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Triggering receptor expressed on myeloid cells 2 (TREM2): a potential therapeutic target for Alzheimer disease?

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Abstract

Introduction: There are currently no effective therapeutics for Alzheimer disease (AD). Clinical trials targeting amyloid beta thus far have shown very little benefit and only in the earliest stages of disease. These limitations have driven research to identify alternative therapeutic targets, one of the most promising is the triggering receptor expressed on myeloid cells 2 (TREM2).

Areas covered: Here, we review the literature to-date and discuss the potentials and pitfalls for targeting TREM2 as a potential therapeutic for AD. We focus on research in animal and cell models for AD and central nervous system injury models which may help understand the role of TREM2 in disease.

Expert opinion: Studies suggest TREM2 plays a key role in AD pathology; however, results have been conflicting about whether TREM2 is beneficial or harmful. More research is necessary before designing TREM2-targeting therapies. Successful therapeutics will most likely be administered early in disease.

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Keywords

TREM2; Alzheimer disease; cerebrospinal fluid; genetic association; microglia

1. Introduction

Approximately 5.5 million individuals have been currently diagnosed with Alzheimer disease (AD) in the United States (US) and as the population 65 years and older increases, that number is estimated to almost triple by the year 2050 [1]. AD is reported to be the sixth-leading cause of death in the US; however, after three decades of research leading to tremendous breakthroughs in identifying much of the underlying neuropathology of AD, there are currently no treatments to prevent or slow progression of the disease. The defining neuropathological hallmarks of AD are extracellular plaques primarily consisting of aggregated β-amyloid (Aβ) deposits and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein (ptau). Mutations in amyloid precursor protein (*APP*), presenilin-1 (*PSEN1*), and presenilin-2 (*PSEN2*) cause rare (< 1% of cases) Mendelian early-onset AD and variants in these genes are also associated with non-Mendelian late-onset AD. Although late-onset AD is highly heritable, estimated as high as 79% in twin studies [2], it is also genetically complex; with more than 25 genetic loci associated with risk identified thus far only about half of the heritability is explained by these associations [3, 4]. The strongest genetic risk factor for AD is a variant in the gene encoding apolipoprotein E (*APOE*) known as the *ε4* allele; individuals carrying one *ε4* allele have a threefold increase in AD risk and two *ε4* alleles confer 8- to 12-fold increased risk [5, 6].

Although promising treatments have been tested in clinical trials none have met with much success. Most of the therapeutic approaches thus far have targeted Aβ, and although immunization against Aβ has reduced plaques and showed some cognitive improvement in transgenic mouse models for AD [7], human clinical trials have shown, at best, very small benefits in patients with mild cognitive symptoms [8]. Phase III trials of anti-Aβ antibodies have not shown any improvement in primary outcomes for patients with mild to moderate AD [9–11] and the field continues to search for effective treatment for this devastating disease. Research has revealed that AD pathology appears at least 10–20 years before the onset of clinical symptoms, and many experts in the field believe that once symptoms of memory decline appear the pathological damage may be irreversible [12]. This suggests that treatment would likely be most effective in the preclinical stage of AD; however, currently there are no biomarkers with the sensitivity and specificity necessary to identify preclinical individuals, presenting another obstacle for clinical research.

Cerebrospinal fluid (CSF) levels of tau, ptau, and Aβ are considered the gold standard for AD biomarkers. In 2013, an extensive review that included a total of 1,172 individuals with MCI at baseline (430 of whom converted to AD within 1–4 years) estimated that CSF tau had a median specificity of 72% and sensitivity of 75% and CSF ptau had a median specificity of 47.5% and sensitivity of 81% [13]. The ratio of CSF tau (or ptau) and $A\beta_{42}$ has been reported to be the most accurate thus far [13–18]. However, inter-individual variability, overlap between preclinical cases and controls, and cross-study measurement

variability reduce diagnostic specificity of these biomarkers, particularly for prodromal AD [19–23]. One promising biomarker of recent interest is CSF soluble triggering receptor expressed on myeloid cells 2 protein (sTREM2) mostly because there is a strong genetic association between *TREM2* and AD; additionally, sTREM2 levels in CSF have been found elevated in individuals with AD and changes were observed in preclinical AD [24–27]. The genetic associations between *TREM2* and disease and potential for sTREM2 as a disease biomarker are discussed further in the next section.

