Scientific Research Publishing

Neuroscience and Medicine, 2025, 16(4), 242-260
https://www.scirp.org/journal/nm
ISSN Online: 2158-2947
ISSN Print: 2158-2912

Alzheimer's Disease Pharmacotherapy: The Potential for Drug Repurposing

Aniqa Niha[1], Zvi G. Loewy[1,2*]

[1]Touro College of Pharmacy, Touro University, New York, NY, USA
[2]School of Medicine, New York Medical College, Valhalla, NY, USA
Email: *zvi.loewy@touro.edu

How to cite this paper: Niha, A. and Loewy, Z.G. (2025) Alzheimer's Disease Pharmacotherapy: The Potential for Drug Repurposing. *Neuroscience and Medicine*, **16**, 242-260.
https://doi.org/10.4236/nm.2025.164024

Received: November 24, 2025
Accepted: December 20, 2025
Published: December 23, 2025

Abstract

Background: Alzheimer's Disease (AD) is characterized by neurodegeneration affecting behavioral and cognitive function including memory, comprehension, language, attention, reasoning, and judgment. As the most prevalent forms of dementia, AD comprises approximately two-thirds of cases involving individuals 65 and older. The pathogenesis of AD is multifactorial-encompassing β-amyloid plaque accumulation, tau neurofibrillary tangles, neurotransmitter imbalances, neuroinflammation, and other causative factors such as oxidative stress and gut dysbiosis. **Objective:** This review aims to explore the emerging approach of drug repurposing by utilizing current FDA-approved drugs for new therapeutic indications. **Methods:** A comprehensive literature review using trusted databases such as PubMed, MEDLINE, EMBASE, and relevant internet sources from 1997 to 2025 was conducted. Relevant search terms included "Alzheimer's pathology," "PAI-1 and Alzheimer's," "current AD therapies," and "drug repurposing." The selection of studies was conducted based on relevance, quality, and clinical significance, and was independently reviewed by two investigators. **Results:** Current treatments for AD only offer symptomatic relief via the modulation of target neurotransmitters and amyloid pathology. Monoclonal antibodies, tau-targeting agents, and neuroprotective compounds are novel investigational agents that are of interest due to their disease-modifying properties. The process of drug repurposing through mechanism-based, computational, and epidemiologic strategies, is a promising tool that has identified candidates like metformin, pioglitazone, statins, and antihypertensives for the treatment of AD. Plasminogen Activator Inhibitor-1 (PAI-1) inhibitory drugs have also emerged as candidates of interest due to involvement in AD-related fibrinolytic and inflammatory pathways. **Conclusion:** Effective disease-modifying treatments remain limited despite significant progress in AD research over the years. Acceleration of therapeutic development can be facilitated by repurposing existing drugs, especially when

this approach is combined with biomarker profiling, computational modeling, and systems biology techniques. Further research into targets such as PAI-1 may lead to breakthroughs in halting or reversing AD progression.

Keywords

Alzheimer's Disease, Neurodegeneration, β-Amyloid, Tau Protein, Drug Repurposing, PAI-1, Biomarkers

1. Introduction

Drug repurposing is an innovative method which consists of finding new uses for existing medications that go beyond their initial intended use. The three essential steps involved in drug repurposing consist of the development of a hypothesis *i.e.*, selecting a suitable candidate drug for a particular indication, thorough evaluation of the drug from preclinical trials, and lastly, assessment of the drug in relevant clinical trials. Prior to the development of high-performance computing and virtual screening strategies, repurposing was predominantly a result of serendipitous encounters [1].

As drug development is a complex, expensive and time-consuming process, repurposing already approved drugs for different purposes not only accelerates the drug development process, but also reduces costs significantly. The process of drug repurposing can be broken down to screening existing drugs against new disease targets, investigating the biological mechanisms of existing drugs, and executing and analyzing data from clinical trials and electronic health records. Another benefit of drug repurposing is the discovery of new therapeutic targets and mechanisms of action which can lead to higher understanding of pathogenesis of diseases and the development of more efficacious therapies. Development of computational methods such as bioinformatic tools, machine learning algorithms, and network-based analyses can be utilized to predict potential relationships between drugs and specific diseases. High-capacity screening of drug libraries against new targets or disease models, in addition to analysis of published clinical data, including electronic health records and clinical trial results are resources that can be used to discover off-target effects that may be therapeutically beneficial. Development of databases and resources such as DrugBank, PharmGKB, ChEMBL, and BindingDB is instrumental in drug repurposing efforts as they encompass data such as drug and drug target information, the impact of genetic variations on therapeutic responses, information about bioactive drug-like small molecules, and bonding affinities for interactions between drugs and specific targets, respectively [2]. Notable examples of successful drug repurposing include methotrexate, originally developed for cancer treatment and now used to manage rheumatoid arthritis; amantadine, originally an influenza medication, now employed in the treatment of Parkinson's disease; and dimethyl fumarate, first used for psoriasis, which is currently used to treat multiple sclerosis [3]. The benefits of drug repurposing

were especially seen during COVID-19 during which researchers used in silico methods to postulate interactions between drugs available on the market and SARS-CoV-2 targets [4] [5]. In silico methods were utilized to postulate the interactions between existing drugs and SARS-CoV-2 targets by screening 6218 drugs against the viral main protease (M^{pro}) which led to the identification of suitable candidates based on docking simulations and interaction similarities [6]. Notably, remdesivir, which was originally developed for Ebola, was repurposed for patients with COVID-19 due to its ability to inhibit the viral RNA-dependent RNA polymerase [7].

This review focuses on potential drug repurposing candidates for AD.

2. Methods

A review of previously published studies was conducted. The search terms used included the following: Alzheimer's pipeline, Alzheimer's pathology, Alzheimer's current medications, PAI-1, PAI-1 and Alzheimer's disease, and amyloid pathology. PUBMED, MEDLINE, EMBASE, related internet websites, and reference lists were searched with a date range of 1997 to 2025 to identify appropriate papers that addressed the objectives of this review. Publications were reviewed independently by two investigators. The investigators extracted the data and inspected each reference identified by the search and applied inclusion criteria. In cases in which the same studies were reported in more than one publication, the study's results were accounted for only once. The electronic search was followed by extensive hand searching using reference lists from the identified articles. Publications written in English were reviewed exclusively.

