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Neuroinflammation in Alzheimer's disease: current evidence and therapeutic targets - Part II

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ABSTRACT

Alzheimer's disease is the most common form of dementia in the world, affecting tens of millions of people. Neuroinflammation is now known to be an important part of the process of Alzheimer's disease (AD) developing. In the past, it was thought of as a secondary byproduct of amyloid-beta (Aβ) plaque and tau neurofibrillary tangle accumulation, but it is now understood to be a central and early-acting pathological mechanism in AD progression. This review looks at how the brain and nervous system are affected by inflammation.

Keywords: neuroinflammation, Alzheimer's disease, microglia, cytokines, therapeutic targets

1. INTRODUCTION

AD is a progressive condition that causes problems with thinking, memory and personality, accounting for around 60–70% of all cases worldwide. The problem of dementia is very big around the world. In 2019, it is thought that 57 million people were living with dementia in the world. Experts think that this will increase to 150 million by year 2050 as the world's population ages (Melchiorri et al., 2023).

In addition to the immense personal suffering, it imposes on patients and their families, AD is one of the costliest conditions for healthcare systems and worldwide societies. Two features cause AD: amyloid-beta (Aβ) plaques and neurofibrillary tangles. Problems in producing amyloid precursor protein (APP) cause both. For decades, therapeutic research concentrated almost completely on these two targets. Despite over 400 amyloid and tau trials, none have shown a clinical benefit.

While a statistically significant though modest slowing of clinical decline was demonstrated by recent approvals of anti-amyloid monoclonal antibodies — lecanemab and donanemab — their limited effect sizes suggest that additional pathological mechanisms must be addressed (Melchiorri et al., 2023).

As well as these mechanisms, neuroinflammation has become the most interesting and relevant for treating. Neuroinflammation - the complex immune response in the brain and spinal cord. It is mostly controlled by special cells called glia, particularly microglia and astrocytes. It involves the production of chemicals

that cause inflammation, reactive oxygen species (ROS), and other substances that can damage tissue (Adamu et al., 2024). Studies of sporadic AD have revealed risk variants in genes that make immune effector proteins, including TREM2, CD33, CR1, BIN1, INPP5D and SPI1. This shows that problems with the brain's inflammation are not just a result of amyloid buildup, but are also genetic, contributing to AD (Melchiorri et al., 2023; Cai et al., 2022).

It is now understood that the relationship between neuroinflammation and the standard progression of AD is two-way and both processes make the condition worse. Aβ plaques activate microglia, which triggers a reaction that causes inflammation. This reaction causes tau to become abnormally folded. Tau pathology causes microglial activation, which in turn accelerates neuronal death and synaptic loss (Chen and Yu, 2023). In other words, neuroinflammation does not just happen with the disease — it makes the disease worse. So, it's really important to understand exactly how neuroinflammation contributes to the development of Alzheimer's disease. This helps to find drug targets and understand mechanisms.

The aim of this study is the provision of a comprehensive and critical synthesis of the current evidence on neuroinflammation in AD, covering: (1) the cells involved in the inflammation of the brain, mainly microglia and astrocytes; (2) the main pathways involved; (3) the genes that are a risk for problems with the brain's inflammation; (4) the two-way interaction between the inflammation of the brain, Aβ, and tau; (5) the new roles for the connection between the gut and the brain and the immune system outside the brain; and (6) the current and new ways to treat the disease, including those being tested in trials. A set of search terms related to "neuroinflammation", "Alzheimer's disease", "microglia", "NLRP3", "TREM2", "therapeutic targets" and similar terms in the PubMed and Google Scholar databases was used. The focus was on publications and communications.

