet entered clinical development for a neurological indication.

6. Modulating DNA methylation

Direct inhibition of DNA methyltransferases with nucleoside analogues such as azacitidine or decitabine is not a realistic option in AD: these agents require incorporation into DNA, act globally, are myelosuppressive, and would be expected to derepress transposable elements in post-mitotic neurons. Attention has therefore focused on the upstream one-carbon pathway supplying the methyl donor S-adenosylmethionine, where intervention is gradual, physiological and reversible.

Fuso and colleagues demonstrated that depletion of B vitamins and folate alters S-adenosylmethionine availability, induces hypomethylation of the PSEN1 and BACE1 promoters, and increases amyloid-β

production, and that supplementation reverses these changes in cellular and murine models [65, 66]. The clinical counterpart of this hypothesis has produced the most positive results obtained with any methylation-directed intervention. In the VITACOG trial, high-dose B-vitamin supplementation slowed the rate of whole-brain atrophy in participants with mild cognitive impairment, with the effect concentrated in those with elevated baseline homocysteine [67]. Voxel-based analysis of the same cohort showed that the protective effect was localised to the grey-matter regions most vulnerable to AD pathology and correlated with cognitive outcomes [68]. The mechanism is unlikely to be purely epigenetic, and later trials in unselected populations were less convincing, but the result supports two principles: that metabolic manipulation of methyl-donor availability can influence the structural trajectory of the ageing brain, and that biomarker-based enrichment can reveal effects that whole-population analyses obscure.

7. Programmable epigenome editing

The limitation common to all small-molecule approaches is that they act on enzymes rather than on loci. An HDAC inhibitor alters acetylation genome-wide; it cannot restore acetylation at a synaptic gene while leaving inflammatory enhancers untouched. In the light of cell-type-specific epigenome erosion, this is not a minor inconvenience but the central obstacle. Programmable epigenome editing removes the constraint by fusing catalytically inactive Cas9 to an effector domain and directing it with a guide RNA.

The foundational demonstrations came from outside neurology. Fusion of dCas9 to the KRAB repressor domain enables highly specific silencing of distal regulatory elements [69], and dCas9 coupled to the TET1 catalytic domain achieves targeted demethylation with heritable, locus-restricted effects [70]. Translation to AD models followed rapidly: targeted methylation of the APP promoter by a dCas9–Dnmt3a fusion suppressed APP expression and reduced amyloid pathology in transgenic mice [71], while ribonucleoprotein complexes delivered by amphiphilic nanocomplexes disrupted BACE1 in post-mitotic brain tissue with reduced amyloid burden, improved behaviour and no detectable off-target editing [72]. Compact dCas9 repressor platforms delivered by adeno-associated virus have been used to silence APOE, exploiting the fact that epigenetic repression permits graded, reversible dose-reduction rather than the permanent loss of function nuclease editing would impose.

Most recently, the approach has been turned toward activation rather than silencing. CRISPR-based epigenetic upregulation of Gad1 in the prefrontal cortex of tau-transgenic mice restored depleted inhibitory synaptic transmission and rescued spatial memory deficits [73]. This is a conceptually important result because it targets a downstream consequence of neurodegeneration — loss of inhibitory tone — rather than a proteinopathic driver, and because it demonstrates that locus-specific activation in post-mitotic neurons is achievable in vivo with behavioural read-out.

The obstacles are substantial and largely technical: adeno-associated virus packaging capacity constrains editor size; immunogenicity against bacterial Cas proteins is a genuine concern under chronic dosing; delivery must reach a sufficient fraction of the relevant cell population; and the durability of an installed mark in post-mitotic neurons over years rather than weeks is essentially untested. It remains, nonetheless, the only approach offering locus- and, through cell-type-specific promoters, cell-level precision.

8. Oligonucleotide and RNA-directed strategies

Approaches that act downstream of chromatin have advanced further clinically than any chromatin-directed agent. Antisense oligonucleotide-mediated reduction of tau prevented neuronal loss and reversed pathological tau deposition and seeding in tauopathy mice [74], and the tau-lowering oligonucleotide MAPT_Rx produced dose-dependent reductions in cerebrospinal fluid total tau and phosphorylated tau in a phase 1b randomised trial in mild AD, establishing target engagement in patients [75]. MicroRNA-directed strategies offer the distinctive advantage of simultaneous modulation of multiple transcripts — a single microRNA may repress APP, BACE1 and tau concurrently — although this same property complicates toxicology [76]. Restoration of miR-206, which represses brain-derived neurotrophic factor, improved memory and increased hippocampal neurogenesis in an AD model [77]. Whether such interventions count as epigenetic is partly semantic; what matters is that they target the same regulatory architecture and that intrathecal delivery has solved, for this class alone, the problem that has defeated most of the others.