3. Drug Repurposing and Alzheimer's Disease

As the global prevalence of individuals with AD dementia is anticipated to increase to 153 million by 2050, the development of new treatments is imperative. Due to the multifactorial pathogenesis of AD, a standard drug development program averages 13 years to complete and often results in failure. As there is an emergent need for new and efficacious treatments for AD, approaches to drug development that are less time-consuming and financially responsible are crucial. Repurposing non-AD drugs is a promising strategy to combat the increasing requirement for efficacious therapies for AD. Drug repurposing for AD is actively being pursued; more than 100 papers have been published in the last decade. Conventional search approaches have focused on review of the scientific literature covering preclinical as well as clinical studies [8]. Advanced computational approaches can be used to identify candidate agents for investigation in non-clinical *in vivo* studies or pharmacoepidemiologic research, with the potential to advance to human Phase 2 or Phase 3 trials if consistent evidence indicates an effect on Alzheimer's disease. DNA/RNA sequencing technologies can be used to obtain genetic and genomic data while transcriptomic, proteomic, lipidomic, and metabolomic studies available through the Alzheimer's Disease Sequencing Project

(ADSP) and AD Knowledge Portal can be utilized to obtain multi-omic data. Approximately 100 AD susceptibility loci have been identified using genome-wide association studies (GWAS). Despite significant progress and availability of databases, challenges in data exploitation coupled with the complexity of AD, has seen limited development of new AD therapies. Due to the difficulty in application of available data, utilization of artificial intelligence (AI) and other computational technologies can aid in the identification of possible drug targets and candidate compounds which can be used as treatments for AD [9]. In a recent study, ChatGPT was shown to generate a short list of drug candidates for testing [8].

Drug repurposing in Alzheimer's disease (AD) employs several complementary strategies.

4. Mechanism-Based Repurposing

This technique involves targeting biological pathways involved in AD-such as neuroinflammation, tau phosphorylation, Aβ aggregation, mitochondrial dysfunction, and synaptic loss-and identifying drugs on the market which modulate these processes [8]. For example, anti-inflammatory agents like NSAIDs and therapies for diabetes such as pioglitazone have been explored in relation to AD [9] [10].

5. Computational and AI-Assisted Screening

Multi-omics data including genomic, proteomic, and metabolomic profiles, can be utilized by machine learning and deep learning algorithms to identify appropriate compounds for repurposing. Network-based inference or knowledge graphs are used to predict associations between particular drugs and diseases. Additionally, transcriptomic signatures have been used to generate AI systems, such as ChatGPT, to prioritize drug candidates which have been validated by real-world evidence [8].

6. Transcriptomic Signature Matching (Connectivity Mapping)

AD brain gene expression profiles are compared with drug-induced transcriptomic changes to determine compounds that reverse disease-associated expression patterns [10]. Bumetanide, an approved loop diuretic indicated for multiple conditions such as heart failure and hypertension, is an example of a drug that has been postulated to be a repurposable candidate based on transcriptomic studies and showing properties suggesting it will be useful for treatment of AD occurring in APOE4 carriers. Through the assembly of APOE4-specific transcriptional signatures from human brain data and cross-referencing these with perturbational drug profiles in the Connectivity Map, bumetanide was found to significantly reverse these signatures. Daily bumetanide was shown to improve electrophysiological deficits, neurological pathology, and cognitive impairments in APOE4 knock-in mice, with and without amyloid pathology. It was revealed via single-nucleus RNA

sequencing that bumetanide normalized disease-altered gene expression in key brain cell types. Results from real-world analysis of electronic health records from individuals over 65 in two independent cohorts showed a significantly lower prevalence of AD among those exposed to bumetanide compared to matched controls [11].

7. Epidemiologic & Real-World Evidence Mining

The association between drugs and reduced AD risks has been demonstrated using retrospective analysis of electronic health records and longitudinal observational cohorts. Statins, which are a class of medication prescribed for hyperlipidemia and cardiovascular disease, are associated with anti-inflammatory and neuroprotective properties which may reduce AD risk [9]. Numerous epidemiological studies have found an association between long-term statin use and reduced incidence of dementia, possibly due to their role in lowering cholesterol, reducing β-amyloid production, and improving cerebrovascular health. A 2018 meta-analysis by Zhang *et al.* involving a total of 3,332,706 participants showed that statin use was linked to a 15% lower risk of dementia (RR 0.85; 95% CI 0.80 - 0.89) [12].

8. High-Throughput Phenotypic Screening

Evaluation of large libraries constituting approved compounds in cellular or animal AD models and focusing on neuroprotective or cognition-enhancing effects, independent of their original indication, is a valuable strategy for identifying repurposing candidates [9].

9. Current Repurposing Candidates for AD

9.1. Metabolic Modulators

9.1.1. Metformin

The link between diabetes and peripheral hyperinsulinemia may aid in explaining the relationship between diabetes and an increased risk of AD. Insulin resistance, which typically precedes diabetes, is associated with elevated insulin levels in the blood (hyperinsulinemia). Insulin resistance, often caused by increased body fat, is linked to other metabolic risk factors such as chronic inflammation, high blood pressure, and abnormal lipid levels—collectively known as metabolic syndrome. Moreover, hyperinsulinemia, diabetes, and metabolic syndrome are all recognized risk factors for cerebrovascular disease. Cerebrovascular disease is increasingly being acknowledged as a contributing factor to the development and clinical symptoms of Alzheimer's dementia. Along with its vascular effects, hyperinsulinemia may impair insulin transport across the blood-brain barrier (BBB), reducing insulin levels in the brain. Consequently, this may lead to decreased activity of insulin-degrading enzyme (IDE), which plays a role in clearing amyloid β (Aβ) from the brain. Peripheral hyperinsulinemia is associated with increased inflammation, oxidative stress, and the accumulation of advanced glycation end prod-

ucts (AGEs), all of which contribute to Alzheimer's pathology. Antidiabetic agents such as metformin may directly impact AD pathological processes by suppression of proinflammatory cytokines and microglial activation blockade, which are both key factors that promote neuroinflammation. Similarly, metformin's activation of the Nrf2 pathway may also allow for cellular oxidative distress protection. Blood-brain barrier protection may also be enhanced in the presence of metformin as autophagy has been proposed to be amplified, removing harmful protein aggregates such as Aβ and tau. While results pertaining to its use benefits are mixed, metformin may play a more significant role as opposed to other antidiabetic agents due to its ability to cross the BBB and exert neuroprotective effects.

The MetMCI trial was a pilot randomized, double-blind, placebo-controlled trial which evaluated metformin's safety, tolerability, and preliminary efficacy in people aged 55 - 90 years with amnestic mild cognitive impairment (aMCI), who were overweight or obese but not diabetic. In this trial, 80 participants were randomized to metformin 1000 mg twice a day or matching placebo for 12 months. The co-primary clinical outcomes were changes from baseline to 12 months in total recall of the Selective Reminding Test (SRT) and the score of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). Although metformin could not be tolerated in 7.5% of the participants, changes in total recall of the SRT favored the metformin group (9.7 ± 8.5 vs. 5.3 ± 8.5; $p = 0.02$). While the trial results were indicative of the feasibility of metformin repurposing with respect to positive memory recall in at-risk individuals with aMCI, careful attention to specific dosage formulation should be prioritized to subvert intolerance effects. Due to the ADAS-Cog results being inconclusive, along with insignificant changes in broader cognitive or imaging markers, a larger trial was warranted [13].

