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NEUROINFLAMMATION AND NEURODEGENERATION IN ALZHEIMER'S DISEASE: A MODERN REVIEW

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ABSTRACT
Alzheimer's disease (AD) is the most prevalent cause of dementia and represents a major global health challenge due to its increasing incidence and lack of effective disease-modifying therapies. While the classical pathological hallmarks of AD include extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein, growing evidence indicates that neuroinflammation is a critical driver of disease onset and progression. Persistent activation of microglia and astrocytes, dysregulation of the innate immune response, excessive production of pro-inflammatory cytokines, oxidative stress, mitochondrial dysfunction, and blood–brain barrier impairment collectively contribute to synaptic dysfunction and progressive neuronal loss. Recent advances in molecular biology have identified several inflammatory signaling pathways, including nuclear factor kappa B (NF-κB), NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, complement cascade, and triggering receptor expressed on myeloid cells-2 (TREM2), as promising therapeutic targets. Furthermore, novel therapeutic approaches involving monoclonal antibodies, small-molecule inhibitors, stem cell therapy, nanotechnology-based drug delivery systems, and natural bioactive compounds have demonstrated encouraging neuroprotective and anti-inflammatory effects in preclinical and clinical studies. Emerging biomarkers based on neuroimaging, cerebrospinal fluid, blood-derived inflammatory mediators, and genetic profiling are also improving the early diagnosis and monitoring of disease progression. This review comprehensively discusses the molecular mechanisms linking neuroinflammation and neurodegeneration in AD, summarizes recent advances in diagnostic biomarkers and therapeutic interventions, and highlights current challenges and future perspectives in the development of targeted strategies to delay disease progression and improve patient outcomes.

KEYWORDS: Alzheimer's disease; Neuroinflammation; Neurodegeneration; Amyloid-β; Tau protein; Microglia; Astrocytes; NLRP3 inflammasome; NF-κB signaling; Oxidative stress; Neuroimmune modulation; Biomarkers; Nanomedicine; Disease-modifying therapy.

1. INTRODUCTION

Alzheimer's disease (AD) accounts for 60-80% of all dementia cases and represents one of the most pressing challenges in global public health, with the number of affected individuals projected to rise sharply as populations age. Clinically, AD manifests as an insidious, progressive decline in episodic memory, executive function, language, and, ultimately, functional independence. Neuropathologically, the disease has traditionally been defined by two hallmark lesions: extracellular plaques composed of aggregated amyloid-beta (Aβ) peptides derived from proteolytic cleavage of the amyloid precursor protein (APP), and intraneuronal neurofibrillary tangles composed of hyperphosphorylated microtubule-associated protein tau.

For much of the last three decades, the amyloid cascade hypothesis dominated AD research, positing that Aβ accumulation is the initiating event that triggers downstream tau pathology, synaptic dysfunction, and neuronal death. While this framework has driven considerable therapeutic effort, the modest clinical benefit of many amyloid-targeted interventions, together with the frequent dissociation between amyloid burden and cognitive severity observed at autopsy, has prompted a broader reconceptualization of AD pathogenesis. A substantial and rapidly growing body of genetic, neuropathological, and experimental evidence now implicates chronic neuroinflammation not merely as a secondary bystander response to protein aggregation, but as an active, and in some contexts causal, contributor to disease initiation and progression.

Neuroinflammation in AD is orchestrated principally by microglia and astrocytes, which undergo profound phenotypic reprogramming in the diseased brain. Genome-wide association studies (GWAS) have been particularly influential in repositioning immune dysregulation at the center of AD biology: a large proportion of AD risk loci identified to date, including TREM2, CR1, CD33, ABCA7, INPP5D, and the MS4A gene cluster, are preferentially or exclusively expressed in microglia, suggesting that innate immune dysfunction is mechanistically upstream of neurodegeneration in at least a subset of patients. This review synthesizes current knowledge of the cellular players, molecular signaling pathways, genetic risk architecture, biomarkers, and therapeutic strategies relevant to the neuroinflammation-neurodegeneration axis in Alzheimer's disease.

2. Epidemiology and Clinical Burden

AD currently affects more than 55 million people worldwide, a figure expected to rise sharply as global life expectancy increases, placing enormous strain on healthcare systems, caregivers, and economies. Advancing age remains the single strongest risk factor, while the apolipoprotein E ε4 (APOE ε4) allele constitutes the most significant common genetic risk factor for late-onset, sporadic disease. Modifiable risk factors, including midlife hypertension, type 2 diabetes, obesity, hearing loss, low educational attainment, social isolation, physical inactivity, and traumatic brain injury, are estimated to account for a substantial proportion of dementia risk, and several of these factors converge mechanistically on chronic low-grade systemic and neural inflammation, reinforcing the centrality of inflammatory processes to disease risk at a population level.

