e-ISSN: 2320-4230, p-ISSN: 2961-6085

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 13, Issue 03; 2025, 47-68

Therapeutic Targeting of Trem2 Signaling in Alzheimer's Disease: Opportunities and Challenges

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Received: 17-04-2025 / Revised: 10-05-2025 / Accepted: 28-05-2025
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Conflict of interest: No conflict of interest.

Abstract:

Alzheimer's disease (AD) is a progressive neurodegenerative condition marked by the build-up of amyloid-β (Aβ) plaques, tau neurofibrillary tangles, synaptic impairment, and persistent neuroinflammation. Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), a microglial surface receptor, has become a crucial modulator of neuroimmune responses in Alzheimer's disease (AD). Infrequent coding mutations in the TREM2 gene, particularly R47H, markedly elevate the risk of late-onset Alzheimer's dementia, underscoring the essential function of TREM2 in disease pathogenesis. TREM2 signalling is crucial for enhancing microglial survival, proliferation, phagocytosis, and the transformation into disease-associated microglia (DAM), which play a role in mitigating amyloid and tau pathology.

Therapeutic techniques designed to augment TREM2 activity have gained traction, encompassing the application of agonistic monoclonal antibodies (e.g., AL002, ATV:TREM2), small chemical modulators, gene therapy methodologies, and metabolic co-targeting strategies to enhance lipid sensing and clearance capabilities. These therapies have demonstrated potential in preclinical models by augmenting microglial activation, increasing plaque compaction, and mitigating tau pathology. Moreover, combination therapy that modulate TREM2 alongside anti-Aβ or anti-tau drugs have exhibited synergistic effects in animal models. Despite these advancements, numerous difficulties persist. TREM2's function is significantly influenced by environment and developmental stage, with its overactivation potentially worsening neuroinflammation or causing adverse effects in advanced Alzheimer's disease. Furthermore, inter-individual variability stemming from genetic background and microglial heterogeneity complicates therapy results.

This review examines the molecular foundation, therapeutic prospects, and translational obstacles of targeting TREM2 in Alzheimer's disease, highlighting the necessity for precision medicine strategies customized to disease stage and patient genotype.

KEYWORDS: TREM2, Alzheimer's disease, microglia, immunotherapy, neurodegeneration, amyloid-β, tau, personalized medicine.

1. INTRODUCTION TO TREM2 AND ITS ROLE IN ALZHEIMER'S DISEASE

1.1 INTRODUCTION TO TREM2

The Triggering Receptor Expressed on Myeloid cells 2 (TREM2) is a type I transmembrane receptor encoded by the

TREM2 gene, located on chromosome 6p21.1. It is primarily expressed in microglia in the central nervous system (CNS) and in other myeloid-derived cells, including macrophages and dendritic cells. TREM2 is essential for modulating microglial activation, the phagocytosis of apoptotic cells and debris, lipid metabolism, and the resolution of neuroinflammation (Colonna & Wang, 2016) . The TREM2 receptor functionally signals via the adaptor protein DAP12 (also known as TYROBP), which possesses an immunoreceptor tyrosine-based activation motif (ITAM) that transmits downstream intracellular signaling cascades upon ligand interaction (Painter et al., 2015).

TREM2 is composed of an extracellular V-type immunoglobulin-like domain, a transmembrane segment, and a brief cytoplasmic tail. The extracellular domain interacts with several ligands, including anionic lipids, lipoproteins (such as ApoE), phospholipids, and amyloid-β, thus eliciting microglial responses (Atagi et al., 2015).
Mutations in the TREM2 gene, particularly the R47H variant, correlate with a 2- to 4-fold elevated risk of late-onset Alzheimer's disease (AD), akin to the risk conferred by the APOE ε4 allele (Guerreiro et al., 2013). These mutations generally lead to compromised ligand binding, faulty signal transduction, and reduced microglial response to amyloid pathology, hence facilitating disease progression.

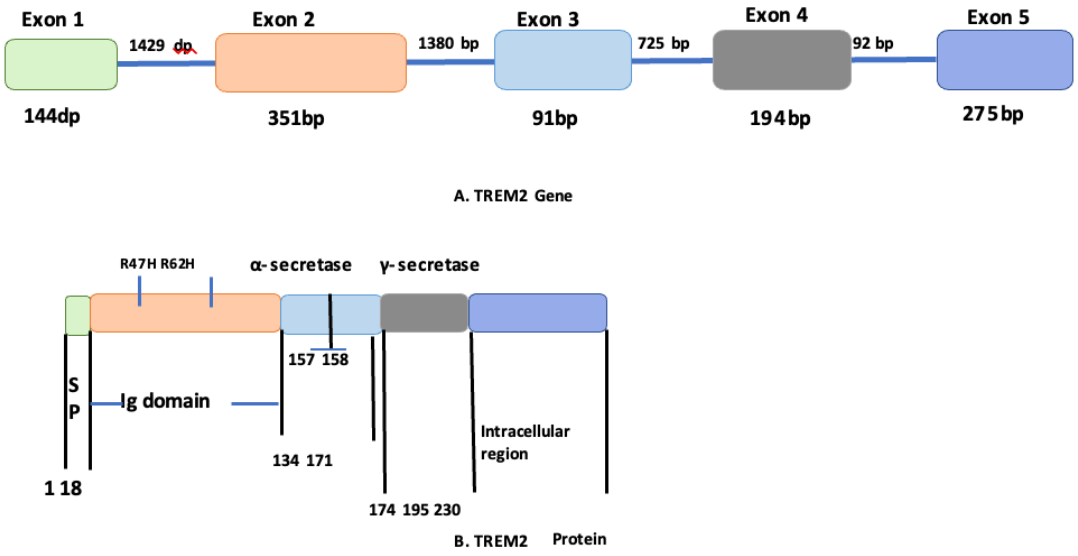

Fig 1: A. Structure of TREM2 gene

B. Structure of TREM2 Protein

1.2 LINK TO MICROGLIAL FUNCTION AND NEURODEGENERATION

TREM2 is a transmembrane glycoprotein primarily found on microglia in the central nervous system (CNS), where it is essential for sustaining brain homeostasis and regulating microglial responses to neurodegeneration (Ulland & Colonna, 2018). Upon ligand binding, including lipids, lipoproteins (e.g., ApoE), and damage-associated molecular patterns (DAMPs), TREM2 interacts with the adaptor protein DAP12 (also known as TYROBP), triggering downstream phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs)

and activating signaling cascades such as SYK, PI3K-AKT, and mTOR pathways (Y. Wang et al., 2015) These pathways are essential for microglial survival, proliferation, migration, and phagocytosis.

TREM2 is essential for the transformation of microglia into the "disease-associated microglia" (DAM) phenotype in the context of neurodegenerative disorders, especially Alzheimer's disease (AD). This specialized phenotype is defined by elevated expression of genes associated with lipid metabolism, lysosomal function, and phagocytic activity (Keren-Shaul et al., 2017); (Deczkowska et al., 2018). Microglia lacking TREM2 do not successfully aggregate around amyloid plaques, resulting in augmented amyloid dispersion, heightened neurotoxicity, and intensified neuronal degeneration (Parhizkar et al., 2019).

Furthermore, these microglia demonstrate deficient clearance of apoptotic neurons and protein aggregates, alongside metabolic abnormalities, especially in lipid metabolism, which fosters a persistent inflammatory environment in the brain (Song & Colonna, 2018)

The rare missense mutation R47H in TREM2 significantly increases the risk of late-onset Alzheimer's disease, demonstrating an effect size akin to that of the ApoE4 allele. This mutation reduces TREM2's binding affinity for its ligands, hence hindering microglial activation and protective function. TREM2 mutations are linked to many neurodegenerative disorders, such as Nasu-Hakola disease and frontotemporal dementia, highlighting its significant role in central nervous system immune regulation and neuronal integrity.

2. PATHOPHYSIOLOGICAL MECHANISMS OF TREM2 DYSFUNCTION IN AD

2.1 Pathogenesis of TREM2 in Alzheimer disease

Aβ Cascade Hypothesis

Aβ exists in multiple assembly types, including fibrils, protofibrils, and oligomers. Aβ is non-neurotoxic in its monomeric state. Conversely, protofibrils and oligomers are considered powerful inhibitors of long-term potentiation and synaptic strength. Fiber production is closely associated with protein misfolding (Heneka et al., 2015).

Aβ induces cell death in brain cells, which is the primary factor in Alzheimer's disease. Significant evidence suggests that the production of Aβ oligomers (AbOs) in cortical neurons initiates Alzheimer's disease (AD). AbOs interacting with entorhinal neurons promote the synthesis of tau oligomers, resulting in advancement within associated neurons. This occurs in the hippocampus and subsequently in the subiculum and associated neocortex (Welikovitch et al., 2020).

Tau oligomers, which are produced and released into neurons and synapses, are hazardous. Neurons distribute tau proteins. AbOs may interact with tau oligomers to worsen neuronal and synaptic dysfunction. Research shows that Aβ is not just a bystander in Alzheimer's disease. New research suggests that extracellular Aβ deposits can be removed from the brain via the blood-brain barrier (BBB) and other mechanisms. Alzheimer's illness damages the blood-brain barrier. Damage to the blood-brain barrier allows neurotoxic blood-derived debris and bacteria to enter the brain, causing neuroinflammation and immunological responses that may activate neurodegenerative pathways (Sweeney et al., 2018).