Building on the results of the pilot trial, the Metformin in Alzheimer's dementia Prevention (MAP) study (NCT04098666) is a Phase II/III randomized, double-blind, placebo-controlled clinical trial which aims to investigate whether metformin can be effective in preventing cognitive decline in non-diabetic adults at risk for Alzheimer's dementia. The primary endpoint of this trial consists of change in verbal memory (FC-SRT Total Recall Score), with secondary endpoints involving changes in biomarkers and imaging studies such as changes in cortical thickness in areas affected by AD on brain MRI and white matter hyperintensities (WMH) volume on brain MRI [14].

9.1.2. Pioglitazone

Pioglitazone is an insulin-sensitizing medication that activates peroxisome proliferator-activated receptor gamma (PPAR-γ) and is commonly used to treat type 2 diabetes. It has been linked to the treatment of AD due to its beneficial effects on brain glucose and lipid metabolism, as well as its anti-inflammatory properties. Compared to other agents within its class such as rosiglitazone, pioglitazone is associated with amplified BBB penetration and is not as limited by active efflux mechanisms. Individuals who carry two copies of the APOE ε4 allele (associated with a high risk of Alzheimer's) exhibit reduced glucose metabolism in specific

brain regions up to two decades before the expected onset of symptoms, mirroring the regions affected in AD patients. Maintaining or stabilizing brain glucose metabolism can therefore be a promising strategy to delay the onset of AD. Epidemiological studies have demonstrated that individuals with diabetes who are treated with PPAR-γ agonists have a lower risk of developing dementia. In terms of pioglitazone's mechanism, it correlates with reduction of Aβ by enhancing expression of insulin-degrading enzyme (IDE) and inhibiting β-secretase (BACE1). Synaptic protection is also offered by blocking cyclin-dependent kinase 5 (CDK5) activity, thereby preventing downstream tau hyperphosphorylation. Results from early clinical studies involving the use of pioglitazone in patients with mild AD showed that the drug was generally well tolerated and showed some cognitive benefit at doses used for diabetes [10].

The TOMMORROW trial was a large, phase 3, double-blind study that aimed to evaluate whether the onset of mild cognitive impairment (MCI) due to AD could be delayed using low-dose pioglitazone (0.8 mg/day SR) in cognitively normal older adults classified as high-risk using a biomarker-based risk assignment algorithm (BRAA). Out of a total of 3494 participants aged 65 - 83 enrolled, 3061 were deemed high-risk and randomized to either pioglitazone or placebo, while 433 low-risk participants received placebo only. Over the length of the study, the incidence of MCI was higher in the high-risk placebo group compared to the low-risk group (3.3% vs. 1.0%), indicating some enrichment by the BRAA. However, this did not meet the pre-specified statistical significance ($p = 0.023$; required $p < 0.01$). Moreover, pioglitazone did not significantly reduce the incidence of MCI in high-risk participants (HR = 0.80, $p = 0.307$). Overall, while the trial did not provide evidence for low-dose pioglitazone preventive use, utilization of enrichment strategies such as BRAA may be relevant in determining which individuals are at higher near-term risk. Although the TOMMORROW trial was terminated early due to lack of efficacy, it provided insight into the challenges involving risk stratification and clinical trial design in preventative Alzheimer's research [10].

9.2. Cardiovascular Agents

9.2.1. Statins

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are first-line drug therapy for the treatment of hyperlipidemia and for the prevention of coronary heart disease. Risk factors such as high-cholesterol diet, elevated serum cholesterol, and high blood pressure, are not only associated with coronary artery disease, but can contribute to an increased risk of AD. Excess cholesterol in the hippocampus can promote the breakdown of amyloid precursor protein (APP) to β-amyloid, the neurotoxic peptide responsible for neuronal degeneration and the development of AD. Statins may be helpful in reducing the formation of β-amyloid peptide by decreasing cholesterol levels. Statins are involved in the regulation of isoprenoid intermediates, such as isoprene, which are often reduced in individuals with dementia. These intermediates are necessary for cell growth, mitosis, and signal transduction. Apolipoprotein E4 is involved in β-amyloid aggregation

and the formation of senile plaques. Astrocytes and microglia produce apoE, a process requiring isoprenylation and dependent on derivatives of mevalonate, such as isoprene. Statins inhibit the synthesis of mevalonate, thereby reducing apoE formation and reducing extracellular apoE levels. This mechanism may help prevent the formation of neurotoxic plaques and improve cognitive function in patients at risk for or affected by AD. A 2018 meta-analysis by Zhang *et al.* showed a dose-dependent relationship between statin use and dementia: each additional year of statin use corresponded to a 20% lower dementia risk (RR = 0.80 per year) and every 5 mg/day increase in statin dosage was linked to an 11% lower dementia risk (RR = 0.89 per 5 mg). However, the studies involved were all observational (no randomized controlled trials focused on dementia). Additionally, there was variability in study durations, populations, and statin regimens [12].

A randomized, double-blind, placebo-controlled trial of simvastatin was conducted in individuals with mild to moderate AD and normal lipid levels. A total of 406 individuals were randomized to either receive simvastatin 20 mg/day, for 6 weeks then 40 mg per day for the remainder of 18 months or identical placebo. Although simvastatin reduced lipid levels in the participants, it had no effect on the primary outcome which was the change in ADAS-Cog score or the secondary outcome measures. Class I evidence was provided by the study that simvastatin at a dose of 20 mg daily does not slow the clinical progression of Alzheimer's disease despite seemingly robust clinical reasoning in theory and influenced future studies to assess its possible benefit in prevention [15].

The Pravastatin in elderly individuals at risk of vascular disease (PROSPER) trial investigated the benefits of pravastatin in an elderly cohort of men and women with, or at high risk of developing, cardiovascular disease and stroke. A secondary endpoint of this trial was cognitive function assessed by neuropsychological tests, including the Mini-Mental State Examination (MMSE) and other memory/executive function tools. Results of this trial showed no improvement or worsening in cognitive function in these individuals treated with pravastatin [16]. While the trial did not show cognitive function improvements, it allows for future research involving statin therapy to take into account elderly, high-risk individuals rather than excluding them as risk of coronary heart disease events was reduced in this patient population.