2. *TREM2* associated with disease

2.1. Nasu-Hakola disease causal variants

Nasu-Hakola disease (NHD), also known as polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), is a rare recessively-inherited disease characterized by the presence of bone cysts and progressive presenile dementia that usually begins around the ages of 25 – 40 years and leads to death by the age of 50 [28]. The first identified causal gene for NHD was the gene encoding TYRO protein tyrosine kinase binding protein (*TYROBP* also known as *DAP12*) which is a transmembrane protein important in innate immune signaling [29]. TYROBP is expressed in microglia in the brain and is an adapter protein for the triggering receptor expressed on myeloid cells 2 protein (TREM2). In 2002, researchers identified variants in *TREM2* that were associated with NHD in families who did not carry previously identified *TYROBP* mutations [30]. In addition to a splice-site mutation, researchers identified four other *TREM2* mutations in two families and four individuals who did not carry *TYROBP* mutations: p.W78X, p.W44X, p.K186N, and p.D134G [30]. Dendritic cells taken from three NHD patients carrying a shared ancestral deletion within *TYROBP* that was identified in a Finnish population, referred to as the $PLOSL_{Fin}$ *DAP12* mutation, and from two NHD patients carrying *TREM2* (p.Q33X or p.V126G) mutations showed differential expression of several genes associated with inflammatory and innate immune response when compared to cells taken from non-carriers [31]. Interestingly, *TREM2* expression was significantly down-regulated in dendritic cells from patients with *TYROBP* mutations similarly to the *TREM2* mutation carriers, but the *TREM2* mutations did not appear to influence the expression levels of *TYROBP* [31]. This suggests that disrupted expression of *TREM2*, not *TYROBP*, may be responsible for NHD symptoms and that TREM2 may be the best therapeutic target for NHD.

2.2. *TREM2* risk variants for Human acquired colesteatoma and dementia

TREM2 gene expression was recently reported to be associated with a disease that is classified by bone destruction, but no cognitive symptoms. Human acquired cholesteatoma causes hearing loss and vestibular neuritis, usually in response to bacterial infection, and is characterized by proliferation of keratinized epithelia inside the ear as well as erosion of ossicles and temporal bone [32]. Inflammatory response is considered the most important factor in the bone destruction observed in acquired cholesteatoma [32]. RT-PCR of mRNA extracted from skin taken from patients and healthy controls revealed that *TREM2* gene expression was significantly upregulated in patients with acquired cholesteatoma. Analyses of TREM2-deficient ($Trem2^{-/-}$) mouse models of experimentally acquired cholesteatoma revealed that TREM2 appears to act through the TLR4 signaling pathway [32].

A number of studies have identified *TREM2* variants associated with dementia and FTD-like disease without the presence of bone cysts. Functional neuroimaging (^{99m}Tc-ECD SPECT) and neuropsychological analyses of unaffected individuals from an Italian family with two homozygous p.Q33X carriers who were diagnosed with NHD, revealed that heterozygous p.Q33X carriers had visuo-spatial memory deficits associated with hypoperfusion in the basal ganglia [33]. A linkage study of a Lebanese family identified a novel splice-site deletion within the first intron of *TREM2* in three individuals who had presented with early-onset dementia beginning around the ages 30–35 but had no signs of bone cysts [34]. This study also determined that although the *TREM2* transcripts appeared normal in lymphocytes and cultured fibroblasts taken from family members, the expression of *TREM2* was significantly down-regulated and the expression of other genes were disrupted as well (*BCL3*, *FSCN*, *NFKBIA*, *NEDD9*, and *SPP1*) [34]. More recently a few studies have reported associations between *TREM2* missense variants and FTD or FTD-like dementia [35–38].