9. Clinical experience and the translational gap

The clinical record is summarised in Table 2, and it is sobering. Chronic divalproex sodium, a weak HDAC inhibitor, was tested in a large randomised trial in mild-to-moderate AD and not only failed to attenuate cognitive or functional decline but was associated with greater adverse events [78]; a nested imaging substudy showed accelerated hippocampal and whole-brain atrophy in treated patients [79]. A phase 1b study of vorinostat in mild AD was terminated for insufficient recruitment rather than for safety or futility. The nicotinamide and resveratrol trials were safe but, at best, equivocal.

Four explanations deserve emphasis, and they are not mutually exclusive. First, selectivity: agents such as valproate and vorinostat inhibit many isoforms with opposing roles, so the net effect of a promiscuous compound is unpredictable. Second, exposure: the blood–brain barrier excludes most hydroxamate and benzamide HDAC inhibitors at tolerable systemic doses, and the nicotinamide data make the consequence

explicit — a mechanistically sound intervention cannot work if it does not reach its compartment [59]. Third, cellular heterogeneity: the response to AD pathology differs profoundly between neurons, microglia, astrocytes and oligodendrocytes, and disease-associated microglia adopt a distinct regulatory state [80, 32], so a change that is restorative in neurons may be deleterious in glia. Fourth, timing: epigenetic clocks indicate that the regulatory architecture of the brain changes progressively with age [81, 82], and interventions delivered after extensive synaptic loss may be attempting to restore programmes whose cellular substrate no longer exists.

It is instructive to contrast this record with that of the tau-directed antisense oligonucleotides, which produced an unambiguous demonstration of central target engagement in cerebrospinal fluid within a phase 1b study [75]. The difference is not that the biology was better understood but that the route of administration bypassed the barrier, and that an assay existed to confirm the drug had done what it was designed to do. The nicotinamide trial, by contrast, reached its primary endpoint with no interpretable answer as to whether the target had been engaged at all [58]. Until chromatin-directed agents are developed alongside comparable pharmacodynamic readouts, negative results in this field will remain uninformative in precisely the way that makes a research programme difficult either to advance or to abandon.

Table 2. Epigenetic-directed agents evaluated in Alzheimer's disease models and in clinical trials.

Agent	Molecular target	Highest level of evidence	Principal outcome
Valproate / divalproex sodium	Class I HDACs (weak)	Randomised phase 3, mild–moderate AD	No attenuation of decline; excess adverse events; accelerated brain atrophy on imaging substudy
Vorinostat (SAHA)	Class I HDACs and HDAC6	Phase 1b dose escalation, mild AD	Terminated for insufficient recruitment; restores memory and transcriptome in murine models
Sodium 4-phenylbutyrate	Class I HDACs	Transgenic mouse (Tg2576)	Improved cognition, reduced tau phosphorylation, restored dendritic spine density
RGFP966	HDAC3 (selective)	Transgenic mouse (3xTg-AD)	Reduced amyloid-β and phospho-tau; improved spatial memory; anti-inflammatory
Tubastatin A	HDAC6 (selective)	Tauopathy mouse (rTg4510)	Increased α-tubulin acetylation; reduced total tau; improved memory
CM-414	HDAC and phosphodiesterase 5 (dual)	Transgenic mouse	Rescued hippocampal synaptic impairment at sub-threshold doses for either target
Resveratrol	SIRT1 activation	Randomised phase 2, 52 weeks, n = 119	Safe and CNS-penetrant; attenuated decline in CSF Aβ40 and daily-living scores; no cognitive benefit
Nicotinamide	Sirtuins / NAD^+ metabolism	Randomised phase 2a, 48 weeks, n = 47	Safe; primary endpoint (CSF p-tau231) not met; CSF exposure inadequate in most participants
JQ1	BET bromodomain proteins	Transgenic mouse (3xTg-AD)	Reduced neuroinflammation and tau phosphorylation; impairs memory in healthy mice
UNC0642 / BIX01294	EHMT1 and EHMT2 (G9a/GLP)	Transgenic mouse (FAD, 5XFAD)	Restored synaptic transmission and memory; reduced H3K9me2, oxidative stress and plaque burden
High-dose B vitamins	One-carbon metabolism / SAM supply	Randomised trial in MCI (VITACOG)	Slowed whole-brain and regional grey-matter atrophy in participants with elevated homocysteine
dCas9–Dnmt3a (APP-targeted)	Locus-specific DNA methylation	Transgenic mouse	Suppressed APP expression and reduced amyloid pathology in vivo
dCas9 activator (Gad1-targeted)	Locus-specific transcriptional activation	Tauopathy mouse (P301S)	Restored inhibitory synaptic transmission and rescued spatial memory deficits
MAPT_Rx (BIIB080)	MAPT transcript (antisense	Randomised phase 1b, mild AD	Dose-dependent reduction of CSF total tau and phospho-tau; target