Global Burden of Disease (GBD) 2019 estimates placed the age-standardized worldwide prevalence of dementia at 682.5 cases per 100,000 people, corresponding to approximately 57.4 million affected individuals; this figure is projected to reach 152.8 million by 2050. Women bear a disproportionate share of this burden, with a female-to-male prevalence ratio of approximately 1.7, projected to persist through 2050. The geographic distribution of projected growth is highly uneven: while high-income Asia-Pacific and Western Europe are forecast to see comparatively modest increases (53% and 74%, respectively), eastern sub-Saharan Africa and North Africa/the Middle East are projected to experience increases exceeding 350%, driven predominantly by population growth and aging rather than by changes in age-specific risk. Table 1 summarizes key quantitative epidemiological indicators.

Table 1. Global epidemiological burden of dementia/Alzheimer's disease: current estimates and projections to 2050.

Indicator	2019 (or baseline)	2050 (projected)	Source / Notes
Global dementia cases	~57.4 million	~152.8 million	GBD 2019 (Lancet Public Health); ~2.7-fold increase
Age-standardized prevalence (per 100,000)	682.5	~stable (+0.1%)	Absolute case growth is driven by demographic aging, not rising per-person risk.
Female-to-male prevalence ratio	1.69	1.67 (projected)	Women consistently show higher lifetime prevalence and mortality.
Share of cases in low/middle-income countries	~60%	~71%	Alzheimer's Disease International, World Alzheimer Report
Regional case growth (North Africa / Middle East)	-	+367%	Largest projected regional increase, GBD 2019
Regional case growth (eastern sub-Saharan Africa)	-	+357%	Second-largest projected regional increase
Regional case growth (western Europe)	-	+74%	Among the smallest projected regional increases
Proportion of AD attributable to APOE ε4 carriage	40-70% of sporadic cases	-	Varies by population ancestry

3. Classical Pathological Hallmarks: Amyloid and Tau

Amyloid-beta is generated through sequential cleavage of APP by β-secretase (BACE1) and the γ-secretase complex, yielding peptides of variable length (predominantly Aβ40 and the more aggregation-prone Aβ42) that self-assemble into soluble oligomers, protofibrils, and ultimately insoluble fibrils deposited as extracellular plaques. Soluble Aβ oligomers are now widely considered the most synaptotoxic species, disrupting long-term potentiation and glutamatergic signaling well before overt plaque formation. In parallel, tau, a microtubule-stabilizing protein normally enriched in axons, becomes hyperphosphorylated at multiple serine and threonine residues, detaches from microtubules, and aggregates into paired helical filaments that form intraneuronal neurofibrillary tangles. Unlike amyloid pathology, the regional spread and burden of tau pathology correlate closely with the topography and severity

of cognitive decline, and tau is increasingly understood to propagate between anatomically connected neurons in a prion-like manner.

Critically, neither amyloid nor tau pathology occurs in isolation from the brain's immune compartment. Aβ oligomers and fibrils are potent activators of microglial pattern-recognition receptors, while tau aggregates themselves engage innate immune sensors including the NLRP3 inflammasome, positioning neuroinflammation as a mechanistic bridge that links these two canonical hallmarks rather than a downstream epiphenomenon.

4. Cellular Mediators of Neuroinflammation

4.1 Microglia: Guardians Turned Aggressors

Microglia are the resident tissue-macrophage population of the central nervous system and, under physiological conditions, continuously survey the parenchyma, prune synapses, and clear debris and misfolded proteins. In AD, microglia cluster densely around Aβ plaques, where they can be found in states historically described using the reductive M1 (pro-inflammatory) versus M2 (anti-inflammatory/reparative) dichotomy; single-cell and single-nucleus RNA sequencing studies have since revealed a far more complex spectrum of disease-associated microglia (DAM) states characterized by downregulation of homeostatic genes (e.g., P2RY12, TMEM119) and upregulation of phagocytic and inflammatory genes (e.g., TREM2, APOE, TYROBP, CST7).

Chronically activated microglia exhibit impaired phagocytic clearance of Aβ despite plaque-associated clustering, alongside sustained secretion of pro-inflammatory cytokines and reactive oxygen species that damage neighboring synapses and neurons. This dual failure, insufficient clearance combined with excessive inflammatory output, is thought to be a central driver of disease progression. Microglial energy metabolism, particularly a shift toward glycolysis and mitochondrial dysfunction, has also been implicated in sustaining this maladaptive inflammatory phenotype.