2.3. Alzheimer disease risk variants

Several studies have demonstrated that *TREM2* variants are associated with AD risk [39–43]. In 2013, two groups independently identified, for the first time, a rare variant in *TREM2* (p.R47H) that increased risk for AD almost three-fold, the greatest genetic risk for AD identified since *APOE ε4* [40, 43]. Guerreiro et al. also observed other *TREM2* variants in AD cases, but not controls, in their discovery set: p.H157Y, p.R98W, p.D87N, p.T66M, p.Y38C, and p.Q33X [40]. Pooled sequencing of *TREM2* allowed researchers to identify additional AD risk variants, and revealed that disparities in minor allele frequency resulted in a different set of risk variants in African Americans compared to Europeans [41, 42]. Other studies have demonstrated that different populations have different *TREM2* risk variants [44, 45].

Further evidence for the association of TREM2 in AD is that TREM2 protein levels were found elevated in post-mortem temporal brain tissue taken from AD patients [46]. The increased TREM2 protein levels were positively correlated with ptau and caspase 3 and negatively correlated with SNAP25, suggesting an association between TREM2 levels, apoptosis, and synapse loss in AD [46]. Additionally, microglia associated with neuropathology stained positively for TREM2, supporting previous research that associated TREM2 with microglia [46]. The role of TREM2 in microglia is discussed further in section 3.

2.4. Soluble TREM2 as a disease biomarker

There is evidence that TREM2 may be involved in multiple sclerosis (MS) although no *TREM2* variants have been reported to be associated with MS. Soluble TREM2 (sTREM2) can be measured in CSF and was found elevated in patients with MS in the relapsing-remitting phase (RRMS), the secondary progressive phase (SPMS), and the primary progressive phase (PPMS) [47, 48]. RRMS patients treated with natalizumab (a humanized monoclonal antibody against the cell adhesion molecule α4-integrin) showed CSF sTREM2 levels were reduced to levels similar to controls after 12 months of treatment and patients showed improvement of clinical symptoms [48].

Studies have also demonstrated that CSF sTREM2 levels are elevated in early stages of AD [24–26] and changes in CSF sTREM2 can be observed in preclinical individuals after amyloid deposition, increasing approximately five years before the onset of clinical symptoms and remaining significantly elevated five years after onset [27]. CSF levels of sTREM2 were positively correlated with tau and ptau levels, but were not correlated with CSF Aβ [24–26]. CSF levels of sTREM2 have also been associated with increased gray matter volume suggestive f brain swelling during neuroinflammation [49].

There is evidence that CSF levels of sTREM2 are influenced by previously identified *TREM2* risk variants, and that the risk variants for different diseases have very different effects on sTREM2 levels [25, 50]. The *TREM2* p.R47H AD risk variant was associated with higher levels of CSF sTREM2, whereas carriers of variants associated with NHD had lower CSF sTREM2 levels compared to controls [25]. Levels of sTREM2 were virtually undetectable in CSF from individuals who were homozygous for the p.T66M mutation, which has been primarily associated with FTD risk, and a heterozygous p.T66M carrier was reported to have significantly lower levels similar to NHD-risk variant carriers [25, 50].

There is a great deal of interest in the field to identify biomarkers that are less invasive than CSF biomarkers, so researchers have tested sTREM2 levels in blood as well. One of the earlier studies that found higher sTREM2 in CSF from MS patients did not find a difference in sTREM2 levels measured in blood from the same individuals [47]. TREM2 protein levels and mRNA were measured in blood extracted from 116 individuals with “probable” AD and 116 sex- and age-matched healthy controls and were reported to be significantly higher in AD patients; however, the reported sensitivity (68%) and specificity (72%) were too low for blood levels of TREM2 to be a reliable biomarker [51]. Another study in 2014, which had reported higher sTREM2 levels in CSF taken from AD patients, did not find a significant difference in plasma levels of sTREM2 between AD cases (n = 51) and controls (n = 86) [50]. This finding was replicated in a more recent study that analyzed sTREM2 levels in CSF and plasma taken from a well-characterized AD cohort (73 cases and 107 healthy controls) which showed significantly elevated CSF sTREM2 in AD cases but no difference in sTREM2 plasma levels [25]. Based on research thus far, it appears that although CSF levels of sTREM2 may be a promising AD biomarker, plasma sTREM2 levels probably are not going to be as informative.