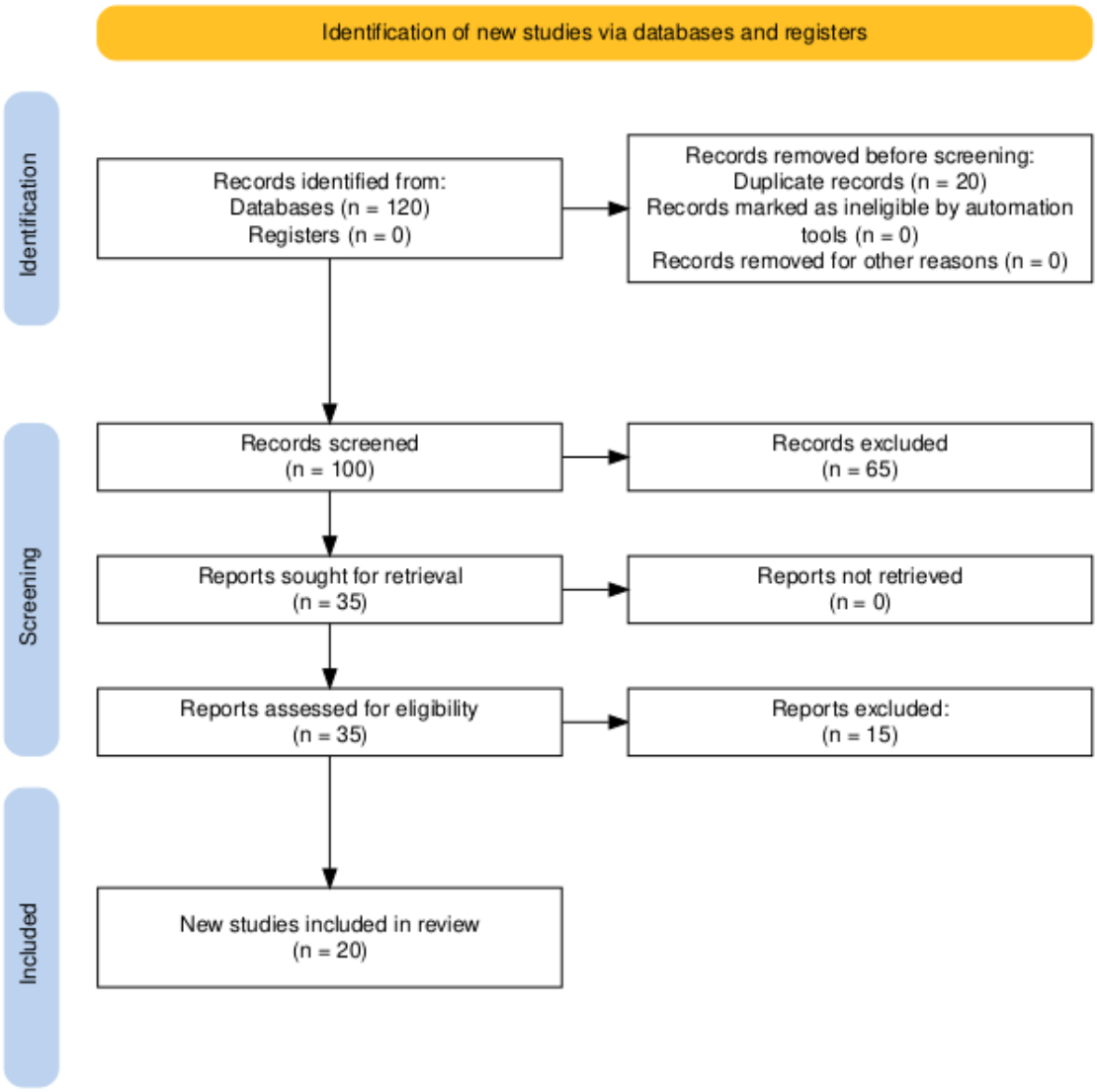

Figure 1. PRISMA flow diagram.

2. REVIEW METHODS

A search of the PubMed and Google Scholar databases was conducted using a comprehensive literature search between 2018 and 2025. The search strategy combined the following keywords: "Neuroinflammation", "Alzheimer's disease", "microglia", "NLRP3", "TREM2", and "therapeutic targets". Articles were selected based on their relevance to the cellular, molecular, immunological, and genetic mechanisms of neuroinflammation in Alzheimer's disease, as well as target-specific therapeutic approaches. The selection process is illustrated in the PRISMA flowchart (Figure 1).

Initially, 120 records were identified, but 20 were duplicate records. Then, 100 records underwent screening based on titles and abstracts, resulting in the exclusion of 65 articles. The 35 remaining full-text reports were assessed for eligibility; 15 were ultimately excluded due to a lack of peer-reviewed empirical data or relevance to the target population. Ultimately, 20 studies met all the inclusion criteria and were included in the final narrative synthesis (Figure 1).