4.2 Astrocytes: The A1/A2 Reactive Spectrum

Astrocytes, the most abundant glial cell type, provide metabolic support, regulate the blood-brain barrier, and participate in glutamate and potassium homeostasis at the tripartite synapse. In response to CNS injury or inflammatory cytokines, astrocytes become reactive, adopting morphological and transcriptional changes broadly classified into a neurotoxic A1-like phenotype, induced by microglia-derived IL-1α, TNF-α, and complement component C1q, and a neuroprotective A2-like phenotype associated with the marker S100A10 and secretion of trophic factors. Post-mortem studies of AD brain tissue have demonstrated an imbalance favoring the neurotoxic A1-like state, with increased density of complement C3-immunopositive reactive astrocytes, particularly in association cortices bearing high pathological burden.

Reactive astrocytes contribute to disease progression through several mechanisms: loss of glutamate uptake capacity promoting excitotoxicity, impaired aquaporin-4 (AQP4) polarization that disrupts glymphatic clearance of Aβ and tau, and direct secretion of neurotoxic factors that induce neuronal and oligodendrocyte death. Plasma and CSF glial fibrillary acidic protein (GFAP), a marker of astrocyte reactivity, is now one of the most robust and earliest-changing fluid biomarkers across the AD continuum, rising before overt cognitive symptoms in some cohorts.

4.3 Peripheral Immunity, the Blood-Brain Barrier, and CNS Border Compartments

Although long considered an immunologically privileged organ, the brain maintains active bidirectional communication with peripheral immune compartments through the blood-brain barrier (BBB), the choroid plexus, and meningeal lymphatic vessels. BBB breakdown is now recognized as an early event in AD, often preceding overt amyloid and tau pathology, and correlates with markers of pericyte injury (e.g., soluble PDGFRβ) and glial activation (GFAP, YKL-40). A compromised barrier permits infiltration of peripheral monocytes, T lymphocytes, and inflammatory mediators such as high-mobility group box 1 (HMGB1) and thrombin, which further potentiate central neuroinflammation. Regulatory T cells (Tregs) have emerged as an important modulator of this crosstalk, capable of dampening microglial and astrocytic reactivity in preclinical models, highlighting the adaptive immune system as an additional, and potentially therapeutically tractable, contributor to disease pathophysiology.

Figure 1. The Self-Amplifying Neuroinflammation-Neurodegeneration Cycle in AD

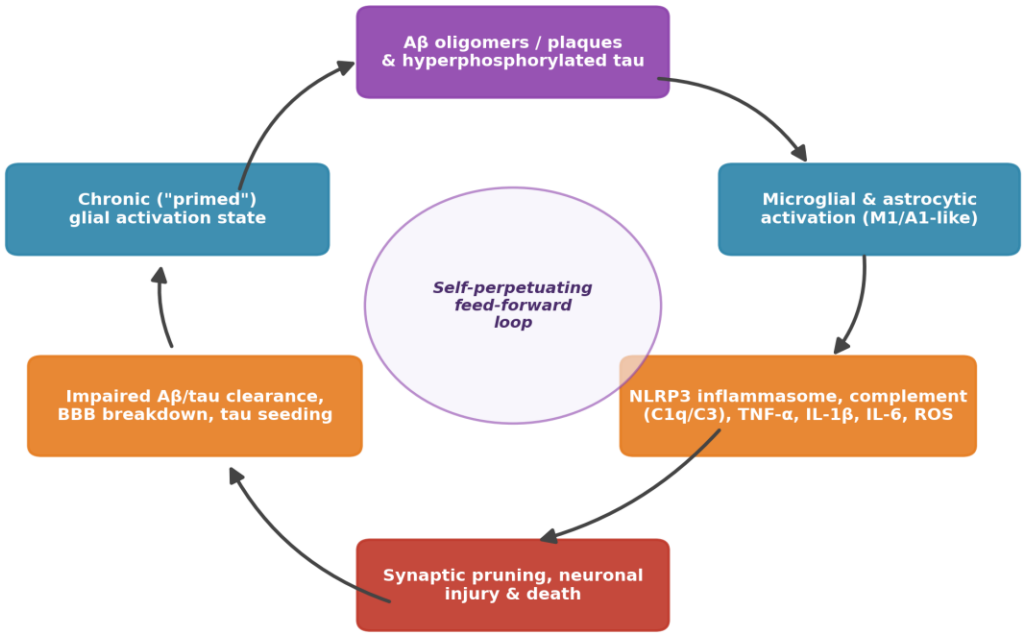

Figure 1. The neuroinflammation-neurodegeneration cycle in Alzheimer's disease. Aβ and hyperphosphorylated tau activate microglia and astrocytes, driving release of inflammasome-dependent cytokines and reactive oxygen species that injure synapses and neurons. Resulting tissue damage and impaired clearance mechanisms further prime glia, creating a chronic, self-amplifying feed-forward loop that sustains disease progression.