9.2.2. Antihypertensives

Studies have shown lower incidences of AD with angiotensin receptor blocking drugs (ARBs) and angiotensin converting enzyme inhibitors (ACEIs) compared to other classes of anti-hypertensive drugs, with ARBs being significantly more beneficial than ACEIs. Levels of angiotensin converting enzyme (ACE) and neprilysin, which is involved in the production of angiotensin II (AngII), are elevated in the AD brain. Additionally, AngII promotes the production of inflammatory mediator tumor necrosis factor-α, and has been shown to have anticholinergic and antiglutamatergic effects all of which are associated with AD pathology. Losartan is an angiotensin type 1 receptor antagonist which crosses the BBB and may

decrease amyloid-beta plaques by increased degradation via neprilysin and by diminishing effects of Ang II which otherwise promotes inflammation. Evidence from the literature also suggests that losartan's cognitive benefits may be brought about by activating AngIV receptors, a separate pathway from the one targeted by other ARBs. Losartan has also been observed to be associated with reduced incidences of AD. Additionally, losartan improves cerebral blood flow and has been shown to limit neuronal damage following ischemia in stroke rat models. In low doses, losartan has shown reduced pathology and improved cognitive performance in transgenic mouse models of AD [17].

The Reducing Pathology in Alzheimer's Disease through Angiotensin TaRgeting (RADAR) Trial was a two-arm, double-blind, placebo-controlled, multi-center, randomized, trial comparing 100 mg losartan or placebo effects on MRI brain imaging in patients with mild-to-moderate AD (both hypertensive and normotensive) over the course of 12 months. Results from this trial showed no significant slowing of whole-brain atrophy—losartan group lost 19.1 mL, placebo lost 20.0 mL (difference: −2.29 mL; 95% CI −6.46 to 0.89; p = 0.14). The findings of the trial suggested further research is required to assess the potential therapeutic benefit from earlier treatment in patients with milder cognitive impairment or from longer treatment periods [17]. Similarly, results of this trial may prompt researchers to pivot and explore other components of the renin-angiotensin-aldosterone system (RAAS) or synergistic effects with other amyloid-beta/tau-targeting treatment modalities.

Another trial investigated the effects of candesartan compared to lisinopril on neurocognitive function in older adults with executive mild cognitive impairment. This double-blind, randomized controlled trial involved 176 adults randomized to receive daily oral candesartan (up to 32 mg) or lisinopril (up to 40 mg) for 12 months. Results of this study showed that the candesartan group showed significant improvement whereas the lisinopril group showed decline. As candesartan provided superior neurocognitive protection over lisinopril in individuals with MCI despite equal blood pressure lowering, further investigation of ARBs (especially candesartan) in the prevention and treatment of cognitive decline and Alzheimer's disease is necessary [18].

Nilvadipine is a dihydropyridine (DHP) calcium channel blocker primarily used in the treatment of hypertension. Additionally, it is reported to have neuroprotective mechanisms of action which include lowering Amyloid beta 40 and 42 amino acid peptides (Aβ40 and Aβ42) production both *in vitro* and *in vivo* in transgenic mouse models of AD, and increasing Aβ clearance across the BBB in *in vivo* mouse models. These characteristics are specific to nilvadipine as many other DHPs do not share these additional properties. Moreover, nilvadipine has shown efficacy against other Alzheimer disease pathological mechanisms, including tau-phosphorylation, reduced cerebral blood flow, and neuroinflammation. Nilvadipine has been shown to stabilize cognitive decline and reduce conversion to AD in a small study of patients with hypertension and mild cognitive impair-

ment. A 6-week open label study demonstrated that nilvadipine was safe and well tolerated in AD patients without causing a reduction in blood pressure in nonhypertensive patients. The NILVAD trial was an 18-month, randomized, placebo-controlled, double-blind trial in which participants were randomly assigned to 8 mg sustained-release nilvadipine or matched placebo. The primary outcome was progression on the Alzheimer's Disease Assessment Scale Cognitive Subscale-12 (ADAS-Cog 12). No statistically significant treatment effect was observed for the first primary outcome analysis. The nilvadipine difference from placebo, in change from baseline in the ADAS-Cog 12 score, was −0.22 (95% CI, −2.01 - 1.57). The authors observed a trend suggesting that patients with very mild AD (MMSE ≥ 25) might have had a slower rate of cognitive decline on nilvadipine compared to placebo, and although this was not statistically definitive, it may warrant further investigation as nilvadipine may be more beneficial in earlier stages of AD [19].

9.3. Neurotransmitter Modulators

Levetiracetam

Seizures can manifest in the early stages of AD and worsen cognitive symptoms. Approximately 10% to 22% of patients with AD develop unprovoked seizures, with familial and early-onset cases having higher rates. Subclinical epileptiform activity can be seen using overnight electroencephalography (EEG) and 1-hour magnetoencephalography with simultaneous EEG (MEG-EEG) in 22% to 54% of patients with AD. A faster decline in cognitive function is seen in patients with AD and seizures or subclinical epileptiform. According to preclinical studies, suppression of epileptiform activity with anti-seizure drugs was associated with improvements in behavior and histopathological signs of chronic network hyperexcitability in the hippocampus of transgenic mouse models of AD. The widely used anti-seizure medication, levetiracetam has been reported to suppress epileptiform spikes and improve synaptic and cognitive function in mouse models of AD and treatment with this drug has been shown to be well tolerated and effective at suppressing seizures among patients with AD and seizure disorders. Compared to other antiepileptic drugs, levetiracetam may exert this neuroprotective effects without concomitant cognitive adverse effects seen in other medications within the class such as topiramate. The Levetiracetam for Alzheimer's Disease–Associated Network Hyperexcitability (LEV-AD) study was an investigator-initiated phase 2a randomized double-blinded placebo-controlled crossover clinical trial that evaluated the ability of levetiracetam treatment to improve executive function (measured by the National Institutes of Health Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research [NIH-EXAMINER] composite score). Participants were divided into two groups- Group A received placebo twice daily for 4 weeks followed by a 4-week washout period, then oral levetiracetam, 125 mg, twice daily for 4 weeks whereas Group B received treatment using the reverse sequence. Secondary outcomes of this study were cognition (measured by the Stroop Color and Word Test [Stroop] interference naming

subscale and the Alzheimer's Disease Assessment Scale-Cognitive Subscale) and disability. The results demonstrated that treatment with levetiracetam did not change NIH-EXAMINER composite scores (mean difference vs placebo, 0.07 points; 95% CI, −0.18 to 0.32 points; p = 0.55) or secondary measures. Nevertheless, among participants with epileptiform activity, levetiracetam treatment improved performance on the Stroop interference naming subscale (net improvement vs placebo, 7.4 points; 95% CI, 0.2 - 14.7 points; p = 0.046) and the virtual route learning test (t = 2.36; Cohen f^2 = 0.11; p = 0.02) [20]. The trial informed that network hyperexcitability may be a key phenotypic target in such subgroups of patients, emphasizing a personalized treatment approach.