3. RESULTS AND DISCUSSION

The Cellular basis of Neuroinflammation in Alzheimer's disease

Microglia: The Brain's Primary Immune Sentinels

Microglia make up about 10–15% of all brain cells and are the immune cells that are always there to protect the nervous system. Healthy brain cells are always at work, repairing the brain, eliminating dead cells and promoting the growth of new ones (Cai et al., 2022). A build-up of two proteins, Aβ plaques and tau tangles, causes microglia, a type of cell in the brain, to change over time in people with Alzheimer's disease (AD).

In very early AD, microglia play an initially protective role. They gathers around nascent Aβ plaques, phagocytosing amyloid peptides and releasing anti-inflammatory chemicals in an attempt to limit damage (Melchiorri et al., 2023). This early protective response relies heavily on the expression of TREM2 by microglia. TREM2 is a transmembrane receptor that senses a range of lapidated ligands, and its expression is required for the transition of microglia from a homeostatic state to a disease-associated state known as disease-associated microglia (DAM). Variants in TREM2 that impair its function increase the risk of late-onset AD by 4.5-fold, underscoring the importance of protective microglial function in disease prevention. Variants in TREM2 don't work well will increase the risk of late-onset AD by 4.5 times. This suggests that having protective microglial function is important in preventing disease (Melchiorri et al., 2023).

However, with sustained exposure to amyloid deposits and tau pathology, the microglial response shifts from protective to detrimental. Microglia are chronically activated in AD, releasing harmful chemicals. These chemicals include tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and IL-18, as well as ROS and nitric oxide (NO). These chemicals can directly harm the brain (Thakur et al., 2023). High-resolution transcriptomic profiling has revealed that activated microglia in the brains of patients with Alzheimer's are not a homogeneous population (a group of cells that are all identical) but encompass several distinct sub-states (different types of cells): There are different types of microglia, such as DAM, interferon-response microglia (IFN-R), MHC class II-expressing microglia, and cycling microglia.Each type has different functions and is active at different times during disease progression (Melchiorri et al., 2023). These states change and mix together to decide if microglia protect or harm neurons.

The role of specific genetic variants expressed in microglia is also interesting. The CD33 gene produces a protein that is found on the surface of cells and binds to sialic acid. This protein has a role in restricting the process by which microglia clear away waste. Variants of CD33 that increase the expression of a particular form of the protein (hCD33M) are linked to a reduced ability to clear away a substance called Aβ, and to a higher level of amyloid (Cai et al., 2022). On the other hand, certain changes to the CD33 gene can protect against AD by increasing the body's ability to clear away unwanted cells. In a similar way, a gene called APOE ε4 is the strongest known genetic danger factor for sporadic AD. It is found in two types of brain cell, called microglia and astrocytes. It causes the cells to respond to inflammation in the wrong way and makes it hard for the body to get rid of a substance called Aβ. (Adamu et al., 2024).

Astrocytes: Neuroinflammatory Amplifiers

Despite being the most abundant type of brain cell, astrocytes play an equally important yet often underestimated role in the inflammation of the brain associated with Alzheimer's disease (AD). This is because of a build-up of Aβ and pro-inflammatory cytokines released by activated microglia. As a result, astrocytes change from a quiescent homeostatic state to a reactive state. The

reactive state is characterized by changes to their shape, increased GFAP expression, and altered gene expression profiles (Liu et al., 2022).

Reactive astrocytes are classified into two broad phenotypes: A1 (pro-inflammatory) and A2 (neuroprotective), though more nuanced intermediate states exist. A1 astrocytes are induced by TNF-α, IL-1α, and complement C1q released from activated microglia, and they produce neurotoxic cytokines that directly kill neurons and oligodendrocytes (Adamu et al., 2024). Astrocytes surrounding Aβ plaques - a characteristic feature of AD pathology - have been observed to progressively lose their neuroprotective functions, including glutamate buffering and supply of reduced glutathione (GSH) to neurons, thereby exacerbating the pro-inflammatory and oxidative microenvironment (Melchiorri et al., 2023).

Astrocytes can break down the protein Aβ inside their cells. However, this ability is reduced when they are exposed to Aβ for a long time. This can lead to cell death (Melchiorri et al., 2023) Reactive astrocytes also contribute to blood-brain barrier (BBB) disruption by activating MMP9, leading to BBB permeability that allows peripheral immune infiltration and neuroinflammation (Onyango et al., 2021).