3. TREM2 in microglia

With this strong association between TREM2, dementia, and Alzheimer disease, it became important to understand what the normal function of TREM2 is in the brain and how dysfunction of TREM2 may contribute to disease. To identify the most important functions of TREM2 in microglia that is known to-date, a careful literature review was conducted by first using the search terms ‘TITLE-ABS-KEY (trem2 AND microglia) AND (LIMIT-TO (DOCTYPE, “ar”))’ in Scopus in February 2018. Figure 1 illustrates the most cited research of TREM2 and microglia, with the primary findings depicted in a Sankey plot generated using the googleVis version 0.6.2 package in R version 3.4 [52]. We evaluated the 20 most cited research articles in depth and selected 14 of the 20 most cited articles. Figure 1

describes 1. the main conclusion, 2. related TREM2 variants or disturbance, 3. disease background, 4. research model, and 5. reference.

TREM2 is part of the triggering receptor expressed on myeloid cells family which regulate innate immune response and are expressed on a variety of myeloid cells including microglia, macrophages, monocytes, osteoclasts, dendritic cells, and neutrophils. *TREM1* was the first *TREM* identified and is the best characterized. Both *TREM1* and *TREM2* encode proteins that form transmembrane receptor-signaling complexes with the TYRO binding protein (aka DNAX-activating protein of 12 kDa, or DAP12). TREM1 is highly expressed on monocytes, macrophages, and neutrophils; whereas TREM2 is highly expressed on macrophages, dendritic cells, osteoclasts, and microglia[53]. Studies suggest that TREM2 is necessary for maturation of dendritic cells and osteoclasts [54, 55]. In the central nervous system, direct RNA sequencing of murine microglia demonstrated that TREM2 is one of the highest expressed receptors in microglia and is specifically enriched on microglia compared to astrocytes and neurons [56]. TREM2 appears to be necessary for microglial survival, inflammatory response, and induced phagocytosis (Figure 2). Studies of cuprizone-induced demyelination in *Trem2*$^{-/-}$ mice showed reduced clearance of myelin debris, increased axonal pathology, and worse clinical symptoms than WT mice [57]. There was also evidence that microglial activation was reduced in the *Trem2*$^{-/-}$ mice when measuring major histocompatibility complex class II (MHC II) and inducible nitric oxide synthase (iNOS) expression, and differential expression analyses suggested that deficient lipid metabolism may be responsible [57].

Animal model studies have suggested that TREM2 plays a key role in modulating microglial response in the presence of AD pathology [50, 58–61]. There have been conflicting conclusions from these studies about whether this role is beneficial or harmful, key evidence from these studies is summarized in Figure 3. *Trem2* knockdown in microglia from APPswe/PS1dE9 (APP/PS1) mice showed reduced microglial phagocytosis of Aβ and increased pathology, suggesting that TREM2 is necessary for keeping amyloid pathology in check by phagocytosis [62]. Analyses of *Trem2*$^{-/-}$ 5XFAD crossbred mice showed significant Aβ deposition in the hippocampus and reduced survival of microglia due to apoptosis [60]. However, other studies suggest that inhibiting *Trem2* may be beneficial instead [63, 64]. Four-month-old *Trem2*$^{-/-}$ APP/PS1 mice had fewer plaque-associated macrophages and reduced neuroinflammation, amyloid accumulation in the hippocampus, and tau pathology [63]. Knockout of *Trem2* in a PS19 mouse model for tauopathy (expressing human tau (1N4R) with the FTD-linked P301S mutation) showed a reduction of neurodegeneration and inflammation [64]. One possible reason for the apparently conflicting evidence for TREM2 having a protective or harmful role in disease could be that these studies represent different stages of AD and the presence of different disease pathology. The 5XFAD transgenic mice carry mutations in both *PSEN1* and *APP*, resulting in early and rapid Aβ accumulation (by 6 months) and cognitive deficits (by 5 months) [65]. The APP/PS1 transgenic mice carry fewer mutations in both *APP* and *PSEN1*, resulting in slower accumulation of Aβ (beginning at 6 months and abundant by 9 months) and show a later cognitive decline (by 12 months) [66]. The PS19 mice carry a human tau transgene with the p.P301S mutation which causes FTD in humans, resulting in extensive tangle

pathology and gliosis by 9 months as well as severe neurodegeneration, all in the absence of amyloid pathology [67].