5. Molecular Pathways and Inflammatory Mediators

5.1 The NLRP3 Inflammasome

The NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome is a cytosolic multiprotein complex assembled from NLRP3, the adaptor ASC, and pro-caspase-1, and is one of the most extensively studied inflammatory signaling platforms in AD. Fibrillar Aβ, along with a wide array of damage- and pathogen-associated molecular patterns (mitochondrial dysfunction, lysosomal destabilization, ion flux, oxidative stress, and gut dysbiosis-derived metabolites), triggers NLRP3 assembly, leading to caspase-1-dependent cleavage and release of the pro-inflammatory cytokines IL-1β and IL-18, as well as gasdermin D-mediated pyroptotic cell death. Notably, experimental work has demonstrated a direct, reciprocal relationship between the NLRP3 inflammasome and tau pathology: NLRP3 or ASC deficiency substantially reduces tau hyperphosphorylation and aggregation in tau transgenic mice, while fibrillar Aβ promotes tau pathology in an NLRP3-dependent manner, and ASC specks released from activated microglia can cross-seed Aβ aggregation extracellularly. This bidirectional relationship positions the NLRP3 inflammasome as a mechanistic nexus linking the two canonical AD proteinopathies to neuroinflammation, and has generated substantial interest in NLRP3 and caspase-1 inhibitors as candidate disease-modifying therapeutics.

5.2 The Complement System

The classical complement cascade, particularly C1q, C3, and C3b/iC3b opsonization acting through microglial complement receptor 3 (CR3), plays a physiological role in activity-dependent synaptic pruning during development. In AD, this pathway becomes aberrantly reactivated: complement tagging of synapses in the vicinity of Aβ oligomers drives excessive, pathological microglial synaptic engulfment, contributing to the synapse loss that correlates most closely with cognitive decline in AD. Complement components additionally shape reactive astrocyte polarization toward the neurotoxic A1-like phenotype, further linking innate immune opsonization pathways to both cell types implicated in neurodegeneration.

5.3 Pro-Inflammatory Cytokines and Oxidative Stress

Activated microglia and astrocytes secrete a range of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and interferon-gamma, that act on neurons, oligodendrocytes, and vascular cells to impair synaptic plasticity, promote excitotoxicity, and increase BBB permeability. Chronic cytokine exposure also upregulates BACE1 expression and amyloidogenic APP processing, creating a direct biochemical link between inflammation and Aβ production. In parallel, activated glia generate substantial quantities of reactive oxygen and nitrogen species, overwhelming endogenous antioxidant defenses and contributing to mitochondrial dysfunction, lipid peroxidation, and DNA damage in neurons, all of which further sensitize the tissue to inflammatory injury.

5.4 TREM2 and Microglial Genetic Risk Architecture

The triggering receptor expressed on myeloid cells 2 (TREM2) is a microglia-specific immunoreceptor that partners with the adaptor DAP12 to regulate microglial survival, proliferation, phagocytosis, chemotaxis, and metabolic reprogramming. Rare loss-of-function TREM2 variants, most notably R47H, confer a 2- to 4-fold increased risk of late-onset AD, an effect size comparable to a single APOE ε4 allele, providing compelling human genetic evidence that impaired microglial immune function can be causally upstream of neurodegeneration rather than purely reactive. TREM2 binds apolipoproteins (including ApoE), phospholipids, and Aβ itself, and is required for the transition of homeostatic microglia into the disease-associated microglia (DAM) state that clusters around and compacts amyloid plaques. Soluble TREM2 (sTREM2), released by ADAM10/17-mediated ectodomain shedding, rises in CSF across the AD continuum and correlates with tau pathology, establishing it as a candidate fluid biomarker of microglial activation. Beyond TREM2, large GWAS meta-analyses have identified dozens of additional AD risk loci strongly enriched in microglial and myeloid gene expression signatures, including CR1, CD33, ABCA7, INPP5D, MS4A4A/MS4A6A, PLCG2, and SPI1, collectively reinforcing microglial immune dysfunction as a core, genetically supported axis of AD susceptibility.

Table 2 summarizes representative effect sizes for the major genetic risk and protective loci identified through GWAS and sequencing studies, illustrating the wide range of odds ratios spanning rare, high-penetrance variants (APOE ε4/ε4, TREM2 R47H) to common, low-penetrance immune-gene variants that individually confer only modest risk but collectively implicate innate immunity as a core susceptibility pathway.

Table 2. Representative Alzheimer's disease genetic risk and protective loci with approximate reported odds ratios.