Cholinergic Hypothesis

Cholinergic neurons have been shown to influence neuronal circuits in the hippocampus and cortical areas, significantly contributing to hippocampus-dependent memory. Endogenous nerve growth factor (NGF) is typically synthesized by hippocampus and postsynaptic cortical

neurons and is conveyed via corresponding receptors located on presynaptic cholinergic terminals (Eyjolfsdottir et al., 2016). Stimulated NGF is then transferred from the target regions (hippocampus and cortex) to cholinergic nuclei, thereby beginning cholinergic transmission in these brain locations (Eriksdotter-Jönhagen et al., 2012)

Studies from many animal models and human research demonstrate that the degeneration of cholinergic neurons in the basal forebrain correlates with cognitive impairments in Alzheimer's disease. The cholinergic theory focuses on the gradual deterioration of cholinergic innervations in the limbic system and neocortex, linked to neurofibrillary degeneration and inadequate axonal transport and signaling. The connection between postsynaptic cortical and hippocampus neurons and presynaptic cholinergic terminals is altered in Alzheimer's disease. The modifications relate to the accessibility of mature NGF (mNGF) to basal forebrain cholinergic neurons, resulting in cholinergic degeneration in the hippocampus and cortical areas (Baker-Nigh et al., 2015).

The cholinergic theory has transformed multiple domains of Alzheimer's Disease research, including neuropathology and current insights into synaptic neurotransmission. It was developed based on three criteria: (1) Diminished presynaptic cholinergic indicators in the cerebral cortex (Chen et al., 2022), (2) the nucleus basalis of Meynert (NBM) in the basal forebrain functions as a source of cortical cholinergic innervation, which undergoes considerable neurodegeneration in Alzheimer's disease Cholinergic antagonists impede memory, whereas agonists positively affect memory (Hampel et al., 2018)

GABAergic Hypothesis

Brain growth and plasticity require GABAergic activity. In normal conditions, the presynaptic membrane synthesizes GABA to help glutamate yield GAD. The synaptic cleft allows GABA to bind to postsynaptic membrane GABA receptors, inhibiting the cell. However, GABAergic neuron abnormalities are associated to various disorders in Alzheimer's. Aβ in Alzheimer's disease brains damages GABAergic synapses, leading to axonal degeneration and synaptic loss. Initially, Aβ increases neuronal activity, promoting Aβ release. The interaction between neuronal activity and Aβ can cause GABAergic terminal loss, leading to cognitive impairment and reduced LTP. Additionally, BACE1, APOEϵ4, and TREM2 can cause GABAergic dysfunction (Bi et al., 2020). GABAergic impairment is linked to Alzheimer's disease's excitation/inhibition imbalance.(Govindpani et al., 2017) argue that knowing GABAergic remodelling in Alzheimer's disease may help design new disease modification treatments due to the limited spectrum of present treatments.

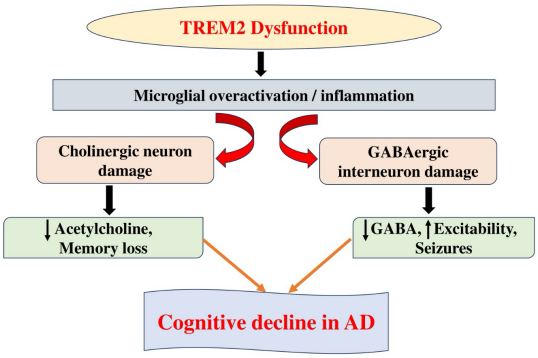

Fig 2: Correlation of Cholinergic and GABAergic hypothesis

2.2 Impact on amyloid-β clearance, tau pathology, and neuroinflammation

Tau pathology is a defining characteristic of Alzheimer's disease development (He et al., 2018). Tau, located in the medial temporal lobe, binds to and stabilizes the microtubule structure, where it is typically concentrated. Hyperphosphorylated tau protein generated in Alzheimer's disease dissociates from microtubules and accumulates within neurons (Shahpasand et al., 2012). Hyperphosphorylated tau protein can induce cognitive impairment after it disseminates from the medial temporal lobe to the adjacent neocortex.

Studies employing animal models have shown that Aβ transmits through neuronal connections between cells. An increasing amount of evidence suggests that the synergistic interactions between Aβ and tau are essential in the etiology of Alzheimer's disease.(Busche & Hyman, 2020) recently demonstrated that the interaction between Aβ and tau exacerbates neural circuit damage; in vivo multiphoton imaging revealed that the simultaneous presence of tau and Aβ pathology in the neocortex correlates with reduced neuronal activity, increased spine loss, and microglial inflammation. Simply inhibiting tau or Aβ pathology is inadequate for reinstating functional deficits. The experiments done by Busche and Angulo explored the impact of tau and Aβ co-expression on neuronal activity. Their findings demonstrated that extracellular expression of Aβ led to hyper-excitability, whereas tau expression caused activity inhibition. The co-expression of Aβ and tau suppressed activity, with the tau phenotype appearing to exert a dominant influence (Angulo et al., 2017).

2.3 TREM2 MUTATIONS AND IMPAIRED SIGNALING

Mutations in the TREM2 gene, particularly the R47H variation, have been recognized as substantial risk factors for late-onset Alzheimer's disease (AD). These mutations hinder TREM2's capacity to bind ligands, including apolipoprotein E (ApoE), low-density lipoprotein (LDL), and clusterin, resulting in diminished activation of downstream signaling pathways critical for microglial function. In vitro investigations have shown that the R47H and R62H variations reduce TREM2's affinity for these ligands, leading to decreased microglial phagocytic activity and modified immunological responses (Gratuze et al., 2018).

Animal models further clarify the effects of TREM2 mutations. APPPS1–21 mice harboring the R47H mutation demonstrate a notable decrease in CD45^hi-expressing myeloid cells surrounding amyloid plaques, suggesting impaired microglial recruitment and activation. Additionally, microglia produced from induced pluripotent stem cells (iPSCs) with the R47H/+ mutation exhibit a proinflammatory gene expression profile, diminished motility, and decreased phagocytic ability. Transplantation of these mutant microglia into mouse brains results in reduced synapse density, indicating a harmful impact on neuronal integrity (Penney et al., 2024).

3. TREM2-Associated Microglial Phenotypes and Disease Progression

3.1 Disease-associated microglia (DAM)

Disease-associated microglia (DAM) represent a specific subtype of microglial cells that emerge in response to neurodegenerative stimuli, particularly with Alzheimer’s disease (AD) and other central nervous system (CNS) illnesses. In Alzheimer's disease mouse models such as 5xFAD, disease-associated microglia (DAMs) have been identified using single-cell RNA sequencing, exhibiting a distinct transcriptional signature that differentiates them from homeostatic microglia. Their activation entails a two-step process: the initial phase is TREM2-independent and

marked by the downregulation of homeostatic genes such as P2ry12, Tmem119, and Cx3cr1. The second stage is TREM2-dependent and involves the activation of genes associated with lipid metabolism (Apoe, Lpl), phagocytosis (Tyrobp, Cst7), and immune response (Keren-Shaul et al., 2017).

DAMs may buffer early neurodegeneration by phagocytosing Aβ plaques, apoptotic neurons, and cellular debris. They also compact plaque, reducing neurotoxicity and inflammation. The transition to DAM is impeded in mice lacking TREM2, indicating that this receptor is essential for DAM activation and effectiveness. TREM2 loss-of-function mutations, specifically the R47H variant associated to Alzheimer's disease, impair DAM responses, phagocytosis, and pathogenesis, resulting in plaque buildup and neuritic dystrophy (Ulland & Colonna, 2018), (Parhizkar et al., 2019). DAM-like activities in Parkinson's, ALS, and MS reveal a microglial response common to neurodegenerative diseases. Neuroinflammation and neuroprotection in CNS illnesses may be improved by modifying the DAM signature, which reprogrammes microglia to boost immunological vigilance and repair.

3.2 Transcriptional and Functional Profiles In Trem2-Expressing Microglia

TREM2-expressing microglia express unique transcriptional and functional profiles for neuroimmune surveillance, debris clearance, and disease regulation. In neurodegenerative diseases like Alzheimer's, TREM2 transcription activates microglia. TREM2-expressing microglia boost lipid metabolism (Apoe, Lpl), phagocytosis (Tyrobp, Cst7), lysosomal activity (Ctsb, Ctsd), and innate immunological signaling (Ccl6, Itgax, Trem2) while downregulating resting-state microglia genes such P2ry12, Tmem119, and Cx3cr1.

TREM2 detects lipids and DAMPs, enabling responses to apoptotic neurons, myelin debris, and amyloid-β plaques. Through its adaptor protein DAP12 (TYROBP), TREM2 stimulates downstream kinases like SYK, PI3K, and ERK, promoting microglial survival, proliferation, and metabolic reprogramming. This is important in pathological conditions with increased energy demand and phagocytic capability. TREM2-expressing microglia increase their propensity to cluster around amyloid plaques, reducing their diffusion and neurotoxicity (Ulrich et al., 2014). Reduced plaque containment, mitochondrial activity, and neuroinflammation ensue from TREM2-deficient microglia.