Key Molecular Signaling Pathways in Neuroinflammation

The NF-κB Pathway

A special type of cell in the brain called microglia and astrocytes can make a protein called nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). NF-κB helps to make more of another protein called "pro-inflammatory genes". In the AD brain, NF-κB is activated by Aβ oligomers and tau. This activates the genes that produce TNF-α, IL-1β, IL-6, COX-2, and iNOS (Thakur et al., 2023). Under resting conditions, NF-κB is kept in the cytoplasm by inhibitor proteins (IκB). When they are activated, a type of enzyme called IKK phosphorylates IκB, marking it for destruction. Then NF-κB can move to the nucleus and turn on the genes that make inflammatory chemicals (Cai et al., 2022). A significant part of Alzheimer's disease (AD) is when a protein called NF-κB is constantly active. These changes can cause tau to become misfolded. Research shows that this process is associated with inflammation of the brain and the accumulation of tau proteins (Zhang et al., 2023).

The NLRP3 Inflammasome

The NOD-like receptor protein 3 (NLRP3) inflammasome is a group of proteins that work together to detect danger signals in the body. It is also important in causing the inflammation that is a feature of Alzheimer's disease (AD). Aβ fibrils, tau aggregates, ATP, and ROS all activate the NLRP3 inflammasome in microglia, which triggers the cleavage and activation of a protein called caspase-1. This, in turn, processes pro-IL-1β and pro-IL-18 into their mature, secreted forms (Adamu et al., 2024). NLRP3 activation is also linked to gasdermin D-mediated pyroptosis. This is a form of cell death that causes inflammation by releasing cellular contents and making the inflammation worse (Thakur et al., 2023).

The link between NLRP3 and tau pathology is very interesting. Studies in mice showed that not having enough of the NLRP3 gene stopped tau from becoming abnormally folded. However, tau has also been shown to activate the NLRP3 inflammasome, and the presence of fibrillar Aβ brain homogenates can cause tau spreading in a way that depends on NLRP3 (Melchiorri et al., 2023). Importantly, stopping the NLRP3 process reduces inflammation in the brain and helps microglia get rid of Aβ deposits, which suggests two possible benefits for treatment. This makes NLRP3 one of the most important targets for new treatments for AD neuroinflammation.

The JAK/STAT Pathway

The Janus kinase/signal transducer, activator of transcription (JAK/STAT) pathway is important for sending signals between immune cells in the body. In certain brain cells, a process called JAK/STAT activation is driven by molecules called interferons and interleukins. This leads to two different responses in these cells: an inflammatory response (M1) and a response that protects the brain (M2). The latter response is triggered by a molecule called IL-4 and is dependent on a different set of genes (called STAT6). In AD, the body's own immune system is overactive, and this makes it hard for the brain to clear away the build-up of a substance called Aβ. Machine learning analysis of AD brain gene expression profiles identified the JAK inhibitor baricitinib as a compound that reverses pathological inflammatory signatures in AD. This led to its inclusion in clinical trials (Melchiorri et al., 2023).

The p38 MAPK Pathway

MAPKs (mitogen-activated protein kinases), especially p38α MAPK, are activated in neurons and glial cells by Aβ and tau. MAPKs represent a meeting point for multiple upstream inflammatory signals. In microglia and astrocytes, p38 MAPK activation results in the release of inflammatory cytokines; in neurons, p38α MAPK directly promotes the build-up of tau, which can cause damage to neurons. The AD brain has higher amounts of a molecule called activated p38 MAPK, particularly in the early parts of tau pathology. This pathway has been targeted by investigational drugs like neflamapimod (VX-745) and MW150 in clinical trials (Melchiorri et al., 2023).

The Nrf2 Antioxidant Pathway

The nuclear element erythroid 2-related factor 2 (Nrf2) pathway is an endogenous cytoprotective mechanism that counteracts neuroinflammation and oxidative stress by inducing expression of antioxidant enzymes, including heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and superoxide dismutase (SOD). This is because in AD, Nrf2 activity is significantly reduced. This leads to impaired antioxidant defense and enhanced oxidative neuroinflammatory damage. Nrf2 activation suppresses NF-κB signaling, inhibits NLRP3 inflammasome assembly, stops microglia from becoming pro-inflammatory, and reduces Aβ-induced neurotoxicity. Scientists are already testing whether substances like sulforaphane and dimethyl fumarate can activate Nrf2 in the body. This could be a new way to treat AD (Saha et al., 2022).