9.4. Antimicrobials and Antivirals

9.4.1. Valacyclovir

Case-control studies involving plasma samples from 360 individuals who later developed AD, collected on average 9.6 years before diagnosis, were compared with age- and sex-matched controls. Analyses of these measured anti-HSV-1 IgG (HSV-1 exposure) and genotypes for APOE and nine additional AD-risk genes. APOEε4 heterozygotes (*i.e.*, ε2/ε4 or ε3/ε4) who had HSV-1 antibodies faced ~4.6-fold greater odds of developing AD compared to those without the combination (OR 4.55, p = 0.02) [21]. Since valacyclovir reduces inflammation by decreasing levels of pro-inflammatory markers like TNF-α, nuclear factor-kappa B (NF-κB), and IL-6, neuroinflammatory processes can be directly targeted. Since HSV infections otherwise promote amyloid plaque aggregation neurofibrillary tangle production, valacyclovir role in inhibiting viral replication may play a key role in modulating such processes. The VALZ-Pilot study was conducted to assess whether high-dose valacyclovir is safe, tolerable, and feasible for patients with early AD who were HSV-1 seropositive. The intervention consisted of valacyclovir ingested orally as 500-mg tablets (three times daily; one tablet on days 1 - 7, two tablets on days 8 - 28). The primary outcomes were the feasibility, tolerability, and safety, and changes in the cerebrospinal fluid (CSF) levels of t-tau and neurofilament light chain (NfL) during the intervention. The secondary outcomes were changes in the MMSE score, anti-HSV IgG titers, and CSF levels of amyloid beta (Aβ) 42, Aβ40, p-tau, soluble triggering receptor expressed on myeloid cells 2 (sTREM2), YKL-40, glial fibrillary acidic protein (GFAP), IL-6, IL-8, IL-1β, and TNF-α; and the detection, magnitude, and location of replicating herpesvirus in the central nervous system (CNS) by [^{18}F] FHBG PET/CT. Results of this trial showed that a 4-week high-dose oral valacyclovir regimen was feasible, tolerable, and safe for patients with early-stage AD, HSV, and APOE ε4. Furthermore, statistically significant increases in sTREM2 (p = 0.03) and MMSE (p = 0.02, +1.1 points) encourage further investigations to evaluate clinical efficacy of valacyclovir in AD patients [22]. This study showcased that selecting participants based on HSV seropositivity and APOE ε4 carriage may allow for targeted therapeutic exploration and opens doors to exploring other antiviral pharmacological strategies in potentially treating AD.

9.4.2. Minocycline

Minocycline is a semisynthetic tetracycline used to treat a variety of infectious diseases. As it can cross the BBB due to its high lipophilicity while also blocking proinflammatory cytokines, it is a suitable candidate for treating the diseases of the CNS. Along with being a powerful inhibitor of matrix metalloproteinases (MMPs), minocycline has been reported to have anti-inflammatory, antioxidant, and anti-apoptotic properties. Cyclin-dependent kinase 5 (Cdk5) has been linked with the pathogenesis of AD as Cdk5/p25 is involved in the development of synaptic functions and cognitive impairment. Over-activation of Cdk5/p25 signaling induces hyperphosphorylation of APP, tau, and neurofilament, causing AD-like pathology. A 2022 study conducted by Zhao *et al*., investigated the effect of minocycline in inhibiting Cdk5/p25 signaling in APP/PS1 transgenic mice. Mice were given minocycline (50 mg/kg/day) for 30 days and cognitive performance was evaluated using the Morris water maze. Levels of Aβ, tau phosphorylation, synaptic proteins, inflammatory markers, and Cdk5/p25 were analyzed via ELISA, immunofluorescence, and Western blotting. Results showed that minocycline-treated mice showed significantly better spatial learning and memory performance, decreased Aβ40 and Aβ42 levels in cortex and hippocampus, lower expression of β-secretase (BACE1) and components of the γ-secretase complex (PS1, NCT, Aph-1α, Pen-2). Additionally, total tau and multiple hyperphosphorylated tau isoforms (pSer199/pSer202, pThr205/pThr231, pSer396/pSer404) were reduced in minocycline-treated mice. Minocycline-treated mice had significantly reduced levels of p25 and Cdk5, and increased p35, which suggested inhibition of the pathogenic Cdk5/p25 complex [23].

9.5. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Tarenflurbil

Tarenflurbil (also known as R-flurbiprofen) has been shown to decrease Aβ42 production via the modulation of γ-secretase activity, contrary to traditional NSAIDs that work by inhibiting the cyclooxygenase (COX) enzyme. Due to this mechanism of action, tarenflurbil has been hypothesized to be a suitable candidate for AD as it specifically targets the accumulation of amyloid plaques in the brain. As a selective Aβ42-lowering agent, tarenflurbil produces the less toxic Aβ38 and Aβ37. Studies involving mouse models have shown prevention of deficits in learning and memory in addition to reduced brain concentrations of Aβ42 with the use of tarenflurbil. Wilcock *et al.* investigated the efficacy and safety of tarenflurbil in a phase 2 trial involving patients with mild to moderate AD. Efficacy outcomes were assessed via the AD assessment scale cognitive subscale (ADAS-cog), the Alzheimer's Disease Cooperative Study activities of daily living scale (ADCS-ADL), and the clinical dementia rating sum of boxes (CDR-sb). Results of this study showed that in patients with mild Alzheimer's disease, 800 mg tarenflurbil twice daily modestly slowed ADCS-ADL and CDR-sb, but the impact on ADAS-Cog was not statistically significant. Additionally, no benefits were observed in

patients with moderate AD, and delayed treatment initiation was less effective than continuous treatment [24]. The trial results informed future research by emphasizing the importance of CNS target enhancement and utilization of biomarkers in guiding future trial designs.

On the basis of these results, a phase 3, randomized, placebo-controlled trial of tarenflurbil was conducted in patients with mild AD by Green *et al.* Patients were randomized to either receive tarenflurbil 800 mg twice daily or placebo. Participants taking an acetylcholinesterase inhibitor were included in this study provided they had been taking that specific medication for at least 6 months before taking the study drug. The results of this trial showed no significant difference between tarenflurbil and placebo in slowing cognitive decline or functional loss in patients with mild Alzheimer's disease over 18 months. Specifically, the mean treatment difference for ADAS-Cog was 0.1 points (95% CI: −0.9 to 1.1; p = 0.86), and for ADCS-ADL was −0.5 points (95% CI: −1.9 to 0.9; p = 0.48). Although side effects were mild in nature and tarenflurbil was generally well-tolerated, a higher number of participants in the treatment group discontinued due to adverse events. The investigators concluded that the lack of efficacy may be attributed to its low brain penetration (~0.5% - 1%) [25]. This trial also underscored the importance of target validation, pharmacokinetic parameter optimization, and the need to incorporate CSF amyloid measurements and amyloid imaging to confirm CNS target engagement.