Gene / Locus	Variant	Reported Odds Ratio (approx.)	Functional Category
APOE	ε4/ε4 (homozygous)	~8-12	Lipid transport; amyloid clearance
APOE	ε3/ε4 (heterozygous)	~3-4	Lipid transport; amyloid clearance
APOE	ε2 (any copy)	~0.6 (protective)	Lipid transport; amyloid clearance
TREM2	R47H (rare variant)	~2.9-4.5	Microglial phagocytosis / DAM transition
SORL1	Loss-of-function variants	~3-5 (rare variant range)	APP trafficking/sorting
CR1	Common variants	~1.15-1.2	Complement receptor / Aβ clearance
CD33	Common variants	~1.1	Microglial inhibitory immune receptor
BIN1	Common variants	~1.2	Endocytosis/vesicle trafficking
CLU (APOJ)	Common variants	~0.9 (protective)	Lipid metabolism/chaperone
PICALM	Common variants	~0.9 (protective)	Endocytosis / Aβ clearance
ABCA7	Common & rare loss-of-function variants	~1.2 (common); ~2 (rare LOF)	Lipid metabolism/phagocytosis
MS4A4A/MS4A6A	Common variants	~1.1	Modulates soluble TREM2 levels

Common-variant odds ratios are drawn from large GWAS meta-analyses (e.g., Bellenguez et al. 2022); rare-variant effect sizes are drawn from case-control sequencing studies. Values are approximate and vary by population and study.

Figure 2. Microglial Receptor Signaling Converging on Neuroinflammatory Output

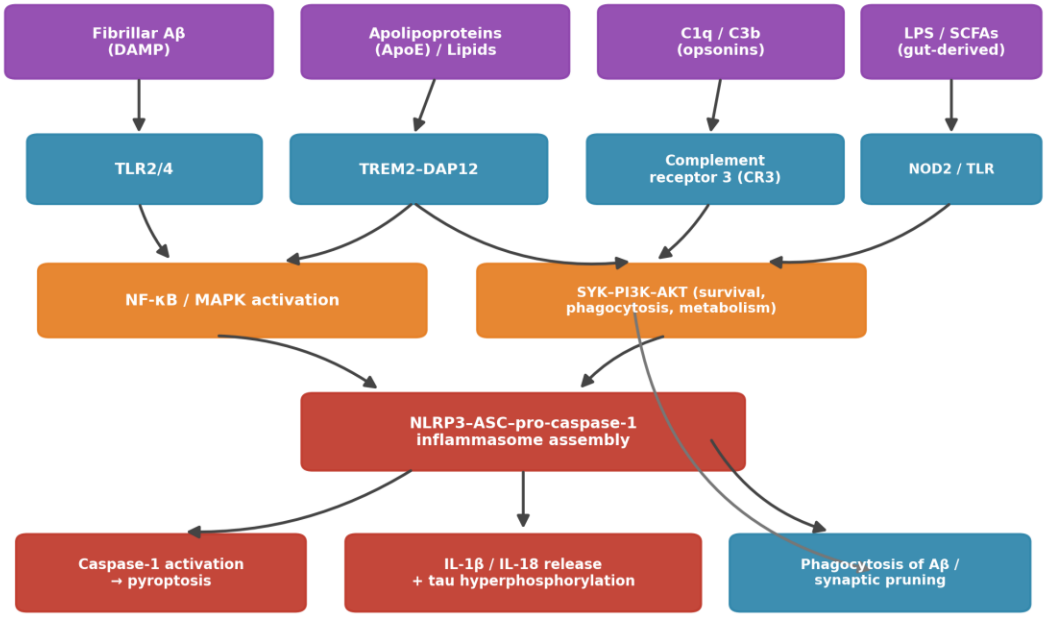

Figure 2. Microglial receptor signaling converging on neuroinflammatory output. Extracellular ligands, including fibrillar Aβ, apolipoproteins, complement opsonins, and gut-derived microbial products, engage TLR, TREM2-DAP12, and complement receptors, activating NF-κB/MAPK and SYK-PI3K-AKT signaling. These pathways converge on NLRP3-ASC-caspase-1 inflammasome assembly, driving IL-1β/IL-18 release, pyroptosis, tau hyperphosphorylation, and phagocytic activity.

6. The Microbiota-Gut-Brain Axis

Accumulating evidence implicates the gut microbiome as a modulator of central neuroinflammation in AD. Gut dysbiosis, characterized by reduced short-chain fatty acid (SCFA)-producing commensals and expansion of pro-inflammatory taxa, compromises intestinal barrier integrity and increases circulating lipopolysaccharide (LPS) and other microbial metabolites capable of crossing a permeabilized BBB. These signals activate microglial pattern-recognition receptors, amplify systemic inflammatory markers such as C-reactive protein, and have been linked in preclinical models to increased Aβ deposition and accelerated cognitive decline. Conversely, SCFAs such as butyrate exert anti-inflammatory, neuroprotective effects, and their depletion in dysbiotic states removes an important brake on microglial activation. Oral microbiota, including Porphyromonas gingivalis, have similarly been implicated in exacerbating central neuroinflammatory tone. This axis has generated interest in probiotics, prebiotics, dietary intervention, and fecal microbiota transplantation as adjunctive strategies to modulate neuroinflammation in AD, although clinical evidence in humans remains preliminary.