Research of acquired brain injury models, in combination with the AD mouse model research, further suggests that some of the conflicting results from studies of TREM2 function are context specific: differences in acute vs chronic injury and time course. Traumatic brain injury (TBI) may increase risk for AD and it is interesting to note that *Trem2* gene expression was found elevated for at least seven days post injury in a lateral fluid percussion injury mouse model for TBI [68]. *Trem2*$^{-/-}$ mice had fewer infiltrating peripheral macrophages and reduced gene expression of *tnfa*, *il-6*, and *il-1β* compared to WT three days post injury [68]. After 120 days post injury, *Trem2*$^{-/-}$ mice showed reduced loss of hippocampal volume and attenuation of cognitive deficits compared to WT, which led the authors to conclude that *Trem2* deficiency is neuroprotective by reducing infiltrating macrophages in response to injury [68]. However, in an experimental stroke mouse model using permanent middle cerebral artery occlusion (MCAO), *Trem2* deficiency resulted in fewer activated microglia, reduced phagocytosis, larger infarct size, and worse neurological recovery fourteen days post ischemia, suggesting TREM2 is necessary for stroke recovery [69]. These disparate results, also summarized in Figure 3, suggest that the role of TREM2 in neuroinflammation, neurodegeneration, and neuroprotection is highly dynamic and depends on cell type (peripheral macrophages or microglia), type of injury, and timing.

TREM2 makes up part of a receptor complex which binds ligands and initiates signaling; therefore, determining which ligands bind this receptor may help understand the function of TREM2 in microglia. Identification of endogenous TREM2 ligands has not been comprehensive, but some *in vitro* studies provide compelling evidence for several ligands including molecules that are important in AD. Several studies have suggested that TREM2 binds anionic ligands on cells, both bacterial and mammalian, such as phospholipids, nucleic acids, and proteoglycans [70]. Other studies have reported other ligands such as heat shock protein 60 (HSP60) and apolipoproteins [70]. The first reported specific TREM2 agonist was HSP60, which was found to induce phagocytosis [71]. Researchers studying an ischemia cell model reported that although they did not find TREM2 signaling in response to HSP60, they did find evidence that high-molecular-weight nucleic acids may act as ligands to initiate TREM2 signaling in response to apoptotic cells [69]. One putative ligand for TREM2 which is of particular interest in AD is APOE and reduced binding affinity for APOE was observed for the TREM2 p.R47H mutation [72]. Another group identified apolipoproteins, including clusterin and APOE, as TREM2 ligands and also reported less binding affinity for not only the p.R47H mutations but p.D87N and p.R62H variants as well [73]. They also found that the loss of function TREM2 mutations associated with NHD (p.Y38C and p.T66M) showed no binding affinity for apolipoproteins [73]. Recent research suggests that APOE signaling, induced by TREM2, drives post-transcriptional changes that cause microglia to promote neurodegeneration and that targeting *Apoe* in mice restored the neuroprotective milieu [58]. APOE influences both amyloid- and tau-mediated AD pathogenesis through multiple mechanisms including metabolism and aggregation of Aβ, lipid transport, synaptic plasticity, neuroinflammation, and many others [74]. Since both *TREM2* and *APOE* are associated with AD risk, this TREM2-APOE pathway in microglia most likely plays a key role in AD pathology.