Neuroinflammation, Amyloid, and Tau: A Bidirectional Cascade

The interaction between neuroinflammation and the classical AD pathological hallmarks — Aβ plaques and tau tangles — is bidirectional and self-reinforcing. Aβ plaques serve as powerful activators of microglia through multiple pattern-recognition receptors, including toll-like receptors (TLR2, TLR4), TREM2, CD36, and RAGE, initiating both protective phagocytosis and, chronically, damaging inflammatory responses (Dhapola et al., 2021). Soluble Aβ oligomers are particularly potent activators of the NLRP3 inflammasome and the NF-κB pathway, inducing the release of IL-1β and TNF-α, which further impair neuronal function and synaptic plasticity (Onyango et al., 2021).

Tau protein deposits are important in both conditions. Tau released by neurons directly activates microglia, causing more inflammation, which then activates more microglia (Chen and Yu, 2023). However, a molecule called IL-1β, released by activated microglia, can cause problems. CDK5 and GSK3β are proteins in neurons that are affected by this. These are proteins that can build up in the brain, and this can cause diseases (Thakur et al., 2023). When this happens, there can be problems like the tau protein misfolding and affecting the stability of the microtubules. The way neurons move their materials around can be disrupted, which leads to the formation of paired helical filaments. NFTs can then be formed by these filaments, which can also be released into the extracellular space. This can further lead to neuroinflammation (Chen and Yu, 2023).

PET scanning studies involving 130 participants showed that the rate of tau spread is determined by Aβ and microglial activity (Melchiorri et al., 2023). This evidence strongly suggests that neuroinflammation is not just a result of proteinopathy, but is actually a key factor in spreading the disease. So, it's best to treat it as soon as possible with drugs that reduce inflammation.

Genetic risk indicators and neuroinflammatory dysregulation

Research has found many genes that raise the risk of Alzheimer's. This phenomenon is due to the properties of these products which boost the immune system and cell communication. Genetic research shows neuroinflammation (the inflammation of the nervous system) is not just a reaction to Alzheimer's disease (AD), but a cause of it (Heneka et al., 2025).

TREM2 rare coding variants (particularly R47H, R62H, T66M, and H157Y) have been shown to disrupt TREM2–DAP12 signals in microglia. Disrupting these signals reduces the ability of microglia to engulf particles, and also reduces the support that microglia provide for the surrounding area of plaques. In addition, it has been shown to increase the build-up of two proteins, Aβ and tau, that are associated with neurodegenerative diseases (Cai et al., 2022). The R47H variant is comparable to APOE ε4 heterozygosity in terms of risk, highlighting its importance. The CD33 rs12459419 variant changes the way hCD33M is expressed, which reduces Aβ clearance and increases plaque build-up. INPP5D, in particular, is important here as it controls how TREM2-DAP12 signals are sent and received. Higher INPP5D levels have been linked to problems in the brain cells called microglia. Complement receptor 1 (CR1) helps with both the body's natural defences against infection and the removal of unwanted proteins, while BIN1 is involved in the process where cells take in and digest other substances. Further examples of immune genes directly linked to the likelihood of developing AD are represented by these two (Andronie-Cioara et al., 2023).

APOE ε4 is especially important here. APOE ε4 is the strongest genetic danger factor for sporadic AD: it has a number of effects on neuroinflammation, including increasing microglial pro-inflammatory activation, reducing the clearance of Aβ through reduced phagocytic efficiency, and promoting tau pathology through mechanisms that don't depend on Aβ (Adamu et al., 2024). APOE ε4 affects the way microglia express a signature that causes neurodegeneration by binding to TREM2 on microglia (Melchiorri et al., 2023). These genetic findings have changed how we understand AD. They show that it is both a proteinopathy and an immunopathic disease. This confirms that neuroinflammatory pathways should be the main targets for new treatments.