7. Biomarkers of Neuroinflammation

The recognition of neuroinflammation as a core, quantifiable component of AD pathophysiology has spurred development of fluid and imaging biomarkers capable of tracking glial activation in vivo, both for diagnostic staging and as pharmacodynamic endpoints in clinical trials. Table 1 summarizes the principal biomarkers currently in use or under active investigation.

Table 3. Fluid and imaging biomarkers of neuroinflammation in Alzheimer's disease.

Biomarker	Compartment	Cellular Source / Target	Clinical Significance
GFAP	Plasma / CSF	Reactive astrocytes	Rises early across the AD continuum; tracks astrogliosis and correlates with amyloid PET positivity

sTREM2	CSF / Plasma	Activated microglia	Marker of microglial activation; correlates with CSF tau and disease stage
YKL-40 (CHI3L1)	CSF	Astrocytes/microglia	Associated with BBB dysfunction and glial activation; rises with age and neurodegeneration
IL-6, TNF-α, IL-1β	CSF / Plasma / Serum	Microglia, astrocytes, peripheral immune cells	Reflect systemic and central inflammatory tone; variable specificity for AD.
C1q, C3, C3b	CSF / brain tissue	Complement cascade	Mark synaptic tagging and complement-mediated synapse loss
TSPO PET ligands (e.g., 11C-PK11195, 18F-DPA-714)	In vivo imaging	Activated microglia/astrocytes (mitochondrial TSPO)	Visualizes regional microglial activation; uptake correlates with amyloid burden and progression
CSF/plasma albumin ratio (QAlb)	CSF & plasma	Blood-brain barrier	Index of BBB permeability; associated with pericyte injury and neuroinflammation
HMGB1, thrombin	Serum	Damaged BBB / activated glia	Candidate markers of BBB breakdown linking neuroinflammation to neurodegeneration

Beyond individual biomarkers, systematic meta-analyses of peripheral inflammatory profiling provide additional quantitative support for the inflammatory hypothesis. A meta-analysis pooling 175 studies (13,344 AD patients versus 12,912 cognitively healthy controls) found significantly elevated peripheral concentrations of multiple pro-inflammatory analytes in AD, with IL-6 levels inversely correlated with Mini-Mental State Examination (MMSE) scores. Table 4 summarizes representative pooled effect sizes from key meta-analyses of peripheral and central cytokine profiling in AD.

Table 4. Pooled effect sizes for peripheral and cerebrospinal fluid cytokines in Alzheimer's disease, drawn from published meta-analyses. SMD = standardized mean difference relative to cognitively healthy controls.

Cytokine / Marker	Compartment	Pooled Effect (SMD or direction)	Source
IL-1β	Peripheral blood	SMD ≈ 1.37 (elevated in AD)	Meta-analysis, elderly AD vs. controls
IL-6	Peripheral blood	SMD ≈ 0.91 (elevated in AD)	Meta-analysis; inversely correlated with MMSE score
IL-6	CSF	SMD ≈ 0.13 (not significant)	Meta-analysis; central IL-6 elevation less consistent than peripheral
IL-18	Peripheral blood	Elevated in AD vs. controls	175-study meta-analysis (13,344 AD; 12,912 controls)
Interferon-γ	Peripheral blood	Elevated in AD vs. controls	175-study meta-analysis
hs-CRP	Serum	Elevated in AD vs. controls	175-study meta-analysis; also modifies genetic risk (SPI1, CD33, CLU)
TNF-α	Peripheral blood	Inconsistent across studies (non-significant in some pooled analyses)	Reflects heterogeneity in assay methods and disease stage
Soluble TNF receptors 1 & 2	Peripheral blood	Elevated in AD vs. controls	175-study meta-analysis

8. Therapeutic Strategies Targeting Neuroinflammation

Therapeutic approaches to AD have historically prioritized removal of amyloid pathology, but growing appreciation of the neuroinflammation-neurodegeneration axis has diversified the pipeline to include agents that directly modulate

glial activation, inflammasome signaling, and peripheral immune-CNS crosstalk. Table 2 summarizes major therapeutic categories under investigation or in clinical use.

Table 5. Therapeutic strategies targeting neuroinflammatory pathways in Alzheimer's disease.