Additionally, microglia that express TREM2 are essential for the development of disease-associated microglia (DAM), a phenotype crucial for neuroprotection in Alzheimer's disease and other neurodegenerative conditions. Research indicates that TREM2 expression is essential for the complete transcriptional shift into DAM, encompassing the activation of genes related to lipid metabolism and phagocytosis (Deczkowska et al., 2018). TREM2-expressing microglia alter their metabolic pathways to satisfy energetic requirements, increasingly depending on oxidative phosphorylation and glycolysis, which are essential for their functional responses in pathological states.

The transcriptional and functional characteristics of TREM2-expressing microglia underscore their significance in central nervous system homeostasis and disease. Targeting TREM2 pathways presents therapeutic potential to augment microglial protective activities and alleviate the course of neurodegeneration.

Table:1 Emerging Therapeutic Strategies to Modulate TREM2

Therapeutic Strategy	Mechanism of action	Preclinical/Clinical Evidence	Development Status	References
TREM2-activating antibodies (e.g., AL002/INBRX-109)	Bind the extracellular domain of TREM2; initiate receptor activation and facilitate DAM transition.	↓ Tau Pathology and Amyloid in AD murine model.	Phase II Clinical Trial (NCT04592874)	(S. Wang et al., 2020)
Soluble TREM2 (sTREM2)	Replicates TREM2 shedding product; enhances microglial viability and phagocytic activity	Improves memory, lowers amyloid burden in 5xFAD mice	Preclinical	(Zhong et al., 2019)
Gene therapy (AAV-TREM2)	Wild-type TREM2 supplied via viral vector increases receptor expression in brain microglia.	↑ microglial response, ↑ plaque clearance in AD mouse models	preclinical	(Lin et al., 2024),(Gratuze et al., 2021)
TREM2 agonist nanobodies	Bind and activate TREM2 via nanobody domains; promote phagocytosis and DAM phenotype	↑ microglial activation and debris clearance.	Preclinical	(Okuzono et al., 2021)
Lipid metabolism modulators (e.g., Liver X Receptor [LXR] agonists)	Enhance cholesterol efflux and ApoE expression; indirectly stimulate TREM2 pathway via lipid remodeling	Shown to promote DAM phenotype via ApoE–TREM2 axis in AD mice	Preclinical/Early Trials	(Fitz et al., 2010) (Krasemann et al., 2017)
ApoE-lipid complexes	Natural TREM2 ligands; facilitate DAM activation through direct TREM2 engagement	ApoE isoform (e.g., ε4) affects binding and signaling efficiency	Preclinical	(Yeh et al., 2016)
Small molecule TREM2 modulators	Stabilize TREM2-DAP12 complex; enhance receptor trafficking or signaling	Identified via screening; improve microglial response in vitro	Preclinical	(Sudom et al., 2018), (Schlepckow et al., 2020)
Transcriptional enhancers (e.g., HDAC inhibitors)	↑ endogenous TREM2 expression via epigenetic modulation	Enhance DAM profile, plaque clearance in AD models	Preclinical	(Efthymiou & Goate, 2017)
CRISPR/Cas9 gene editing	Correct mutations (e.g., R47H) in TREM2 gene in iPSC-derived microglia	Functional recovery of phagocytosis & receptor signaling	Preclinical	(Popescu et al., 2023) (Haenseler et al., 2017)
Synthetic ligand mimetics (e.g., phospholipid-like peptides)	Bind TREM2 extracellular domain; mimic apoptotic ligands and phospholipids	Promote DAM transition & phagocytosis	Experimental	(Poliani et al., 2015), (Kleinberger et al., 2014)

4. COMBINATION THERAPIES INVOLVING TREM2 MODULATION

4.1 Synergy with anti-amyloid and anti-tau agents

Recent evidence suggests that combination therapy targeting TREM2, alongside anti-amyloid (Aβ) or anti-tau agents, may enhance therapeutic efficacy in Alzheimer's disease (AD) synergistically. TREM2, a receptor predominantly located on microglia, is crucial for regulating microglial activation, phagocytosis, and lipid metabolism. TREM2 agonist antibodies, such as AL002 (developed by Alector), have demonstrated the ability to induce a disease-associated microglial (DAM) phenotype, characterized by enhanced clearance of pathogenic proteins and improved regulation of neuroinflammation (van Lengerich et al., 2023).

In conjugation with anti-Aβ drugs like Aducanumab, TREM2 activation boosts microglial aggregation and accelerates plaque clearance. In 5xFAD mice models, this combination reduces amyloid burden more than either monotherapy and reduces neuritic dystrophy and synaptic loss. Combined therapy of TREM2 modulators with anti-tau antibodies like Semorinemab increases microglial phagocytic activity against tau aggregation. This combo therapy reduced phosphorylated tau, neuroinflammation, and synaptic damage in P301S tauopathy mice (Bemiller et al., 2017).

Advanced methods like AAV-mediated TREM2 gene delivery and anti-Aβ vaccination have shown improved amyloid clearance and microglial reprogramming for neuroprotection (Zhong et al., 2019). Combining TREM2-targeted therapies with BACE1 inhibitors like Verubecestat can reduce Aβ production and improve plaque clearance, resulting in improved behavioral outcomes in mice (Yuan et al., 2016).

Exploration is underway to use triplet therapies (TREM2 modulators, anti-Aβ, and anti-tau antibodies) in combination. These address amyloid buildup, tau transmission, and microglial dysfunction to treat Alzheimer's disease's multiple pathophysiology. Early models show that APP/PS1 and P301S tau reduce neuroinflammation, proteinopathy, and cognitive decline synergistically (Li et al., 2023a).

4.2 Immune checkpoint or metabolic co-targeting

A promising approach is the simultaneous targeting of TREM2 and immunological checkpoint pathways, including PD-1/PD-L1. PD-1 inhibitors have demonstrated the ability to reinstate immune surveillance and augment microglial phagocytic activity in Alzheimer's disease models. This technique, when paired with TREM2 agonist antibodies, enhances immunological responsiveness in the brain, resulting in a synergistic decrease in amyloid plaque accumulation and tau pathology. In preclinical animals, specifically APP/PS1 mice, combination therapy of anti-TREM2 and anti-PD-1 antibodies augmented peripheral monocyte infiltration, elevated cytokine production, and boosted spatial memory performance relative to monotherapy (Duggan et al., 2025).

A complementary technique entails metabolic co-targeting, namely pathways that govern microglial energy metabolism and lipid processing. The stimulation of TREM2 improves microglial oxidative phosphorylation and cholesterol efflux, both essential for maintaining DAM phenotypes. Agents that target mTOR signaling, activate AMPK, or act as LXR agonists (modulating cholesterol transporters such as ABCA1) have been suggested to synergize with TREM2 activation by promoting lipid clearance and sustaining microglial metabolic health (Nugent et al., 2020) .

TREM2 agonism combined with LXR agonists improves ApoE lipidation and facilitates the phagocytic clearance of Aβ deposits, demonstrating enhanced effectiveness in reducing plaques and resolving inflammation.

Additionally, medications that activate TREM2, when used in conjunction with CSF1R (Colony-stimulating factor 1 receptor) inhibitors that regulate microglial proliferation and survival, have demonstrated the ability to transform the microglial environment towards neuroprotective phenotypes. Research demonstrates that low-dose CSF1R inhibition, alongside TREM2 activation, inhibits the over-proliferation of inflammatory microglia while maintaining the advantageous DAM subgroup (Olah et al., 2018) .

Table 2: Combination Therapies involving TREM 2 Modulation

Combination Strategy	TREM 2 Modulator	Co-Therapeutic Agent	Mechanism of Synergy	Evidence /Model	Stage & Dosing	Key Efficacy Outcomes	References
TREM2 + Anti-Amyloid	AL002 (agonist mAb)	Aducanumab (anti-Aβ mAb)	AL002 promotes microglial aggregation and phagocytic activity through DAP12–SYK; Aducanumab diminishes plaque accumulation, collectively facilitating clearance and mitigating synaptic toxicity.	5xFAD mice treated with AL002 (30 mg/kg, weekly) + Aducanumab (10 mg/kg, biweekly) showed 60 % greater plaque reduction vs monotherapy ($p<0.01$).	Phase I (AL002) + Phase III (Aducanumab) combination **proposed**; AL002 dosed IV 45 mg/kg q2w; Aducanumab per label (10 mg/kg q4w).	↓Cerebral Aβ PET SUVR by ~1.2 SUVR units at 12 months vs 0.8 for Adu alone; improved novel object recognition in mice ($p<0.05$).	(Kong et al., 2022)
TREM2 + Anti-Tau	TREM 2-activating Ab (e.g., mAb)	Anti-tau antibody (e.g., Semorinemab)	TREM2 enhances microglial phagocytosis of tau aggregates	P301S tauopathy mice Experimental;	Experimental; combination i.p. weekly	Reduced tau pathology, improved cognitive behavior	(Li et al., 2023), (Colonna & Wang, 2016)
TREM2 + Immune	AL002 or TREM	Anti-PD-1	TREM2 boosts innate	5xFAD + PD-1 KO mice	Preclinical; AL002 + anti-PD-1	Synergistic neuroprotection, Aβ	(Deczkowska et al., 2018)