4. TREM2 biological pathways and activity

4.1. TREM2 Cleavage

As mentioned in section 2.4, sTREM2 can be measured in CSF and plasma. In 2014, Jin et al. reported three distinct transcripts for *TREM2* were present in human brain tissue, including a short transcript which was alternatively spliced to exclude exon 4 (which contains the transmembrane domain) encoding for sTREM2 [41]. Other studies reported evidence for sequential proteolytic cleavage of the transmembrane protein also resulting in sTREM2 [75] and recently two groups independently reported a consensus of the exact cleavage site on TREM2 that is targeted by ADAM10 and other proteases to generate sTREM2; though there was some disagreement about which proteases, other than ADAM10, also cleave TREM2 [76, 77]. Through mass spectrometry analyses and targeted *in vivo* experiments, they determined that ADAM-mediated cleavage occurs between histidine 157 and serine 158, which is interestingly where an AD risk variant has been identified in various studies (p.H157Y) [45, 76–79]. Both groups found increased shedding of TREM2 in cells expressing the p.H157Y mutant, which would result in increased levels of sTREM2 and less cell surface expression of TREM2 [76, 77]. Mutations such as p.T66M and p.Y38C, which are in the Ig-like domain and prevent the protein from leaving the endoplasmic reticulum, resulted in both reduced cell surface expression of TREM2 and levels of sTREM2 [50, 79, 80]. The p.R47H variant did not appear to affect glycosylation or normal trafficking of TREM2 to the same extent as p.T66M and p.Y38C, but the glycosylation pattern was different from WT, suggesting some impairment that could affect normal TREM2 function [80]. Together, these studies suggest that the role of *TREM2* mutations in disease may not be simply a gain or loss of function of the receptor.

4.2. Effect of *TREM2* variants on trafficking, shedding, and sTREM2 levels

TREM2 localization can greatly impact TREM2 signaling. TREM2 trafficking appears to be a highly dynamic process involving endocytosis and recycling. Under baseline conditions, TREM2 is localized in the trans-Golgi network [81, 82], endosomes [83], and in exocytic vesicles [81]. TREM2 is internalized in a clathrin-dependent manner and recycled back to the plasma membrane through vacuolar protein sorting 35 (Vps35) and beclin-1 [84, 85]. In the absence of Vps35, TREM2 is degraded by the lysosome [85].

Heterologous expression of *TREM2* variants (p.T66M, p.Y38C, and p.R47H) in various cell lines (Hek293, HeLa, and murine microglial BV2) significantly reduced TREM2 surface expression and the amount of sTREM2 in conditioned media [50, 80]. The p.T66M and p.Y38C variants increased localization of TREM2 to the endoplasmic reticulum [50, 80], affecting proper folding and stability of the protein [86] and consequently degrading TREM2 by the ERAD pathway [80]. However, the p.R47H variant did not appear to alter surface expression of TREM2 [80] or it reduced expression to a lesser extent than the other variants [50]. Also unlike the other variants, p.R47H TREM2 was primarily localized to the trans-Golgi network [50, 80]. Overall, these studies suggest that *TREM2* variants associated with NHD, FTD, or FTD-like disease affect TREM2 maturation, cell surface transport, and proteolytic processing whereas the AD-associated p.R47H mutation has a milder effect on protein maturation and secretion. However, researchers have focused on the cleaved form of

sTREM2 and very little attention has been paid to the alternatively spliced form of sTREM2. Further research will be necessary to determine how the different *TREM2* variants may influence alternative splicing.

5. Current research targeting TREM2

The extensive genetic and biomarker evidence for the potential role of TREM2 in AD risk has prompted several groups to determine whether TREM2 may be a viable therapeutic target for AD. *TREM2* variants that are causal for NHD appear to be loss-of-function and many researchers have hypothesized that the AD risk variants result in some loss-of-function as well. As detailed in Section 3, a great deal of research has focused on this loss-of-function hypothesis and reported conflicting conclusions about the beneficial or harmful effect of TREM2 deficiency. Analyses of *Trem2*$^{-/-}$ 5XFAD crossbred mice showed significant Aβ deposition in the hippocampus and reduced survival of microglia due to apoptosis, suggesting the loss of TREM2 function is harmful [60]. *Trem2* knockdown in microglia cultured from the APPswe/PS1dE9 mice reduced microglial phagocytosis of Aβ, also suggesting TREM2 deficiency is harmful [62]. However, a mouse model for earlier stages of AD showed that *Trem2* depletion resulted in reduced amyloid deposition in the hippocampus, suggesting that loss-of-function of TREM2 is beneficial [87]. In the context of tauopathy without amyloidosis, PS19/*Trem2*$^{-/-}$ mice showed reduced brain atrophy, suggesting a beneficial effect of TREM2 deficiency [64]. These results demonstrate that the role of TREM2 in AD is unlikely to be attributable to a simple partial loss-of-function.