Category	Representative Agent(s)	Mechanism	Status
Anti-amyloid monoclonal antibodies	Lecanemab, Donanemab	Clear soluble protofibrils/plaques; engage Fc receptor-mediated microglial phagocytosis	FDA-approved (2023, 2024); modest slowing of decline; ARIA risk, especially in APOE ε4 carriers
TREM2-targeting antibodies	AL002 and related agonists	Agonize TREM2-DAP12 signaling to enhance microglial phagocytic and metabolic function.	Phase II trials; preclinical results on efficacy have been mixed across models
IL-1 pathway inhibitors	Canakinumab (anti-IL-1β)	Neutralizes IL-1β to reduce downstream inflammatory signaling	Phase II investigation in AD; established in systemic inflammatory disease
TNF-α inhibitors	Pegipanermin (XPro1595)	Selectively inhibits soluble TNF-α without affecting transmembrane TNF	Early-phase clinical evaluation
NLRP3 inflammasome inhibitors	MCC950 and related small molecules; OLT1177	Block NLRP3-ASC assembly, reducing IL-1β/IL-18 release and tau pathology	Preclinical/early clinical; strong mechanistic rationale from animal models
NSAIDs / COX inhibitors	Various (historical trials)	Broad suppression of prostaglandin-mediated inflammation	Epidemiological association with reduced risk, but randomized trials in symptomatic AD largely negative
Microbiome-targeted interventions	Probiotics, prebiotics, dietary SCFA supplementation	Restore eubiosis, reduce LPS-driven microglial activation	Preliminary clinical evidence; adjunctive potential
Regulatory T cell-based approaches	Low-dose IL-2, Treg expansion strategies	Enhance Treg-mediated suppression of neurotoxic glial reactivity	Preclinical / early-phase exploration

8.1 Anti-Amyloid Immunotherapy and Its Inflammatory Dimension

The approval of lecanemab (2023) and donanemab (2024) marked a watershed in AD therapeutics, with both agents producing statistically significant, if modest, slowing of cognitive and functional decline in early symptomatic disease in the pivotal CLARITY-AD and TRAILBLAZER-ALZ 2 trials, respectively. Mechanistically, these antibodies rely substantially on Fc receptor-mediated microglial phagocytosis to clear Aβ, illustrating that even amyloid-centric therapies are fundamentally intertwined with innate immune function. Their principal safety concern, amyloid-related imaging abnormalities (ARIA), manifesting as vasogenic edema (ARIA-E) or microhemorrhage (ARIA-H), occurs more frequently in APOE ε4 carriers and is thought to reflect an inflammatory and vascular response to rapid amyloid clearance from cerebral vessel walls, further underscoring the inseparability of amyloid- and inflammation-directed biology in modern AD therapeutics. Table 6 summarizes quantitative efficacy and safety outcomes from the pivotal phase 3 trials of these agents.

Table 6. Quantitative efficacy and safety outcomes from the pivotal phase 3 trials of lecanemab and donanemab. CDR-SB = Clinical Dementia Rating-Sum of Boxes; iADRS = Integrated Alzheimer's Disease Rating Scale; ARIA-E/H = amyloid-related imaging abnormalities, edema/effusion or hemorrhage.

Metric	Lecanemab (CLARITY-AD, N=1,795)	Donanemab (TRAILBLAZER-ALZ 2, N=1,736)
Primary endpoint change vs. placebo	27% slowing of decline on CDR-SB (Δ = -0.45; p=0.00005)	~35% slowing of decline on iADRS in low/medium tau population

Dosing regimen	10 mg/kg IV every 2 weeks	700 mg IV first 3 doses, then 1400 mg every 4 weeks
ARIA-E incidence (drug vs. placebo)	12.6% vs. 1.7%	24.4% vs. 1.9%
ARIA-H incidence (drug vs. placebo)	17.3% vs. 9.0%	31.3% vs. 13.0%
Total ARIA (any type)	21.3% (drug) vs. 9.3% (placebo)	Higher than lecanemab; majority asymptomatic
Symptomatic ARIA-E	~2.8% of treated patients	5.8% of treated patients
Infusion-related reactions	26.4% (drug) vs. 7.4% (placebo)	Lower than lecanemab; varies by report
FDA approval date	6 July 2023 (traditional approval)	2 July 2024

8.2 Anti-Inflammatory Drug Trials: Lessons from NSAIDs

Epidemiological studies in the 1990s observed reduced AD incidence among long-term users of non-steroidal anti-inflammatory drugs (NSAIDs), generating substantial early enthusiasm for broad anti-inflammatory approaches. However, subsequent randomized controlled trials of NSAIDs in patients with established AD largely failed to demonstrate benefit, and in some cases suggested harm. This disconnect is now understood to likely reflect a critical window-of-opportunity problem: broad COX inhibition may be protective when administered prophylactically, before substantial neurodegeneration, but insufficiently targeted, or simply too late, once irreversible synaptic and neuronal loss has occurred. This lesson has substantially informed the shift toward more mechanistically precise targets, such as NLRP3 and TREM2, and toward biomarker-guided patient selection and earlier intervention in current trial design.