Neuroinflammation, Neurogenesis, and the Blood-Brain Barrier

A frequently underappreciated consequence of sustained neuroinflammation in AD is the suppression of adult neurogenesis — the process by which new neurons are generated, primarily in the hippocampal dentate gyrus, a region critically involved in memory formation. Pro-inflammatory cytokines (chemicals that cause inflammation) like IL-1β, TNF-α, and IFN-γ can stop neural stem cells from growing, differentiation, and survival. This makes it hard for new neurons to grow at a time when they are needed most. It seems that reducing inflammation could help to increase the number of new brain cells in people with Alzheimer's disease. This is good because it could reduce the damage caused by the disease and help the brain to repair itself (Sung et al., 2020).

The blood-brain barrier (BBB) is another important area where the inflammation of the nervous system has a harmful effect. A problem can be caused by reactive astrocytes, which get other cells (endothelial cells) to produce a protein known as MMP9, which can weaken the tight connections between these cells (Onyango et al., 2021). Scans of the fluid around the brain and spine have shown BBB breakdown in early AD. Increased BBB permeability has been shown to precipitate neuroinflammation (Lee and Chang, 2025). Special T cells have been found in people with Alzheimer's, especially CD8+ T cells. This links to tau protein buildup, a key sign of Alzheimer's. This suggests we can use treatments to target and destroy these cells (Heneka et al., 2025).

The Gut-Brain Axis and Neuroinflammation

Emerging evidence implicates the gut microbiome as an important modulator of neuroinflammation in AD via the gut-brain axis—a bidirectional communication network linking intestinal microbial communities to CNS function via immune, neural, and metabolic pathways (Cerovic et al., 2019). Dysbiosis — the pathological alteration of gut microbial composition — has been documented in both AD patients and AD mouse models, characterized by reduced bacterial diversity, increased abundance of pro-inflammatory bacterial taxa, and decreased grades of short-chain fatty acid (SCFA)-producing bacteria. SCFAs — including butyrate, propionate, and acetate — are key regulators of microglial activation and the BBB integrity; their reduction in AD dysbiosis thus removes an important anti-neuroinflammatory brake (Cerovic et al., 2019).

Gut-derived LPS and bacterial amyloids can cross the intestinal barrier and BBB, directly activating microglia and astrocyte TLR4 and TLR2, amplifying central neuroinflammation. Preclinical studies show that altering the bacteria in the gut can reduce neuroinflammation, decrease Aβ deposits and improve cognitive performance in models of AD (Cerovic et al., 2019). Although these strategies are still in the early stages for use in treating AD, they show promise as a way of reducing central neuroinflammation through the gut microbiome.

Therapeutic Targets and Strategies

NLRP3 Inflammasome Inhibitors

Given what has been learned about the role of the NLRP3 inflammasome in AD neuroinflammation, the use of drugs to block it is a very promising way to treat the disease. MCC950 (CMPD-4) is a small molecule that can inhibit NLRP3, reducing the key markers of Alzheimer's disease in mouse models (Thakur et al., 2023; Adamu et al., 2024). Scientists are developing ways to take these medicines into the brain. Some new drugs called NLRP3 inhibitors, such as JC-124, have shown promising results in early tests. Several of these drugs are now moving on to first-in-human trials.

TNF-alpha Modulators

TNF-α is significantly elevated in the serum and CNS of AD patients, and its overproduction by activated microglia drives neuroinflammation, synaptic dysfunction, and neuronal death. First-generation non-selective TNF inhibitors were ineffective in AD due to issues with how well they got through the BBB and the complicated TNF receptor biology (Melchiorri et al., 2023). XPro1595

(pegipanermin) is a second-generation selective TNFR1 inhibitor that gets into the brain and blocks TNFR1 while letting TNFR2 do its neuroprotective work.

A Phase II clinical trial (NCT03943264) is currently evaluating XPro1595 in early AD patients with evidence of neuroinflammation, stratified by inflammatory biomarkers (Melchiorri et al., 2023).

Kinase Inhibitors Targeting p38 MAPK and JAK/STAT

Neflamapimod (VX-745), a drug that inhibits p38α MAPK, is a promising treatment for mild-to-moderate AD. The main things we wanted to see in the study didn't happen in the whole group of people we studied, but when we looked at the patients who had the highest drug concentrations, we saw some good signs. The drug also reduced a certain protein in the brain called phospho-tau, which is a sign of treatment success. MW150, a special part of the drug that is really good at fighting p38α MAPK, has shown that it can be taken orally without too many problems and can get into the brain in Phase I safety trials (Melchiorri et al., 2023). It was being tested in Phase II to see if it could help people with mild to moderate Alzheimer's disease.