TREM2 gene transcript and protein levels appear to be elevated in human AD brains [88, 89]. AD patients carrying the p.R47H variant showed a trend toward increased TREM2 protein levels, suggesting that the p.R47H mutation does not appear to have a negative influence on protein levels but actually the opposite [89]. The authors suggested that the p.R47H variant may affect TREM2 binding function instead of expression levels [89]. Some research suggests that increasing TREM2 levels or activity may be beneficial in AD. TREM2 protein levels were upregulated in a transgenic mouse model for AD (APPswe/PS1dE9) at 7-months of age when amyloid deposition and cognitive impairment is present, and TREM2 levels were positively correlated with levels of $A\beta_{42}$ [62]. Lentiviral overexpression of *Trem2 in vivo* significantly reduced neuropathology and improved cognitive symptoms, suggesting that upregulation of TREM2 is a protective response to AD pathology [62]. However, overexpression of TREM2 by lentivirus did not improve cognitive performance or reduce neuropathology in older (18 months old) APPswe/PS1dE9 mice, suggesting that TREM2 may only be a viable therapeutic target early in disease [90].

It is unclear how different *TREM2* variants affect protein levels or activity, so it is useful to study specific variants rather than manipulating gene expression. The AD-associated p.R47H TREM2 mutation has been shown to impair binding of phospholipids and lipoproteins in TREM2 reporter cells [60]. Human brain tissue from p.R47H carriers showed less microglia enveloping amyloid plaques resulting in larger plaques with branched amyloid fibrils [91]. Based on these (and similar) findings, TREM2 activating antibodies have been proposed as a potential therapeutic tool. TREM2 activating antibodies can activate ERK and calcium signaling and appear to improve maturation and migration of osteoclasts and

dendritic cells [54, 92]. However, there are challenges with this approach. TREM2 appears to influence phagocytosis and anti-TREM2 antibodies may appear as a substrate for cellular uptake [81]. Alternatively, anti-TREM2 antibodies may inhibit binding and internalization of TREM2 ligands [60]. In considering anti-TREM2 antibodies as a potential therapeutic, it is also important to note that the role of sTREM2 in health and disease is not yet understood [93] and most anti-TREM2 antibodies against the extracellular domain target both membranous and soluble forms of TREM2. Chronic treatment with TREM2-activating antibodies could also have toxic effects through increased activation of microglia and extra-CNS macrophages, so the timing of this type of therapeutic would be absolutely crucial to reduce treatment duration. Although there are currently no *in vivo* examples of TREM2 antibody-stimulated agonism successfully reducing AD-related pathology, a patent application search suggests this is the most active pharmacological interest thus far. As shown in Figure 4, the number of TREM2-related patent applications sharply increased after the first reported TREM2 agonist (Hsp60) in 2009 [71] and increased dramatically again after the first reported association between *TREM2* and AD at the beginning of 2013 [40, 43].

An alternative strategy to using activating antibodies may be to increase *TREM2* gene expression or protein levels, making more TREM2 available. Analyses of murine primary microglial cultures have shown that *Trem2* knockdown increased protein levels of TNFα and inhibited phagocytosis while overexpression of *Trem2* not only increased phagocytosis but also reduced proinflammatory response [94]. Follow-up studies in experimental autoimmune encephalomyelitis (EAE) mouse models for MS supported these findings [95]. Ectopic gene expression of *Trem2* in myeloid precursor cells injected intravenously improved MS-like clinical symptoms via increased phagocytosis by *Trem2*-transduced myeloid cells, decreased expression of proinflammatory genes (*TNFα*, *IFNγ*, and *IL-1β*), and increased expression of anti-inflammatory *IL-10* [95]. It is important to note that the *Trem2*-transduced myeloid cells injected into healthy mice showed no signs of activation, and activated cells in the EAE-diseased mice were localized to the inflammatory lesions in the spinal cord [95]. A more recent study of APPswe/PS1dE9 mice demonstrated that lentiviral overexpression of *Trem2* in the brain ameliorated AD-associated neuropathology and cognitive function [62].