	oligonucleotide)		engagement demonstrated

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-β; CNS, central nervous system; CSF, cerebrospinal fluid; HDAC, histone deacetylase; MCI, mild cognitive impairment; NAD^+, nicotinamide adenine dinucleotide; SAM, S-adenosylmethionine.

10. Future directions

Several developments would materially change the prospects of this field. The first is already under way: cell-type-resolved epigenomics. Bulk-tissue profiling has reached its explanatory limit, and the large single-cell chromatin atlases now available make it possible to ask which regulatory changes are causal, in which cells each occurs, and at what point in the disease course [31, 32]. A target can now be specified not merely as an enzyme but as an enzyme acting in a defined cell type at a defined stage.

The second is chemistry with genuine isoform selectivity and brain penetration: HDAC6 and HDAC3 inhibitors with favourable central exposure, and EHMT inhibitors suitable for chronic dosing, are the immediate priorities. The third is delivery. Receptor-mediated transcytosis, focused-ultrasound barrier opening, engineered extracellular vesicles and intrathecal administration have each delivered therapeutics to the central nervous system, and tau antisense oligonucleotides illustrate what becomes possible once exposure is solved [83].

The fourth is biomarkers. Without a measure of central target engagement — cerebrospinal fluid histone acetylation, methylation signatures in brain-derived extracellular vesicles, or an imaging readout — a negative trial cannot distinguish a wrong hypothesis from an undosed one, and the nicotinamide experience shows how costly that ambiguity is. Blood-based epigenetic markers, although imperfect reflections of brain state, are maturing quickly and may serve both for enrichment and for monitoring [22]. The fifth is trial design: enrichment by epigenetic stratification, intervention in preclinical or prodromal disease, and combination with amyloid- or tau-directed agents, on the reasoning that restoring transcriptional competence is most likely to help once the proteinopathic driver has been reduced.

11. CONCLUSION

Epigenetic dysregulation is now firmly established as a feature of the Alzheimer brain rather than a speculative one. Reproducible methylation changes across the cortex, a reconfigured histone acetylation landscape, elevated repressive methylation at synaptic genes, and cell-type-specific erosion of regulatory elements have been documented in human tissue by independent groups using independent methods. The therapeutic inference drawn from these observations rests on a genuinely striking experimental result: in animal models, the transcriptional repression that accompanies neurodegeneration can be lifted, and apparently lost cognitive capacity recovered, by manipulating chromatin.

What the clinical record shows is that this inference has not yet been tested properly. Trials conducted to date have used compounds that inhibit too many enzymes at once, that reach the brain in inadequate concentrations, that are given at a stage when the cellular substrate for recovery may already be depleted, and that have been evaluated without any measure of target engagement. These are correctable deficiencies in experimental design and pharmaceutical chemistry, not refutations of the hypothesis, and distinguishing between the two is the central task facing the field. Epigenetic therapy is unlikely to constitute a stand-alone cure. It is considerably more plausible as a component of combination treatment, in which proteinopathy is reduced by one agent while the capacity of surviving neurons for plasticity and synaptic gene expression is restored by another.

Acknowledgments

Not applicable.

Funding

This work was supported by the Russian Science Foundation (Grant № 25-75-10016).

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

A.V.B.: conceptualization, writing – original draft, supervision, funding acquisition. A.A.V.: writing – review and editing, literature analysis. G.A.O.: writing – review and editing, data curation. A.O.M.: writing – review and editing, visualization. A.N.O.: writing – review and editing, supervision. All authors have read and approved the final version of the manuscript.

Data Availability Statement

No new data were generated or analysed in support of this review. All data discussed are available in the cited published literature.

Ethics Approval Statement

Not applicable. This review did not involve human participants or animals.

Generative AI Statement

The authors declare that generative artificial intelligence tools were used to assist with language editing and improvement of clarity. The authors take full responsibility for the accuracy and integrity of the content.

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