Baricitinib, a drug that is currently used to treat rheumatoid arthritis, is being used to treat Alzheimer's disease. This is because it has been shown to reverse changes in the genes that are linked to the disease. A group of patients with MCI or mild AD whose CSF levels of the chemokine CCL2 are high are taking part in a trial to test a drug called baricitinib. The first things we look at are whether the drug gets into the brain and how much it reduces inflammation.

TREM2-Targeted Therapies

TREM2 agonism represents a strategy to restore and amplify protective microglial responses in AD.AL002, a monoclonal antibody, was evaluated in a trial (NCT04592874) that demonstrated engagement of the TREM2 pathway in the CNS, as measured by changes in CSF and biomarkers. Further Phase II trials are ongoing. TB006, a monoclonal antibody targeting galectin-3 — a microglial activating ligand that promotes pro-inflammatory signaling — is also under clinical investigation (Melchiorri et al., 2023). These TREM2-directed approaches aim to shift the microglial response from a pro-inflammatory to a disease-associated protective phenotype, directly addressing the genetic risk encoded by TREM2 loss-of-function variants.

Nrf2 Pathway Activators

Nrf2 activation reduces neuroinflammation via several mechanisms, including NF-κB and NLRP3 suppression, microglia shift reduction, and increased antioxidant enzymes (Saha et al., 2022).

Sulforaphane, a naturally occurring compound located in cruciferous vegetables, has been shown in laboratory tests to fight neuroinflammation and protect the brain in patients with Alzheimer's disease. Dimethyl fumarate is already approved to treat multiple sclerosis and is now being studied as a possible treatment for Alzheimer's. Nrf2 activators have two important jobs: they can stop inflammation and protect cells. These activators are very useful in multi-target AD treatment plans.

Regulatory T Cells

Regulatory T cells (T-regs) maintain peripheral and central immune homeostasis and have been shown to suppress microglia-mediated inflammation by promoting neuroprotective microglial phenotypes. In AD patients at the clinical dementia stage, T-reg suppressive activity is significantly impaired, suggesting a loss of a critical anti-neuroinflammatory brake at a key point in disease progression. VT301 — an autologous T-reg cell therapy developed by VT BIO — is undergoing Phase I/II trials in AD patients (NCT03865017), exploring whether ex vivo expanded autologous T-regs can restore immune homeostasis and attenuate neuroinflammation in the AD brain (Melchiorri et al., 2023).

Gut Microbiome Modulation

In view of the evident dysbiosis in AD patients, as well as the mechanistic correlations between the composition of the gut microbiome and central neuroinflammation, therapeutic strategies that target the gut-brain axis represent a novel and emerging approach. Studies show probiotics (e.g. Lactobacillus and Bifidobacterium) and faecal microbiota transplantation (FMT) can reduce neuroinflammation in preclinical Alzheimer's disease models. Human studies support the hypothesis that this intervention can reduce inflammation. However, its efficacy in treating neuroinflammation in AD remains to be fully established, requiring larger clinical trials (Cerovic et al., 2019; Kiraly et al., 2023).

Novel Molecular Targets: sEH, IL-34, and the Complement System

Several additional therapeutic targets have emerged from recent research. Soluble epoxide hydrolase (sEH), an enzyme involved in the regulation of epoxyeicosatrienoic acids (EETs) — endogenous lipid mediators with potent anti-inflammatory properties — has been identified as a promising target. A novel sEH inhibitor developed at the University of Barcelona demonstrated neuroprotective and anti-neuroinflammatory effects in two AD mouse models, improving spatial and working memory, reducing pro-inflammatory cytokine transcription, and preserving neuronal network integrity — effects sustained for at least one month after drug cessation, suggesting disease-modifying rather than merely symptomatic activity.

IL-34 is a cytokine that signals through CSF-1R on activated microglia and is being explored as a modulator of microglial phenotype; CSF-1R inhibitors such as PLX5622 have shown preclinical promise (Adamu et al., 2024). The complement cascade, and more specifically C1q, C3, and CR3, has been demonstrated to drive synapse elimination in AD — an early pathological event — and complement inhibitors targeting C1q or downstream components represent the emergence of another significant therapeutic avenue (Hampel et al., 2020) (Table 1).