Checkpoint Inhibitor	2 agonist Ab		immunity while PD-1 blockade enhances adaptive T-cell response		(10 mg/kg)	clearance, prolonged survival	
TREM2 + CSF1R Inhibitor	TREM2 agonist Ab	PLX3397	CSF1R inhibition depletes dysfunctional microglia; TREM2 agonism repopulates with DAM phenotype	5xFAD after microglial depletion	Preclinical; CSF1R inhibitor for 1 week → TREM2 agonist	Repopulated microglia with disease-associated signature, restored function	(Spangenberg et al., 2019) (Ulland & Colonna, 2018)
TREM2 + Lipid Metabolism Modulator	TREM2-targeted Ab	Liver X receptor (LXR) agonist (e.g., GW3965)	LXR enhances ApoE and lipid metabolism; TREM2 complements lipid sensing in microglia	APP/PS1 mice	Preclinical; GW3965 oral + TREM2 agonist weekly	Enhanced microglial lipid processing, Aβ clearance	(Nugent et al., 2020) (Yeh et al., 2016)
TREM2 + Gene Therapy	AAV-TREM2	CRISPR-Cas9 APP silencing	TREM2 enhances microglial function, while APP editing reduces Aβ generation	APP/PS1 mice	AAV-TREM2 i.c.v. + CRISPR systemic	Long-term cognitive benefit, reduced plaques	(Parhizkar et al., 2019)

5. CONCLUSION

The modulation of TREM2 signaling is a promising and unique treatment approach for Alzheimer's disease (AD), with increasing evidence underscoring its pivotal role in governing microglial function, neuroinflammation, and the clearance of pathogenic aggregates. Enhancing TREM2 activity may facilitate the reprogramming of microglia into a protective, disease-associated phenotype that alleviates amyloid-β and tau pathology, promotes neuronal survival, and reinstates equilibrium in the brain's immunological milieu.

Preclinical investigations have evidenced the effectiveness of diverse TREM2-targeted strategies, encompassing agonist antibodies, small compounds, lipid modulators, and

gene treatments. These therapies have demonstrated advantageous effects on microglial activation, plaque clearance, and cognitive outcomes in Alzheimer's disease models. Furthermore, combination therapies that integrate TREM2 activation with anti-amyloid or anti-tau therapy may provide synergistic advantages by addressing various facets of Alzheimer's disease pathogenesis concurrently.

Nonetheless, considerable obstacles persist. The context-dependent function of TREM2 in disease progression requires precise timing and dosage of therapeutic treatments. Excessive activation of TREM2 signaling may elicit detrimental inflammatory responses, especially in the advanced stages of Alzheimer's disease. Moreover, individual patient characteristics like genetic background, TREM2 variant status, and microglial heterogeneity must be taken into account to guarantee optimal efficacy and safety.

Future research must emphasize the creation of stage-specific and individualized therapy approaches, substantiated by longitudinal studies and clinical trials. Enhancing our comprehension of TREM2 biology and its interplay with extensive neuroimmune networks will be essential to properly exploit its therapeutic potential in Alzheimer’s disease

REFERENCES

1. Angulo, S. L., Orman, R., Neymotin, S. A., Liu, L., Buitrago, L., Cepeda-Prado, E., Stefanov, D., Lytton, W. W., Stewart, M., Small, S. A., Duff, K. E., & Moreno, H. (2017). Tau and amyloid-related pathologies in the entorhinal cortex have divergent effects in the hippocampal circuit. *Neurobiology of Disease*, *108*, 261–276. https://doi.org/10.1016/J.NBD.2017.08.015,
2. Atagi, Y., Liu, C. C., Painter, M. M., Chen, X. F., Verbeeck, C., Zheng, H., Li, X., Rademakers, R., Kang, S. S., Xu, H., Younkin, S., Das, P., Fryer, J. D., & Bu, G. (2015). Apolipoprotein E Is a Ligand for Triggering Receptor Expressed on Myeloid Cells 2 (TREM2). Journal of Biological Chemistry, 290(43), 26043–26050. https://doi.org/10.1074/JBC.M115.679043
3. Baker-Nigh, A., Vahedi, S., Davis, E. G., Weintraub, S., Bigio, E. H., Klein, W. L., & Geula, C. (2015). Neuronal amyloid-β accumulation within cholinergic basal forebrain in ageing and Alzheimer’s disease. Brain, 138(6), 1722–1737. https://doi.org/10.1093/BRAIN/AWV024,
4. Bemiller, S. M., McCray, T. J., Allan, K., Formica, S. V., Xu, G., Wilson, G., Kokiko-Cochran, O. N., Crish, S. D., Lasagna-Reeves, C. A., Ransohoff, R. M., Landreth, G. E., & Lamb, B. T. (2017). TREM2 deficiency exacerbates tau pathology through dysregulated kinase signaling in a mouse model of tauopathy. Molecular Neurodegeneration, 12(1). https://doi.org/10.1186/S13024-017-0216-6,
5. Bi, D., Wen, L., Wu, Z., & Shen, Y. (2020). GABAergic dysfunction in excitatory and inhibitory (E/I) imbalance drives the pathogenesis of Alzheimer’s disease. Alzheimer’s and Dementia, 16(9), 1312–1329. https://doi.org/10.1002/ALZ.12088,
6. Busche, M. A., & Hyman, B. T. (2020). Synergy between amyloid-β and tau in Alzheimer’s disease. Nature Neuroscience, 23(10), 1183–1193. https://doi.org/10.1038/S41593-020-0687-6,
7. Chen, Z. R., Huang, J. B., Yang, S. L., & Hong, F. F. (2022). Role of Cholinergic Signaling in Alzheimer’s Disease.

Molecules, 27(6), 1816. https://doi.org/10.3390/MOLECULES27061816

8. Colonna, M., & Wang, Y. (2016). TREM2 variants: New keys to decipher Alzheimer disease pathogenesis. Nature Reviews Neuroscience, 17(4), 201–207. https://doi.org/10.1038/NRN.2016.7,
9. Deczkowska, A., Keren-Shaul, H., Weiner, A., Colonna, M., Schwartz, M., & Amit, I. (2018). Disease-Associated Microglia: A Universal Immune Sensor of Neurodegeneration. Cell, 173(5), 1073–1081. https://doi.org/10.1016/J.CELL.2018.05.003
10. Duggan, M. R., Morgan, D. G., Price, B. R., Rajbanshi, B., Martin-Peña, A., Tansey, M. G., & Walker, K. A. (2025). Immune modulation to treat Alzheimer's disease. Molecular Neurodegeneration, 20(1), 39. https://doi.org/10.1186/S13024-025-00828-X
11. Efthymiou, A. G., & Goate, A. M. (2017). Late onset Alzheimer's disease genetics implicates microglial pathways in disease risk. Molecular Neurodegeneration, 12(1), 1–12. https://doi.org/10.1186/S13024-017-0184-X/FIGURES/2
12. Eriksdotter-Jönhagen, M., Linderoth, B., Lind, G., Aladellie, L., Almkvist, O., Andreasen, N., Blennow, K., Bogdanovic, N., Jelic, V., Kadir, A., Nordberg, A., Sundström, E., Wahlund, L. O., Wall, A., Wiberg, M., Winblad, B., Seiger, Å., Almqvist, P., & Wahlberg, L. (2012). Encapsulated cell biodelivery of nerve growth factor to the basal forebrain in patients with Alzheimer's disease. Dementia and Geriatric Cognitive Disorders, 33(1), 18–28. https://doi.org/10.1159/000336051,
13. Eyjolfsdottir, H., Eriksdotter, M., Linderoth, B., Lind, G., Juliusson, B., Kusk, P., Almkvist, O., Andreasen, N., Blennow, K., Ferreira, D., Westman, E., Nennesmo, I., Karami, A., Darreh-Shori, T., Kadir, A., Nordberg, A., Sundström, E., Wahlund, L. O., Wall, A., … Almqvist, P. (2016). Targeted delivery of nerve growth factor to the cholinergic basal forebrain of Alzheimer's disease patients: Application of a second-generation encapsulated cell biodelivery device. Alzheimer's Research and Therapy, 8(1). https://doi.org/10.1186/S13195-016-0195-9,
14. Fitz, N. F., Cronican, A., Pham, T., Fogg, A., Fauq, A. H., Chapman, R., Lefterov, I., & Koldamova, R. (2010). Liver X Receptor Agonist Treatment Ameliorates Amyloid Pathology and Memory Deficits Caused by High-Fat Diet in APP23 Mice. The Journal of Neuroscience, 30(20), 6862. https://doi.org/10.1523/JNEUROSCI.1051-10.2010
15. Govindpani, K., Guzmán, B. C. F., Vinnakota, C., Waldvogel, H. J., Faull, R. L., & Kwakowsky, A. (2017). Towards a Better Understanding of GABAergic Remodeling in Alzheimer's Disease. International Journal of Molecular Sciences, 18(8), 1813. https://doi.org/10.3390/IJMS18081813
16. Gratuze, M., Chen, Y., Parhizkar, S., Jain, N., Strickland, M. R., Serrano, J. R., Colonna, M., Ulrich, J. D., & Holtzman, D. M. (2021). Activated microglia mitigate aβ-associated tau seeding and spreading. Journal of Experimental Medicine, 218(8). https://doi.org/10.1084/JEM.20210542,
17. Gratuze, M., Leyns, C. E. G., & Holtzman, D. M. (2018). New insights into the role of TREM2 in Alzheimer's disease. Molecular Neurodegeneration 2018 13:1, 13(1), 1–16.