10. Future Directions

Emerging targets and strategies in drug repurposing for Alzheimer's disease underscore promising directions for therapeutic innovation. Plasminogen activator inhibitor-1 (PAI-1) is a target of interest due to its involvement in neuroinflammation and BBB dysfunction. Immunohistochemical analyses in rat and human brain tissues showed PAI-1 expression is increased in the vicinity of amyloid deposits in the brain. In the AD brain, PAI-1 binds to tissue plasminogen activator (tPA), blocking its activity in converting plasminogen into plasmin, the protease that degrades Aβ aggregates. Therefore, treatment with PAI-1 inhibitors is proposed to block interaction between PAI-1 and tPA, restoring tPA activity. PAZ-417, an orally active small molecule inhibitor of PAI-1 was developed to assess plasmin formation and proteolysis of Aβ. PAZ-417 was used in transgenic mouse models of AD and results showed transgenic increased tPA and plasmin activity, leading to significant reductions in brain and plasma Aβ levels. This effect translated into restored hippocampal long-term potentiation and full reversal of cognitive deficits in behavioral assays. The findings of this study solidified PAI-1 inhibition as a promising target for improving synaptic and cognitive function in AD [26]. Similarly, another small molecule inhibitor of PAI-1, TM5275, was shown to reduce Aβ accumulation in the hippocampus and cortex and improved learning and memory when administered to APP/PS1 mice for 6 weeks. Protein abundance of low-density lipoprotein related protein-1 (LRP-1) which transports Aβ out of

the brain were increased, showing TM5275 aided in both degradation and clearance of Aβ [27]. Tiplaxtinin (PAI-039), an indole oxoacetic acid derivative, which was shown to be selective in binding to PAI-1 *in vivo* in two different models of acute arterial thrombosis, was evaluated for its potential role in the treatment of AD [28]. Preclinical models with tiplaxtinin have demonstrated neuroprotective effects by normalizing brain-derived neurotrophic factor (BDNF) maturation (via plasmin pathway), reducing tau hyperphosphorylation, and improving cognition in Tg2576 AD mouse models. However, since tiplaxtinin failed to significantly change the Aβ plaque, further large-scale studies are needed to provide an accurate conclusion on its efficacy in AD [29].

Another newer small molecule PAI-1 inhibitor called TM5A15, has been evaluated for its ability to prevent or reverse memory deficits and decrease Aβ levels and plaque deposition in APP/PS1 mice. Results of this study showed treatment with TM5A15 for 6 months in younger mice protected against recognition and short-term working memory impairment. For mice at 9 months of age, TM5A15 decreased oligomer levels and amyloid plaques, and increased mBDNF (mature brain-derived neurotrophic factor) expression. Although 9 months of treatment with TM5A15 in older mice did not significantly improve memory function nor decrease amyloid plaques, mice at 18 months of age showed a trend in decreasing oligomer levels when treated with this inhibitor [30]. The PAI-1 inhibitors investigated in AD have been summarized in **Table 1**.

Table 1. Summary PAI-1 inhibitors investigated for AD.

0.6	Model	Effects on Aβ	Notes
TM5275	APP/PS1 mice	↓ Aβ total load	Clear amyloid reduction
PAZ-417	APP/Aβ-transgenic mice	↓ Aβ + ↑ long-term potentiation (LTP)	Required brain penetration
PAI-039	Tg2576 mice	↔ Plaques, ↑ BDNF	Targeted neurotrophic pathway
TM5A15	APP/PS1 mice	↓ Aβ (early), ↓ oligomers	Timing-dependent effect

Targeting the mammalian target of rapamycin (mTOR) pathway involved in the regulation of autophagy and cellular metabolism using drugs like everolimus and sirolimus, is also an area of increased interest. By inhibiting mTOR, such pharmacological agents may advance autophagy, clearing the toxic protein aggregates that are hallmarks of the pathophysiology of the disease [31]. Valproate, a histone deacetylase (HDAC) inhibitor, is also under investigation for epigenetic modulation and influence on gene expression patterns associated with AD progression. By increasing histone acetylation and enhancing expression of genes important for synaptic plasticity, reduction in amyloid-beta accumulation and tau hyperphosphorylation along with improvements in synaptic function and neuroprotection may ensue [32]. Novel targets such as the calcitonin gene-related peptide (CGRP) and transient receptor potential vanilloid 1 (TRPV1) pathways, which are involved in neurovascular regulation and inflammation, are being repurposed

from pain management for potential cognitive applications [33] Due to its anti-inflammatory effect and pivotal role in the obstruction of macrophage effect, CGRP and its receptor have been proposed to be therapeutic targets for neuroinflammation reduction. Transient receptor potential vanilloid 1 (TRPV1) has also been hypothesized to improve long-term potentiation (LTP), decrease Aβ deposition in the brain, and clear cellular waste associated with AD.

Integrated and individualized approaches are necessary for future directions in AD drug repurposing. Polypharmacology and combination therapies that concurrently target multiple disease mechanisms may enhance efficacy. Identification of repurposable drugs is being accelerated by AI-driven discovery pipelines via predictive modeling, virtual screening, and toxicity profiling [34]. Precision medicine techniques that involve patient stratification based on genetic profiles such as APOE4 status, tau levels, or inflammatory biomarkers, are likely to optimize therapeutic outcomes [35]. Regulatory innovations such as adaptive trial designs and expedited pathways for repurposed drugs may allow for more efficient clinical evaluation. Improvement in CNS drug delivery technologies, including nanoparticles, lipid-based systems, and focused ultrasound, is being explored to overcome the challenges of BBB penetration and improve drug bioavailability in the brain [36].

11. Conclusions

Alzheimer's disease continues to prevail as one of the most complex neurodegenerative disorders due to its multifactorial pathogenesis involving amyloid-β plaques, tau neurofibrillary tangles, neurotransmitter imbalances, neuroinflammation, oxidative stress, and disruptions in the gut-brain axis. Decades of research have only amounted to drugs only offering symptomatic relief, with few agents demonstrating significant disease-modifying effects but with the price of serious adverse effects such as amyloid-related imaging abnormalities (ARIA) which are primarily associated with anti-amyloid monoclonal antibody therapies. Although biomarker development and diagnostic tools, such as PET imaging and cerebrospinal fluid analysis, have enhanced early detection, effective pharmacotherapy with the ability of altering disease progression remain scarce. The clinical pipeline has promising candidates—including anti-amyloid and anti-tau strategies, neuroprotective agents, and immune-modulating approaches—however, failures of several large-scale trials emphasize the challenges in translating clinical understanding into successful treatments.

The process of drug repurposing provides a pragmatic and promising solution to accelerate the identification of effective therapies for AD. The repositioning of metabolic modulators, cardiovascular agents, antimicrobial drugs, and other compounds allows for manipulation of existing pharmacokinetic, safety, and efficacy data, thereby streamlining the progression to clinical trials.