9. The Emerging Neuroinflammation-Targeted Drug Pipeline

The overall AD drug development pipeline has diversified substantially beyond amyloid clearance. As of the 2026 pipeline review, 158 agents were being evaluated across 192 active clinical trials, with nearly three-quarters classified as disease-modifying candidates; inflammation-targeted and tau-directed programs now constitute a growing share of this landscape alongside metabolic and neuroprotective approaches such as GLP-1 receptor agonists. Table 7 lists representative neuroinflammation-directed candidates currently in active clinical development, illustrating the shift toward centrally penetrant, mechanistically precise immunomodulators.

Table 7. Representative neuroinflammation-targeted agents in active Alzheimer's disease clinical development, illustrating the diversification of the pipeline beyond amyloid-clearing antibodies.

Agent	Sponsor	Mechanism	Phase (as of 2026)
ACI-19764	AC Immune	Oral, brain-penetrant NLRP3 inflammasome inhibitor	Phase 1 (healthy volunteers; initiated Feb 2026)
VTX3232	Ventyx Biosciences	CNS-penetrant NLRP3 inhibitor	Phase 2 (neurodegenerative/inflammatory indications)
Selnoflast	Roche	NLRP3 inflammasome inhibitor	Phase 2, multiple indications
NT-0796	NodThera	Brain-penetrant NLRP3 inhibitor	Phase 1b/2a completed; Phase 2 recruiting (obesity, neurology programs)
AL002	Alector / AbbVie	TREM2 agonist antibody	Phase 2
Pegipanermin (XPro1595)	INmune Bio	Selective soluble TNF-α inhibitor	Early-phase clinical evaluation
BIIB080	Biogen / Ionis	Antisense oligonucleotide targeting MAPT mRNA (tau-lowering, indirectly anti-inflammatory)	Phase 2
Semaglutide	Novo Nordisk	GLP-1 receptor agonist; anti-inflammatory and metabolic effects	Phase 3 (EVOKE/EVOKE+ trials)
Emtricitabine ± tenofovir alafenamide	Academic / NIH-sponsored	Reverse transcriptase inhibition; suppresses LINE-1-driven NLRP3 activation	Phase 1/2

10. Challenges and Future Directions

- Disentangling cause from consequence: distinguishing neuroinflammation as a primary driver versus a secondary response to neurodegeneration remains difficult in cross-sectional human studies, and requires longitudinal, biomarker-anchored cohorts spanning the preclinical-to-symptomatic continuum.
- Context-dependent glial function: microglia and astrocytes exhibit both protective (clearance, trophic support) and detrimental (excessive pruning, cytotoxic secretion) roles depending on disease stage, making blunt anti-inflammatory strategies risky; therapies must be temporally and mechanistically precise.
- Heterogeneity of patient populations: genetic background (e.g., TREM2 or APOE genotype), comorbidities, and gut microbiome composition likely influence individual neuroinflammatory trajectories, arguing for precision-medicine approaches to trial design and treatment selection.
- Translational gap between rodent models and human disease: many transgenic AD mouse models overexpress mutant APP/PS1 and do not fully recapitulate the chronic, age-dependent immune dysregulation seen in human AD, limiting predictive validity of preclinical inflammation-targeted interventions.
- Need for combination therapy: given the interlocking nature of amyloid, tau, and inflammatory pathology, sequential or combined regimens pairing anti-amyloid clearance with glial-modulating or inflammasome-targeted agents represent a rational, though logistically complex, path forward.
- Biomarker standardization: harmonizing assay platforms, cutoffs, and reference ranges for fluid biomarkers such as GFAP and sTREM2 across cohorts and laboratories remains necessary for their reliable use as trial endpoints.

11. CONCLUSION

Neuroinflammation has evolved from a peripheral observation in Alzheimer's disease neuropathology to a central, mechanistically integrated component of disease biology, standing alongside amyloid and tau pathology as a driver of neurodegeneration. Microglia and astrocytes, acting through receptor systems such as TREM2 and the complement cascade, and converging on the NLRP3 inflammasome and downstream cytokine release, establish a self-perpetuating cycle that links protein misfolding to synaptic loss and neuronal death. Human genetics, fluid and imaging biomarkers, and the partial success and instructive failures of both amyloid-directed and broadly anti-inflammatory therapeutics collectively support a model in which precisely targeted, stage-appropriate immunomodulation will be essential to achieving durable disease modification. Continued integration of genomic, cellular, and clinical data, alongside more faithful preclinical models and better-stratified clinical trials, will be critical to translating the growing understanding of the neuroinflammation-neurodegeneration axis into effective therapies for this devastating disease.

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