Table 1. A comparison of the main drugs being studied for their effect on the inflammation of the brain in people with Alzheimer's disease.

Drug	Target	Mechanism	Phase	Key Findings
Neflamapimod	p38α MAPK	Kinase inhibition	II	Reduced CSF p-tau; no primary cognitive endpoint
MW150	p38α MAPK	Selective kinase inhibitor fragment	II	Safety confirmed in Phase I
Baricitinib	JAK1/2	Kinase inhibition	I/II	Reversed AD inflammatory gene signature
XPro1595	Soluble TNF-α	Selective TNFR1 blockade	II	Ongoing; targets high-inflammation AD subgroup
AL002	TREM2	Agonistic antibody	II	Engaged TREM2 pathway per CSF biomarkers
TB006	Galectin-3	Microglial modulation	II	Anti-neuroinflammatory in preclinical models
MCC950	NLRP3 inflammasome	Small molecule inhibitor	Preclinical	Reduced Aβ, tau, and cognitive deficit in mice
VT301	T-regulatory cells	Autologous cell therapy	I/II	Restoration of T-reg suppressive function
Sulforaphane	Nrf2	Pathway activator	Preclinical/I	Reduced NF-κB, NLRP3, ROS in AD models

Challenges and Future Directions

Despite the strong scientific rationale for targeting neuroinflammation in AD and the growing number of investigational compounds, several significant challenges remain. The blood-brain barrier makes large molecules, such as monoclonal antibodies, hard for the body to absorb. Meticulous medicinal chemistry is key to achieving adequate exposure of small molecules to the central nervous system (Fu et al., 2018).

Second, the temporal complexity of neuroinflammation in AD — where early microglial activation may be protective while late-stage inflammation is destructive — demands stage-specific therapeutic targeting: the same intervention that is beneficial in early AD may be harmful in late-stage disease (Ozben and Ozben, 2019). Also, the fact that predictions made using animal models don't always work in human clinical trials – a common problem in developing drugs for Alzheimer's disease (AD) – shows major differences

between humans and animals in microglial biology, complement pathways, and how the immune system and nervous system interact (Adamu et al., 2024).

Precision medicine is a way to solve these problems. Scientists can divide patients into groups based on certain molecules in their brains (called 'neuroinflammatory biomarkers') and their genes. This can help identify which patients will benefit most from specific treatments, with combinations of treatments tackling multiple problems being used more and more in cancer treatment. This approach is also being used to treat amyloid and tau protein buildup and brain swelling.

Future research priorities include: developing more selective NLRP3 inhibitors with validated CNS pharmacokinetics; refining TREM2 agonist therapies to maximize protective microglial function; exploring the therapeutic potential of microbiome modulation through rigorous clinical trials; identifying reliable peripheral blood neuroinflammatory biomarkers for patient stratification; and applying single-cell and spatial transcriptomic technologies to better delineate the microglial heterogeneity in human AD brain tissue (Heneka et al., 2025; Sobue et al., 2023).

4. CONCLUSION

Neuroinflammation is a central part of Alzheimer's disease. Genetic evidence and mechanistic studies on microglia, astrocytes, the NLRP3 inflammasome, NF-κB, and JAK/STAT have transformed neuroinflammation from peripheral to therapeutic. A new era in the development of drugs to treat Alzheimer's disease. This is because there are now many medicines being tried in clinical trials that target the processes that cause inflammation in the brain. These medicines include NLRP3 inhibitors, p38 MAPK inhibitors, JAK inhibitors, selective TNF modulators, TREM2 agonists, Nrf2 activators, and T-reg cell therapies. New evidence from the gut-brain axis, the immune system in the body, and other targets such as sEH and complement components is also helping to expand the range of possible treatments. The future of AD treatment involves precision-guided, multi-target approaches. These are tailored to individual patients' neuroinflammatory and genetic profiles. They combine interventions directed at amyloid and tau. All of this is delivered in the early stages of disease. The goal is to halt irreversible neuronal loss. Achieving this vision means investing in translating neuroinflammatory biology into validated biomarkers and in rationally designed clinical trials.

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Conflict of interest

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Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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