The use of computational tools, artificial intelligence, and multi-omics technologies has transformed the drug discovery process, accelerating the identification

of novel repurposing candidates and therapeutic targets. Of particular importance, the role of plasminogen activator inhibitor-1 (PAI-1) and modifying it through repurposed pharmacotherapies presents an innovative avenue for attenuating AD pathology.

As the global burden of AD continues to increase, therapeutic approaches that combine disease-modifying therapies, early diagnostics, and innovative drug repurposing strategies offer promising potential to slow or halt AD progression. Continued interdisciplinary research combined with accelerated clinical trials and safety evaluations is imperative to adapting these advancements into tangible solutions for patients burdened by this disease.

Conflicts of Interest

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

References

[1] Shah, F.A., Qadir, H., Khan, J.Z. and Faheem, M. (2025) A Review: From Old Drugs to New Solutions: The Role of Repositioning in Alzheimer's Disease Treatment. *Neuroscience*, **576**, 167-181. https://doi.org/10.1016/j.neuroscience.2025.03.064

[2] Bhatia, T. and Sharma, S. (2025) Drug Repurposing: Insights into Current Advances and Future Applications. *Current Medicinal Chemistry*, **32**, 468-510. https://doi.org/10.2174/0109298673266470231023110841

[3] Oprea, T.I., Bauman, J.E., Bologa, C.G., Buranda, T., Chigaev, A., Edwards, B.S., *et al.* (2011) Drug Repurposing from an Academic Perspective. *Drug Discovery Today: Therapeutic Strategies*, **8**, 61-69. https://doi.org/10.1016/j.ddstr.2011.10.002

[4] Babayeva, M. and Loewy, Z. (2020) Repurposing Drugs for COVID-19: Pharmacokinetics and Pharmacogenomics of Chloroquine and Hydroxychloroquine. *Pharmacogenomics and Personalized Medicine*, **13**, 531-542. https://doi.org/10.2147/pgpm.s275964

[5] Bock, R., Babayeva, M. and Loewy, Z.G. (2022) COVID-19 Pharmacotherapy: Drug Development, Repurposing of Drugs, and the Role of Pharmacogenomics. In: Yan, Q., Ed., *Pharmacogenomics in Drug Discovery and Development*, Springer, 187-199. https://doi.org/10.1007/978-1-0716-2573-6_8

[6] Jang, W.D., Jeon, S., Kim, S. and Lee, S.Y. (2021) Drugs Repurposed for COVID-19 by Virtual Screening of 6,218 Drugs and Cell-Based Assay. *Proceedings of the National Academy of Sciences of the United States of America*, **118**, e2024302118. https://doi.org/10.1073/pnas.2024302118

[7] Srivastava, K. and Singh, M.K. (2021) Drug Repurposing in COVID-19: A Review with Past, Present and Future. *Metabolism Open*, **12**, Article ID: 100121. https://doi.org/10.1016/j.metop.2021.100121

[8] Yan, C., Grabowska, M.E., Dickson, A.L., Li, B., Wen, Z., Roden, D.M., *et al.* (2024) Leveraging Generative AI to Prioritize Drug Repurposing Candidates for Alzheimer's Disease with Real-World Clinical Validation. *npj Digital Medicine*, **7**, Article No. 46. https://doi.org/10.1038/s41746-024-01038-3

[9] Cummings, J.L., Zhou, Y., Van Stone, A., Cammann, D., Tonegawa-Kuji, R., Fonseca, J., *et al.* (2025) Drug Repurposing for Alzheimer's Disease and Other Neurodegenerative Disorders. *Nature Communications*, **16**, Article No. 1755.

https://doi.org/10.1038/s41467-025-56690-4

[10] Burns, D.K., Alexander, R.C., Welsh-Bohmer, K.A., Culp, M., Chiang, C., O'Neil, J., *et al.* (2021) Safety and Efficacy of Pioglitazone for the Delay of Cognitive Impairment in People at Risk of Alzheimer's Disease (TOMMORROW): A Prognostic Biomarker Study and a Phase 3, Randomised, Double-Blind, Placebo-Controlled Trial. *The Lancet Neurology*, **20**, 537-547. https://doi.org/10.1016/s1474-4422(21)00043-0

[11] Taubes, A., Nova, P., Zalocusky, K.A., Kosti, I., Bicak, M., Zilberter, M.Y., *et al.* (2021) Experimental and Real-World Evidence Supporting the Computational Repurposing of Bumetanide for APOE4-Related Alzheimer's Disease. *Nature Aging*, **1**, 932-947. https://doi.org/10.1038/s43587-021-00122-7

[12] Zhang, X., Wen, J. and Zhang, Z. (2018) Statins Use and Risk of Dementia: A Dose-Response Meta Analysis. *Medicine*, **97**, e11304. https://doi.org/10.1097/md.0000000000011304

[13] Luchsinger, J.A., Perez, T., Chang, H., Mehta, P., Steffener, J., Pradabhan, G., *et al.* (2016) Metformin in Amnestic Mild Cognitive Impairment: Results of a Pilot Randomized Placebo Controlled Clinical Trial. *Journal of Alzheimer's Disease*, **51**, 501-514. https://doi.org/10.3233/jad-150493

[14] Metformin in Alzheimer's Dementia Prevention (MAP) (2021) ClinicalTrials.gov. Identifier NCT04098666. https://clinicaltrials.gov/ct2/show/NCT04098666

[15] Sano, M., Bell, K.L., Galasko, D., Galvin, J.E., Thomas, R.G., van Dyck, C.H., *et al.* (2011) A Randomized, Double-Blind, Placebo-Controlled Trial of Simvastatin to Treat Alzheimer Disease. *Neurology*, **77**, 556-563. https://doi.org/10.1212/wnl.0b013e318228bf11

[16] Shepherd, J., Blauw, G.J., Murphy, M.B., Bollen, E.L., Buckley, B.M., Cobbe, S.M., *et al.* (2002) Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER): A Randomised Controlled Trial. *The Lancet*, **360**, 1623-1630. https://doi.org/10.1016/s0140-6736(02)11600-x

[17] Kehoe, P.G., Turner, N., Howden, B., Jarutyte, L., Clegg, S.L., Malone, I.B., *et al.* (2021) Safety and Efficacy of Losartan for the Reduction of Brain Atrophy in Clinically Diagnosed Alzheimer's Disease (the RADAR Trial): A Double-Blind, Randomised, Placebo-Controlled, Phase 2 Trial. *The Lancet Neurology*, **20**, 895-906. https://doi.org/10.1016/s1474-4422(21)00263-5

[18] Hajjar, I., Okafor, M., McDaniel, D., Obideen, M., Dee, E., Shokouhi, M., *et al.* (2020) Effects of Candesartan vs Lisinopril on Neurocognitive Function in Older Adults with Executive Mild Cognitive Impairment. *JAMA Network Open*, **3**, e2012252. https://doi.org/10.1001/jamanetworkopen.2020.12252