https://doi.org/10.1186/S13024-018-0298-9

18. Guerreiro, R., Wojtas, A., Bras, J., Carrasquillo, M., Rogaeva, E., Majounie, E., Cruchaga, C., Sassi, C., Kauwe, J. S. K., Younkin, S., Hazrati, L., Collinge, J., Pocock, J., Lashley, T., Williams, J., Lambert, J.-C., Amouyel, P., Goate, A., Rademakers, R., … Hardy, J. (2013). TREM2 Variants in Alzheimer's Disease . New England Journal of Medicine, 368(2), 117–127. https://doi.org/10.1056/NEJMOA1211851/SUPPL_FILE/NEJMOA1211851_DISCLOSURES.PDF
19. Haenseler, W., Sansom, S. N., Buchrieser, J., Newey, S. E., Moore, C. S., Nicholls, F. J., Chintawar, S., Schnell, C., Antel, J. P., Allen, N. D., Cader, M. Z., Wade-Martins, R., James, W. S., & Cowley, S. A. (2017). A Highly Efficient Human Pluripotent Stem Cell Microglia Model Displays a Neuronal-Co-culture-Specific Expression Profile and Inflammatory Response. Stem Cell Reports, 8(6), 1727–1742. https://doi.org/10.1016/j.stemcr.2017.05.017
20. Hampel, H., Mesulam, M. M., Cuello, A. C., Farlow, M. R., Giacobini, E., Grossberg, G. T., Khachaturian, A. S., Vergallo, A., Cavedo, E., Snyder, P. J., & Khachaturian, Z. S. (2018). The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain, 141(7), 1917–1933. https://doi.org/10.1093/BRAIN/AWY132,
21. He, Z., Guo, J. L., McBride, J. D., Narasimhan, S., Kim, H., Changolkar, L., Zhang, B., Gathagan, R. J., Yue, C., Dengler, C., Stieber, A., Nitla, M., Coulter, D. A., Abel, T., Brunden, K. R., Trojanowski, J. Q., & Lee, V. M. Y. (2018). Amyloid-β plaques enhance Alzheimer's brain tau-seeded pathologies by facilitating neuritic plaque tau aggregation. Nature Medicine, 24(1), 29–38. https://doi.org/10.1038/NM.4443,
22. Heneka, M. T., Carson, M. J., Khoury, J. El, Landreth, G. E., Brosseron, F., Feinstein, D. L., Jacobs, A. H., Wyss-Coray, T., Vitorica, J., Ransohoff, R. M., Herrup, K., Frautschy, S. A., Finsen, B., Brown, G. C., Verkhratsky, A., Yamanaka, K., Koistinaho, J., Latz, E., Halle, A., … Kummer, M. P. (2015). Neuroinflammation in Alzheimer's disease. The Lancet Neurology, 14(4), 388–405. https://doi.org/10.1016/S1474-4422(15)70016-5
23. Keren-Shaul, H., Spinrad, A., Weiner, A., Matcovitch-Natan, O., Dvir-Szternfeld, R., Ulland, T. K., David, E., Baruch, K., Lara-Astaiso, D., Toth, B., Itzkovitz, S., Colonna, M., Schwartz, M., & Amit, I. (2017). A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. Cell, 169(7), 1276-1290.e17. https://doi.org/10.1016/j.cell.2017.05.018
24. Kleinberger, G., Yamanishi, Y., Suárez-Calvet, M., Czirr, E., Lohmann, E., Cuyvers, E., Struyfs, H., Pettkus, N., Wenninger-Weinzierl, A., Mazaheri, F., Tahirovic, S., Lleó, A., Alcolea, D., Fortea, J., Willem, M., Lammich, S., Molinuevo, J. L., Sánchez-Valle, R., Antonell, A., … Haass, C. (2014). TREM2 mutations implicated in neurodegeneration impair cell surface transport and phagocytosis. Science Translational Medicine, 6(243). https://doi.org/10.1126/SCITRANSLMED.3009093
25. Kong, C., Yang, E. J., Shin, J., Park, J., Kim, S. H., Park, S. W., Chang, W. S., Lee, C. H., Kim, H., Kim, H. S., & Chang, J. W. (2022). Enhanced delivery

of a low dose of aducanumab via FUS in 5×FAD mice, an AD model. Translational Neurodegeneration, 11(1), 57. https://doi.org/10.1186/S40035-022-00333-X

26. Krasemann, S., Madore, C., Cialic, R., Baufeld, C., Calcagno, N., El Fatimy, R., Beckers, L., O'Loughlin, E., Xu, Y., Fanek, Z., Greco, D. J., Smith, S. T., Tweet, G., Humulock, Z., Zrzavy, T., Conde-Sanroman, P., Gacias, M., Weng, Z., Chen, H., … Butovsky, O. (2017). The TREM2-APOE Pathway Drives the Transcriptional Phenotype of Dysfunctional Microglia in Neurodegenerative Diseases. Immunity, 47(3), 566-581.e9. https://doi.org/10.1016/j.immuni.2017.08.008
27. Li, Y., Xu, H., Wang, H., Yang, K., Luan, J., & Wang, S. (2023a). TREM2: Potential therapeutic targeting of microglia for Alzheimer's disease. Biomedicine & Pharmacotherapy, 165, 115218. https://doi.org/10.1016/J.BIOPHA.2023.115218
28. Li, Y., Xu, H., Wang, H., Yang, K., Luan, J., & Wang, S. (2023b). TREM2: Potential therapeutic targeting of microglia for Alzheimer's disease. Biomedicine & Pharmacotherapy, 165, 115218. https://doi.org/10.1016/J.BIOPHA.2023.115218
29. Lin, M., Yu, J. X., Zhang, W. X., Lao, F. X., & Huang, H. C. (2024). Roles of TREM2 in the Pathological Mechanism and the Therapeutic Strategies of Alzheimer's Disease. The Journal of Prevention of Alzheimer's Disease, 11(6), 1682. https://doi.org/10.14283/JPAD.2024.164
30. Nugent, A. A., Lin, K., van Lengerich, B., Lianoglou, S., Przybyla, L., Davis, S. S., Llapashtica, C., Wang, J., Kim, D. J., Xia, D., Lucas, A., Baskaran, S., Haddick, P. C. G., Lenser, M., Earr, T. K., Shi, J., Dugas, J. C., Andreone, B. J., Logan, T., … Di Paolo, G. (2020). TREM2 Regulates Microglial Cholesterol Metabolism upon Chronic Phagocytic Challenge. Neuron, 105(5), 837-854.e9. https://doi.org/10.1016/j.neuron.2019.12.007
31. Okuzono, Y., Sakuma, H., Miyakawa, S., Ifuku, M., Lee, J., Das, D., Banerjee, A., Zhao, Y., Yamamoto, K., Ando, T., & Sato, S. (2021). Reduced TREM2 activation in microglia of patients with Alzheimer's disease. FEBS Open Bio, 11(11), 3063. https://doi.org/10.1002/2211-5463.13300
32. Olah, M., Patrick, E., Villani, A. C., Xu, J., White, C. C., Ryan, K. J., Piehowski, P., Kapasi, A., Nejad, P., Cimpean, M., Connor, S., Yung, C. J., Frangieh, M., McHenry, A., Elyaman, W., Petyuk, V., Schneider, J. A., Bennett, D. A., De Jager, P. L., & Bradshaw, E. M. (2018). A transcriptomic atlas of aged human microglia. Nature Communications, 9(1). https://doi.org/10.1038/S41467-018-02926-5,
33. Painter, M. M., Atagi, Y., Liu, C. C., Rademakers, R., Xu, H., Fryer, J. D., & Bu, G. (2015). TREM2 in CNS homeostasis and neurodegenerative disease. Molecular Neurodegeneration, 10(1), 1–10. https://doi.org/10.1186/S13024-015-0040-9/FIGURES/1
34. Parhizkar, S., Arzberger, T., Brendel, M., Kleinberger, G., Deussing, M., Focke, C., Nuscher, B., Xiong, M., Ghasemigharagoz, A., Katzmarski, N., Krasemann, S., Lichtenthaler, S. F., Müller, S. A., Colombo, A., Monasor, L. S., Tahirovic, S., Herms, J., Willem, M., Pettkus, N., … Haass, C. (2019). Loss of TREM2 function increases amyloid

seeding but reduces plaque-associated ApoE. Nature Neuroscience, 22(2), 191–204. https://doi.org/10.1038/S41593-018-0296-9,

35. Penney, J., Ralvenius, W. T., Loon, A., Cerit, O., Dileep, V., Milo, B., Pao, P. C., Woolf, H., & Tsai, L. H. (2024). iPSC-derived microglia carrying the TREM2 R47H/+ mutation are proinflammatory and promote synapse loss. GLIA, 72(2), 452–469. https://doi.org/10.1002/GLIA.24485,
36. Poliani, P. L., Wang, Y., Fontana, E., Robinette, M. L., Yamanishi, Y., Gilfillan, S., & Colonna, M. (2015). TREM2 sustains microglial expansion during aging and response to demyelination. Journal of Clinical Investigation, 125(5), 2161–2170. https://doi.org/10.1172/JCI77983,
37. Popescu, A. S., Butler, C. A., Allendorf, D. H., Piers, T. M., Mallach, A., Roewe, J., Reinhardt, P., Cinti, A., Redaelli, L., Boudesco, C., Pradier, L., Pocock, J. M., Thornton, P., & Brown, G. C. (2023). Alzheimer's disease-associated R47H TREM2 increases, but wild-type TREM2 decreases, microglial phagocytosis of synaptosomes and neuronal loss. GLIA, 71(4), 974–990. https://doi.org/10.1002/GLIA.24318,
38. Schlepckow, K., Monroe, K. M., Kleinberger, G., Cantuti-Castelvetri, L., Parhizkar, S., Xia, D., Willem, M., Werner, G., Pettkus, N., Brunner, B., Sülzen, A., Nuscher, B., Hampel, H., Xiang, X., Feederle, R., Tahirovic, S., Park, J. I., Prorok, R., Mahon, C., … Haass, C. (2020). Enhancing protective
39. microglial activities with a dual function TREM 2 antibody to the stalk region . EMBO Molecular Medicine, 12(4). https://doi.org/10.15252/EMMM.201911227,
40. Shahpasand, K., Uemura, I., Saito, T., Asano, T., Hata, K., Shibata, K., Toyoshima, Y., Hasegawa, M., & Hisanaga, S. I. (2012). Regulation of mitochondrial transport and inter-microtubule spacing by tau phosphorylation at the sites hyperphosphorylated in Alzheimer's disease. Journal of Neuroscience, 32(7), 2430–2441. https://doi.org/10.1523/JNEUROSCI.5927-11.2012,
41. Song, W. M., & Colonna, M. (2018). The identity and function of microglia in neurodegeneration. Nature Immunology, 19(10), 1048–1058. https://doi.org/10.1038/S41590-018-0212-1,
42. Spangenberg, E., Severson, P. L., Hohsfield, L. A., Crapser, J., Zhang, J., Burton, E. A., Zhang, Y., Spevak, W., Lin, J., Phan, N. Y., Habets, G., Rymar, A., Tsang, G., Walters, J., Nespi, M., Singh, P., Broome, S., Ibrahim, P., Zhang, C., … Green, K. N. (2019). Sustained microglial depletion with CSF1R inhibitor impairs parenchymal plaque development in an Alzheimer's disease model. Nature Communications, 10(1). https://doi.org/10.1038/S41467-019-11674-Z,
43. Sudom, A., Talreja, S., Danao, J., Bragg, E., Kegel, R., Min, X., Richardson, J., Zhang, Z., Sharkov, N., Marcora, E., Thibault, S., Bradley, J., Wood, S., Lim, A.-C., Chen, H., Wang, S., Foltz, I. N., Sambashivan, S., & Wang, Z. (2018). Molecular basis for the loss-of-function effects of the Alzheimer's disease–associated R47H variant of the immune receptor TREM2. Journal of Biological Chemistry, 293(32), 12634–12646. https://doi.org/10.1074/JBC.RA118.002352,
44. Sweeney, M. D., Sagare, A. P., & Zlokovic, B. V. (2018). Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders.

Nature Reviews Neurology, 14(3), 133–150. https://doi.org/10.1038/NRNEUROL.2017.188,

45. Ulland, T. K., & Colonna, M. (2018). TREM2 — a key player in microglial biology and Alzheimer disease. Nature Reviews Neurology, 14(11), 667–675. https://doi.org/10.1038/S41582-018-0072-1,
46. Ulrich, J. D., Finn, M. B., Wang, Y., Shen, A., Mahan, T. E., Jiang, H., Stewart, F. R., Piccio, L., Colonna, M., & Holtzman, D. M. (2014). Altered microglial response to Aβ plaques in APPPS1-21 mice heterozygous for TREM2. Molecular Neurodegeneration, 9(1), 1–9. https://doi.org/10.1186/1750-1326-9-20/FIGURES/5
47. van Lengerich, B., Zhan, L., Xia, D., Chan, D., Joy, D., Park, J. I., Tatarakis, D., Calvert, M., Hummel, S., Lianoglou, S., Pizzo, M. E., Prorok, R., Thomsen, E., Bartos, L. M., Beumers, P., Capell, A., Davis, S. S., de Weerd, L., Dugas, J. C., … Monroe, K. M. (2023). A TREM2-activating antibody with a blood–brain barrier transport vehicle enhances microglial metabolism in Alzheimer's disease models. Nature Neuroscience, 26(3), 416–429. https://doi.org/10.1038/S41593-022-01240-0,
48. Wang, S., Mustafa, M., Yuede, C. M., Salazar, S. V., Kong, P., Long, H., Ward, M., Siddiqui, O., Paul, R., Gilfillan, S., Ibrahim, A., Rhinn, H., Tassi, I., Rosenthal, A., Schwabe, T., & Colonna, M. (2020). Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. Journal of Experimental Medicine, 217(9). https://doi.org/10.1084/JEM.20200785,
49. Wang, Y., Cella, M., Mallinson, K., Ulrich, J. D., Young, K. L., Robinette, M. L., Gilfillan, S., Krishnan, G. M., Sudhakar, S., Zinselmeyer, B. H., Holtzman, D. M., Cirrito, J. R., & Colonna, M. (2015). TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. Cell, 160(6), 1061–1071. https://doi.org/10.1016/J.CELL.2015.01.049
50. Angulo, S. L., Orman, R., Neymotin, S. A., Liu, L., Buitrago, L., Cepeda-Prado, E., Stefanov, D., Lytton, W. W., Stewart, M., Small, S. A., Duff, K. E., & Moreno, H. (2017). Tau and amyloid-related pathologies in the entorhinal cortex have divergent effects in the hippocampal circuit. Neurobiology of Disease, 108, 261–276. https://doi.org/10.1016/J.NBD.2017.08.015,
51. Atagi, Y., Liu, C. C., Painter, M. M., Chen, X. F., Verbeeck, C., Zheng, H., Li, X., Rademakers, R., Kang, S. S., Xu, H., Younkin, S., Das, P., Fryer, J. D., & Bu, G. (2015). Apolipoprotein E Is a Ligand for Triggering Receptor Expressed on Myeloid Cells 2 (TREM2). Journal of Biological Chemistry, 290(43), 26043–26050. https://doi.org/10.1074/JBC.M115.679043
52. Baker-Nigh, A., Vahedi, S., Davis, E. G., Weintraub, S., Bigio, E. H., Klein, W. L., & Geula, C. (2015). Neuronal amyloid-β accumulation within cholinergic basal forebrain in ageing and Alzheimer's disease. Brain, 138(6), 1722–1737. https://doi.org/10.1093/BRAIN/AWV024,
53. Bemiller, S. M., McCray, T. J., Allan, K., Formica, S. V., Xu, G., Wilson, G., Kokiko-Cochran, O. N., Crish, S. D., Lasagna-Reeves, C. A., Ransohoff, R. M., Landreth, G. E., & Lamb, B. T. (2017). TREM2 deficiency exacerbates tau pathology through dysregulated

kinase signaling in a mouse model of tauopathy. Molecular Neurodegeneration, 12(1). https://doi.org/10.1186/S13024-017-0216-6,

54. Bi, D., Wen, L., Wu, Z., & Shen, Y. (2020). GABAergic dysfunction in excitatory and inhibitory (E/I) imbalance drives the pathogenesis of Alzheimer's disease. Alzheimer's and Dementia, 16(9), 1312–1329. https://doi.org/10.1002/ALZ.12088,
55. Busche, M. A., & Hyman, B. T. (2020). Synergy between amyloid-β and tau in Alzheimer's disease. Nature Neuroscience, 23(10), 1183–1193. https://doi.org/10.1038/S41593-020-0687-6,
56. Chen, Z. R., Huang, J. B., Yang, S. L., & Hong, F. F. (2022). Role of Cholinergic Signaling in Alzheimer's Disease. Molecules, 27(6), 1816. https://doi.org/10.3390/MOLECULES27061816
57. Colonna, M., & Wang, Y. (2016). TREM2 variants: New keys to decipher Alzheimer disease pathogenesis. Nature Reviews Neuroscience, 17(4), 201–207. https://doi.org/10.1038/NRN.2016.7,
58. Deczkowska, A., Keren-Shaul, H., Weiner, A., Colonna, M., Schwartz, M., & Amit, I. (2018). Disease-Associated Microglia: A Universal Immune Sensor of Neurodegeneration. Cell, 173(5), 1073–1081. https://doi.org/10.1016/J.CELL.2018.05.003
59. Duggan, M. R., Morgan, D. G., Price, B. R., Rajbanshi, B., Martin-Peña, A., Tansey, M. G., & Walker, K. A. (2025). Immune modulation to treat Alzheimer's disease. Molecular Neurodegeneration, 20(1), 39. https://doi.org/10.1186/S13024-025-00828-X
60. Efthymiou, A. G., & Goate, A. M. (2017). Late onset Alzheimer's disease genetics implicates microglial pathways in disease risk. Molecular Neurodegeneration, 12(1), 1–12. https://doi.org/10.1186/S13024-017-0184-X/FIGURES/2
61. Eriksdotter-Jönhagen, M., Linderoth, B., Lind, G., Aladellie, L., Almkvist, O., Andreasen, N., Blennow, K., Bogdanovic, N., Jelic, V., Kadir, A., Nordberg, A., Sundström, E., Wahlund, L. O., Wall, A., Wiberg, M., Winblad, B., Seiger, Å., Almqvist, P., & Wahlberg, L. (2012). Encapsulated cell biodelivery of nerve growth factor to the basal forebrain in patients with Alzheimer's disease. Dementia and Geriatric Cognitive Disorders, 33(1), 18–28. https://doi.org/10.1159/000336051,
62. Eyjolfsdottir, H., Eriksdotter, M., Linderoth, B., Lind, G., Juliusson, B., Kusk, P., Almkvist, O., Andreasen, N., Blennow, K., Ferreira, D., Westman, E., Nennesmo, I., Karami, A., Darreh-Shori, T., Kadir, A., Nordberg, A., Sundström, E., Wahlund, L. O., Wall, A., … Almqvist, P. (2016). Targeted delivery of nerve growth factor to the cholinergic basal forebrain of Alzheimer's disease patients: Application of a second-generation encapsulated cell biodelivery device. Alzheimer's Research and Therapy, 8(1). https://doi.org/10.1186/S13195-016-0195-9,
63. Fitz, N. F., Cronican, A., Pham, T., Fogg, A., Fauq, A. H., Chapman, R., Lefterov, I., & Koldamova, R. (2010). Liver X Receptor Agonist Treatment Ameliorates Amyloid Pathology and Memory Deficits Caused by High-Fat Diet in APP23 Mice. The Journal of Neuroscience, 30(20), 6862.