[19] Lawlor, B., Segurado, R., Kennelly, S., Olde Rikkert, M.G.M., Howard, R., Pasquier, F., *et al.* (2018) Nilvadipine in Mild to Moderate Alzheimer Disease: A Randomised Controlled Trial. *PLOS Medicine*, **15**, e1002660. https://doi.org/10.1371/journal.pmed.1002660

[20] Vossel, K., Ranasinghe, K.G., Beagle, A.J., La, A., Ah Pook, K., Castro, M., *et al.* (2021) Effect of Levetiracetam on Cognition in Patients with Alzheimer Disease with and without Epileptiform Activity. *JAMA Neurology*, **78**, 1345-1354. https://doi.org/10.1001/jamaneurol.2021.3310

[21] Lopatko Lindman, K., Weidung, B., Olsson, J., Josefsson, M., Kok, E., Johansson, A., *et al.* (2019) A Genetic Signature Including Apolipoprotein Eε4 Potentiates the Risk of Herpes Simplex-Associated Alzheimer's Disease. *Alzheimer's & Dementia*: *Translational Research & Clinical Interventions*, **5**, 697-704. https://doi.org/10.1016/j.trci.2019.09.014

[22] Weidung, B., Hemmingsson, E., Olsson, J., Sundström, T., Blennow, K., Zetterberg, H., *et al.* (2022) VALZ-Pilot: High-Dose Valacyclovir Treatment in Patients with Early-stage Alzheimer's Disease. *Alzheimer's & Dementia*: *Translational Research & Clinical Interventions*, **8**, e12264. https://doi.org/10.1002/trc2.12264

[23] Zhao, Y., Wang, C., He, W. and Cai, Z. (2022) Ameliorating Alzheimer's-Like Pathology by Minocycline via Inhibiting Cdk5/p25 Signaling. *Current Neuropharmacology*, **20**, 1783-1792. https://doi.org/10.2174/1570159x19666211202124925

[24] Wilcock, G.K., Black, S.E., Hendrix, S.B., Zavitz, K.H., Swabb, E.A. and Laughlin, M.A. (2008) Efficacy and Safety of Tarenflurbil in Mild to Moderate Alzheimer's Disease: A Randomised Phase II Trial. *The Lancet Neurology*, **7**, 483-493. https://doi.org/10.1016/s1474-4422(08)70090-5

[25] Green, R.C., Schneider, L.S., Amato, D.A., *et al.* (2009) Effect of Tarenflurbil on Cognitive Decline and Activities of Daily Living in Patients with Mild Alzheimer Disease: A Randomized Controlled Trial. *JAMA*, **302**, 2557-2564. https://doi.org/10.1001/jama.2009.1866

[26] Hino, H., Akiyama, H., Iseki, E., Kato, M., Kondo, H., Ikeda, K., *et al.* (2001) Immunohistochemical Localization of Plasminogen Activator Inhibitor-1 in Rat and Human Brain Tissues. *Neuroscience Letters*, **297**, 105-108. https://doi.org/10.1016/s0304-3940(00)01679-7

[27] Akhter, H., Huang, W., van Groen, T., Kuo, H., Miyata, T. and Liu, R. (2018) A Small Molecule Inhibitor of Plasminogen Activator Inhibitor-1 Reduces Brain Amyloid-B Load and Improves Memory in an Animal Model of Alzheimer's Disease. *Journal of Alzheimer's Disease*, **64**, 447-457. https://doi.org/10.3233/jad-180241

[28] Elokdah, H., Abou-Gharbia, M., Hennan, J.K., McFarlane, G., Mugford, C.P., Krishnamurthy, G., *et al.* (2004) Tiplaxtinin, a Novel, Orally Efficacious Inhibitor of Plasminogen Activator Inhibitor-1: Design, Synthesis, and Preclinical Characterization. *Journal of Medicinal Chemistry*, **47**, 3491-3494. https://doi.org/10.1021/jm049766q

[29] Gerenu, G., Martisova, E., Ferrero, H., Carracedo, M., Rantamäki, T., Ramirez, M.J., *et al.* (2017) Modulation of BDNF Cleavage by Plasminogen-Activator Inhibitor-1 Contributes to Alzheimer's Neuropathology and Cognitive Deficits. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular Basis of Disease*, **1863**, 991-1001. https://doi.org/10.1016/j.bbadis.2017.01.023

[30] Rodriguez, G., Eren, M., Haupfear, I., Viola, K.L., Cline, E.N., Miyata, T., *et al.* (2023) Pharmacological Inhibition of Plasminogen Activator Inhibitor-1 Prevents Memory Deficits and Reduces Neuropathology in APP/PS1 Mice. *Psychopharmacology*, **240**, 2641-2655. https://doi.org/10.1007/s00213-023-06459-8

[31] Caccamo, A., Majumder, S., Richardson, A., Strong, R. and Oddo, S. (2010) Molecular Interplay between Mammalian Target of Rapamycin (mTOR), Amyloid-B, and Tau: Effects on Cognitive Impairments. *Journal of Biological Chemistry*, **285**, 13107-13120. https://doi.org/10.1074/jbc.m110.100420

[32] Kilgore, M., Miller, C.A., Fass, D.M., Hennig, K.M., Haggarty, S.J., Sweatt, J.D., *et al.* (2009) Inhibitors of Class 1 Histone Deacetylases Reverse Contextual Memory Deficits in a Mouse Model of Alzheimer's Disease. *Neuropsychopharmacology*, **35**, 870-880. https://doi.org/10.1038/npp.2009.197

[33] Edvinsson, L., Haanes, K.A., Warfvinge, K. and Krause, D.N. (2018) CGRP as the Target of New Migraine Therapies—Successful Translation from Bench to Clinic. *Nature Reviews Neurology*, **14**, 338-350. https://doi.org/10.1038/s41582-018-0003-1

[34] Stokes, J.M., Yang, K., Swanson, K., Jin, W., Cubillos-Ruiz, A., Donghia, N.M., *et al.* (2020) A Deep Learning Approach to Antibiotic Discovery. *Cell*, **180**, 688-702.e13.

https://doi.org/10.1016/j.cell.2020.01.021

[35] Hampel, H., Hardy, J., Blennow, K., Chen, C., Perry, G., Kim, S.H., *et al.* (2021) The Amyloid-β Pathway in Alzheimer's Disease. *Molecular Psychiatry*, **26**, 5481-5503. https://doi.org/10.1038/s41380-021-01249-0

[36] Saraiva, C., Praça, C., Ferreira, R., Santos, T., Ferreira, L. and Bernardino, L. (2016) Nanoparticle-Mediated Brain Drug Delivery: Overcoming Blood-Brain Barrier to Treat Neurodegenerative Diseases. *Journal of Controlled Release*, **235**, 34-47. https://doi.org/10.1016/j.jconrel.2016.05.044