https://doi.org/10.1523/JNEUROSCI.1051-10.2010

64. Govindpani, K., Guzmán, B. C. F., Vinnakota, C., Waldvogel, H. J., Faull, R. L., & Kwakowsky, A. (2017). Towards a Better Understanding of GABAergic Remodeling in Alzheimer's Disease. International Journal of Molecular Sciences, 18(8), 1813. https://doi.org/10.3390/IJMS18081813
65. Gratuze, M., Chen, Y., Parhizkar, S., Jain, N., Strickland, M. R., Serrano, J. R., Colonna, M., Ulrich, J. D., & Holtzman, D. M. (2021). Activated microglia mitigate aβ-associated tau seeding and spreading. Journal of Experimental Medicine, 218(8). https://doi.org/10.1084/JEM.20210542,
66. Gratuze, M., Leyns, C. E. G., & Holtzman, D. M. (2018). New insights into the role of TREM2 in Alzheimer's disease. Molecular Neurodegeneration 2018 13:1, 13(1), 1–16. https://doi.org/10.1186/S13024-018-0298-9
67. Guerreiro, R., Wojtas, A., Bras, J., Carrasquillo, M., Rogaeva, E., Majounie, E., Cruchaga, C., Sassi, C., Kauwe, J. S. K., Younkin, S., Hazrati, L., Collinge, J., Pocock, J., Lashley, T., Williams, J., Lambert, J.-C., Amouyel, P., Goate, A., Rademakers, R., … Hardy, J. (2013). TREM2 Variants in Alzheimer's Disease . New England Journal of Medicine, 368(2), 117–127. https://doi.org/10.1056/NEJMOA1211851/SUPPL_FILE/NEJMOA1211851_DISCLOSURES.PDF
68. Haenseler, W., Sansom, S. N., Buchrieser, J., Newey, S. E., Moore, C. S., Nicholls, F. J., Chintawar, S., Schnell, C., Antel, J. P., Allen, N. D., Cader, M. Z., Wade-Martins, R., James, W. S., & Cowley, S. A. (2017). A Highly Efficient Human Pluripotent Stem Cell Microglia Model Displays a Neuronal-Co-culture-Specific Expression Profile and Inflammatory Response. Stem Cell Reports, 8(6), 1727–1742. https://doi.org/10.1016/j.stemcr.2017.05.017
69. Hampel, H., Mesulam, M. M., Cuello, A. C., Farlow, M. R., Giacobini, E., Grossberg, G. T., Khachaturian, A. S., Vergallo, A., Cavedo, E., Snyder, P. J., & Khachaturian, Z. S. (2018). The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain, 141(7), 1917–1933. https://doi.org/10.1093/BRAIN/AWY132,
70. He, Z., Guo, J. L., McBride, J. D., Narasimhan, S., Kim, H., Changolkar, L., Zhang, B., Gathagan, R. J., Yue, C., Dengler, C., Stieber, A., Nitla, M., Coulter, D. A., Abel, T., Brunden, K. R., Trojanowski, J. Q., & Lee, V. M. Y. (2018). Amyloid-β plaques enhance Alzheimer's brain tau-seeded pathologies by facilitating neuritic plaque tau aggregation. Nature Medicine, 24(1), 29–38. https://doi.org/10.1038/NM.4443,
71. Heneka, M. T., Carson, M. J., Khoury, J. El, Landreth, G. E., Brosseron, F., Feinstein, D. L., Jacobs, A. H., Wyss-Coray, T., Vitorica, J., Ransohoff, R. M., Herrup, K., Frautschy, S. A., Finsen, B., Brown, G. C., Verkhratsky, A., Yamanaka, K., Koistinaho, J., Latz, E., Halle, A., … Kummer, M. P. (2015). Neuroinflammation in Alzheimer's disease. The Lancet Neurology, 14(4), 388–405. https://doi.org/10.1016/S1474-4422(15)70016-5
72. Keren-Shaul, H., Spinrad, A., Weiner, A., Matcovitch-Natan, O., Dvir-Szternfeld, R., Ulland, T. K., David, E., Baruch, K., Lara-Astaiso, D., Toth, B., Itzkovitz, S., Colonna, M., Schwartz, M.,

& Amit, I. (2017). A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. Cell, 169(7), 1276-1290.e17. https://doi.org/10.1016/j.cell.2017.05.018

73. Kleinberger, G., Yamanishi, Y., Suárez-Calvet, M., Czirr, E., Lohmann, E., Cuyvers, E., Struyfs, H., Pettkus, N., Wenninger-Weinzierl, A., Mazaheri, F., Tahirovic, S., Lleó, A., Alcolea, D., Fortea, J., Willem, M., Lammich, S., Molinuevo, J. L., Sánchez-Valle, R., Antonell, A., … Haass, C. (2014). TREM2 mutations implicated in neurodegeneration impair cell surface transport and phagocytosis. Science Translational Medicine, 6(243). https://doi.org/10.1126/SCITRANSLMED.3009093
74. Kong, C., Yang, E. J., Shin, J., Park, J., Kim, S. H., Park, S. W., Chang, W. S., Lee, C. H., Kim, H., Kim, H. S., & Chang, J. W. (2022). Enhanced delivery of a low dose of aducanumab via FUS in 5×FAD mice, an AD model. Translational Neurodegeneration, 11(1), 57. https://doi.org/10.1186/S40035-022-00333-X
75. Krasemann, S., Madore, C., Cialic, R., Baufeld, C., Calcagno, N., El Fatimy, R., Beckers, L., O'Loughlin, E., Xu, Y., Fanek, Z., Greco, D. J., Smith, S. T., Tweet, G., Humulock, Z., Zrzavy, T., Conde-Sanroman, P., Gacias, M., Weng, Z., Chen, H., … Butovsky, O. (2017). The TREM2-APOE Pathway Drives the Transcriptional Phenotype of Dysfunctional Microglia in Neurodegenerative Diseases. Immunity, 47(3), 566-581.e9. https://doi.org/10.1016/j.immuni.2017.08.008
76. Li, Y., Xu, H., Wang, H., Yang, K., Luan, J., & Wang, S. (2023a). TREM2: Potential therapeutic targeting of microglia for Alzheimer's disease. Biomedicine & Pharmacotherapy, 165, 115218. https://doi.org/10.1016/J.BIOPHA.2023.115218
77. Li, Y., Xu, H., Wang, H., Yang, K., Luan, J., & Wang, S. (2023b). TREM2: Potential therapeutic targeting of microglia for Alzheimer's disease. Biomedicine & Pharmacotherapy, 165, 115218. https://doi.org/10.1016/J.BIOPHA.2023.115218
78. Lin, M., Yu, J. X., Zhang, W. X., Lao, F. X., & Huang, H. C. (2024). Roles of TREM2 in the Pathological Mechanism and the Therapeutic Strategies of Alzheimer's Disease. The Journal of Prevention of Alzheimer's Disease, 11(6), 1682. https://doi.org/10.14283/JPAD.2024.164
79. Nugent, A. A., Lin, K., van Lengerich, B., Lianoglou, S., Przybyla, L., Davis, S. S., Llapashtica, C., Wang, J., Kim, D. J., Xia, D., Lucas, A., Baskaran, S., Haddick, P. C. G., Lenser, M., Earr, T. K., Shi, J., Dugas, J. C., Andreone, B. J., Logan, T., … Di Paolo, G. (2020). TREM2 Regulates Microglial Cholesterol Metabolism upon Chronic Phagocytic Challenge. Neuron, 105(5), 837-854.e9. https://doi.org/10.1016/j.neuron.2019.12.007
80. Okuzono, Y., Sakuma, H., Miyakawa, S., Ifuku, M., Lee, J., Das, D., Banerjee, A., Zhao, Y., Yamamoto, K., Ando, T., & Sato, S. (2021). Reduced TREM2 activation in microglia of patients with Alzheimer's disease. FEBS Open Bio, 11(11), 3063. https://doi.org/10.1002/2211-5463.13300
81. Olah, M., Patrick, E., Villani, A. C., Xu, J., White, C. C., Ryan, K. J., Piehowski, P., Kapasi, A., Nejad, P., Cimpean, M.,

Connor, S., Yung, C. J., Frangieh, M., McHenry, A., Elyaman, W., Petyuk, V., Schneider, J. A., Bennett, D. A., De Jager, P. L., & Bradshaw, E. M. (2018). A transcriptomic atlas of aged human microglia. Nature Communications, 9(1). https://doi.org/10.1038/S41467-018-02926-5,

82. Painter, M. M., Atagi, Y., Liu, C. C., Rademakers, R., Xu, H., Fryer, J. D., & Bu, G. (2015). TREM2 in CNS homeostasis and neurodegenerative disease. Molecular Neurodegeneration, 10(1), 1–10. https://doi.org/10.1186/S13024-015-0040-9/FIGURES/1
83. Parhizkar, S., Arzberger, T., Brendel, M., Kleinberger, G., Deussing, M., Focke, C., Nuscher, B., Xiong, M., Ghasemigharagoz, A., Katzmarski, N., Krasemann, S., Lichtenthaler, S. F., Müller, S. A., Colombo, A., Monasor, L. S., Tahirovic, S., Herms, J., Willem, M., Pettkus, N., … Haass, C. (2019). Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE. Nature Neuroscience, 22(2), 191–204. https://doi.org/10.1038/S41593-018-0296-9,
84. Penney, J., Ralvenius, W. T., Loon, A., Cerit, O., Dileep, V., Milo, B., Pao, P. C., Woolf, H., & Tsai, L. H. (2024). iPSC-derived microglia carrying the TREM2 R47H/+ mutation are proinflammatory and promote synapse loss. GLIA, 72(2), 452–469. https://doi.org/10.1002/GLIA.24485,
85. Poliani, P. L., Wang, Y., Fontana, E., Robinette, M. L., Yamanishi, Y., Gilfillan, S., & Colonna, M. (2015). TREM2 sustains microglial expansion during aging and response to demyelination. Journal of Clinical Investigation, 125(5), 2161–2170. https://doi.org/10.1172/JCI77983,
86. Popescu, A. S., Butler, C. A., Allendorf, D. H., Piers, T. M., Mallach, A., Roewe, J., Reinhardt, P., Cinti, A., Redaelli, L., Boudesco, C., Pradier, L., Pocock, J. M., Thornton, P., & Brown, G. C. (2023). Alzheimer's disease-associated R47H TREM2 increases, but wild-type TREM2 decreases, microglial phagocytosis of synaptosomes and neuronal loss. GLIA, 71(4), 974–990. https://doi.org/10.1002/GLIA.24318,
87. Schlepckow, K., Monroe, K. M., Kleinberger, G., Cantuti-Castelvetri, L., Parhizkar, S., Xia, D., Willem, M., Werner, G., Pettkus, N., Brunner, B., Sülzen, A., Nuscher, B., Hampel, H., Xiang, X., Feederle, R., Tahirovic, S., Park, J. I., Prorok, R., Mahon, C., … Haass, C. (2020). Enhancing protective microglial activities with a dual function TREM 2 antibody to the stalk region . EMBO Molecular Medicine, 12(4). https://doi.org/10.15252/EMMM.201911227,
88. Shahpasand, K., Uemura, I., Saito, T., Asano, T., Hata, K., Shibata, K., Toyoshima, Y., Hasegawa, M., & Hisanaga, S. I. (2012). Regulation of mitochondrial transport and inter-microtubule spacing by tau phosphorylation at the sites hyperphosphorylated in Alzheimer's disease. Journal of Neuroscience, 32(7), 2430–2441. https://doi.org/10.1523/JNEUROSCI.5927-11.2012,
89. Song, W. M., & Colonna, M. (2018). The identity and function of microglia in neurodegeneration. Nature Immunology, 19(10), 1048–1058. https://doi.org/10.1038/S41590-018-0212-1,
90. Spangenberg, E., Severson, P. L., Hohsfield, L. A., Crapser, J., Zhang, J., Burton, E. A., Zhang, Y., Spevak, W., Lin, J., Phan, N. Y., Habets, G., Rymar,

A., Tsang, G., Walters, J., Nespi, M., Singh, P., Broome, S., Ibrahim, P., Zhang, C., … Green, K. N. (2019). Sustained microglial depletion with CSF1R inhibitor impairs parenchymal plaque development in an Alzheimer's disease model. Nature Communications, 10(1). https://doi.org/10.1038/S41467-019-11674-Z,

91. Sudom, A., Talreja, S., Danao, J., Bragg, E., Kegel, R., Min, X., Richardson, J., Zhang, Z., Sharkov, N., Marcora, E., Thibault, S., Bradley, J., Wood, S., Lim, A.-C., Chen, H., Wang, S., Foltz, I. N., Sambashivan, S., & Wang, Z. (2018). Molecular basis for the loss-of-function effects of the Alzheimer's disease–associated R47H variant of the immune receptor TREM2. Journal of Biological Chemistry, 293(32), 12634–12646. https://doi.org/10.1074/JBC.RA118.002352,
92. Sweeney, M. D., Sagare, A. P., & Zlokovic, B. V. (2018). Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nature Reviews Neurology, 14(3), 133–150. https://doi.org/10.1038/NRNEUROL.2017.188,
93. Ulland, T. K., & Colonna, M. (2018). TREM2 — a key player in microglial biology and Alzheimer disease. Nature Reviews Neurology, 14(11), 667–675. https://doi.org/10.1038/S41582-018-0072-1,
94. Ulrich, J. D., Finn, M. B., Wang, Y., Shen, A., Mahan, T. E., Jiang, H., Stewart, F. R., Piccio, L., Colonna, M., & Holtzman, D. M. (2014). Altered microglial response to Aβ plaques in APPPS1-21 mice heterozygous for TREM2. Molecular Neurodegeneration, 9(1), 1–9. https://doi.org/10.1186/1750-1326-9-20/FIGURES/5
95. van Lengerich, B., Zhan, L., Xia, D., Chan, D., Joy, D., Park, J. I., Tatarakis, D., Calvert, M., Hummel, S., Lianoglou, S., Pizzo, M. E., Prorok, R., Thomsen, E., Bartos, L. M., Beumers, P., Capell, A., Davis, S. S., de Weerd, L., Dugas, J. C., … Monroe, K. M. (2023). A TREM2-activating antibody with a blood–brain barrier transport vehicle enhances microglial metabolism in Alzheimer's disease models. Nature Neuroscience, 26(3), 416–429. https://doi.org/10.1038/S41593-022-01240-0,
96. Wang, S., Mustafa, M., Yuede, C. M., Salazar, S. V., Kong, P., Long, H., Ward, M., Siddiqui, O., Paul, R., Gilfillan, S., Ibrahim, A., Rhinn, H., Tassi, I., Rosenthal, A., Schwabe, T., & Colonna, M. (2020). Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. Journal of Experimental Medicine, 217(9). https://doi.org/10.1084/JEM.20200785,
97. Wang, Y., Cella, M., Mallinson, K., Ulrich, J. D., Young, K. L., Robinette, M. L., Gilfillan, S., Krishnan, G. M., Sudhakar, S., Zinselmeyer, B. H., Holtzman, D. M., Cirrito, J. R., & Colonna, M. (2015). TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. Cell, 160(6), 1061–1071. https://doi.org/10.1016/J.CELL.2015.01.049,
98. Welikovitch, L. A., Carmo, S. Do, Maglóczky, Z., Malcolm, J. C., Loke, J., Klein, W. L., Freund, T., & Claudio Cuello, A. (2020). Early intraneuronal amyloid triggers neuron-derived inflammatory signaling in APP transgenic rats and human brain. Proceedings of the National Academy of Sciences of the United States of America, 117(12), 6844–6854.

https://doi.org/10.1073/PNAS.1914593117,

99. Yeh, F. L., Wang, Y., Tom, I., Gonzalez, L. C., & Sheng, M. (2016). TREM2 Binds to Apolipoproteins, Including APOE and CLU/APOJ, and Thereby Facilitates Uptake of Amyloid-Beta by Microglia. Neuron, 91(2), 328–340. https://doi.org/10.1016/J.NEURON.2016.06.015,
100. Yuan, P., Condello, C., Keene, C. D., Wang, Y., Bird, T. D., Paul, S. M., Luo, W., Colonna, M., Baddeley, D., & Grutzendler, J. (2016). TREM2 Haplodeficiency in Mice and Humans Impairs the Microglia Barrier Function Leading to Decreased Amyloid Compaction and Severe Axonal Dystrophy. Neuron, 90(4), 724–739. https://doi.org/10.1016/j.neuron.2016.05.003
101. Zhong, L., Xu, Y., Zhuo, R., Wang, T., Wang, K., Huang, R., Wang, D., Gao, Y., Zhu, Y., Sheng, X., Chen, K., Wang, N., Zhu, L., Can, D., Marten, Y., Shinohara, M., Liu, C. C., Du, D., Sun, H., … Chen, X. F. (2019). Soluble TREM2 ameliorates pathological phenotypes by modulating microglial functions in an Alzheimer's disease model. Nature Communications, 10(1). https://doi.org/10.1038/S41467-019-09118-9