Of some concern are the seemingly conflicting results of different studies that suggest TREM2 may enhance inflammatory response or TREM2 reduces inflammatory response. Some researchers suggest that the different cell types expressing TREM2 may influence these different responses [32]. Studies of TREM2 expressed on macrophages or microglia suggest that TREM2 ameliorates the inflammatory response [95–98], whereas studies of dendritic cells suggest TREM2 exacerbates inflammatory response [32, 54]. This hypothesis is plausible considering the roles of these cell types in the innate immune system (macrophages) and the adaptive immune system (dendritic cells). Additionally, microglia clearly play a bigger role in the CNS than that of simple immune cells; they are important for homeostasis, synaptic plasticity, and learning and memory [99–103]. Recent studies have demonstrated that TREM2 is important for microglial metabolism [104]; inhibition of TREM2 would disrupt all of the various microglial roles in the brain.

6. Expert Opinion

There are several factors to consider when developing TREM2-directed therapeutics. First, some argue that TREM2 may not be a broadly applicable therapeutic target for AD since the minor allele frequency of *TREM2* variants which confer a strong risk for developing AD are present in less than 1% of AD patients. However, extensive evidence has shown that neuroinflammation and immune response play a significant role in AD pathology and TREM2 is important in innate immunity. Thus far research has focused on overall *TREM2* expression levels or *TREM2* variants associated with AD risk; however, it is probable that variants in other genes influence TREM2 protein levels or activity, or disrupt other processes within the immune pathway. For instance, it has been shown that *TREM2* expression is disrupted by *TYROBP* mutations in the absence of *TREM2* mutations, suggesting that TREM2 may still be involved in disease in *TREM2* mutation non-carriers [31]. Therefore, although *TREM2* variants are present in a small number of AD patients, targeting TREM2 or other molecules in the same biological pathway will most likely be applicable for many AD cases whether they carry a *TREM2* mutation or not.

The timing of intervention will always be important when designing AD treatment. Cellular and animal models demonstrate that TREM2 deficiency has a changing role throughout the progression of AD, by reducing amyloid pathology early in disease but increasing amyloid accumulation later in disease [60, 63, 87]. These studies, combined with studies that show CSF levels of sTREM2 are significantly elevated in preclinical and early AD [24–26], suggest that trials using TREM2-directed therapies would probably be most successful in earlier stages of disease. However, this brings us to the question about what these TREM2-directed therapeutics would be designed to do.

It is important to understand how the identified *TREM2* variants increase AD risk. Most research has focused on TREM2 expression, with many groups studying *Trem2* knockouts. This approach may not be the best recapitulation of what happens in the presence of these TREM2 mutations. Some researchers concluded that their studies demonstrated there should be less TREM2 expression and some researchers concluded the opposite. Recent research suggests the answer isn't that simple. It is important to remember a few things here: 1. protein expression level does not represent protein activity; 2. there are at least two forms of TREM2 that may be important, the membrane-bound part of the receptor and the soluble form (which can result from cleavage or alternative splicing); and 3. just as microglia can be protective or damaging depending on the situation, TREM2 probably also has the potential to be protective or damaging. Therapeutics aimed at simply reducing or increasing TREM2 expression or activity are unlikely to be successful; it is more likely that effective treatment will focus within the pathways involving TREM2, targeting disrupted processes instead. Researchers very recently reported their findings from BAC transgenic *Trem*$^{-/-}$ mice expressing humanized common variant TREM2 or p.R47H mutant TREM2 crossed with 5XFAD mice [105]. They demonstrated that although shedding of sTREM2 was similar *in vitro*, sTREM2 was found on plaques and neurons in mice expressing WT *Trem2* but not in the mice expressing p.R47H [99]. They also reported that plaque-induced microgliosis was impaired in the p.R47H mice, suggesting that sTREM2 interacts with plaques and may be important for microglial response to amyloidosis [99]. More research is necessary to

determine what role, if any, sTREM2 has in AD pathology and experiments need to be carefully designed to truly model the *TREM2* variants associated with AD risk to better understand their influence on disease.

Therapeutics targeting TREM2, are unlikely to be simple drugs administered orally or injected. If the hypothesis that TREM2 acts differently on the different cell types is correct, not only will interventions need to cross the blood brain barrier, but they will have to be highly specific. Results from the earlier study by Takahashi et al., where they injected myeloid precursor cells expressing wild-type *Trem2* into the EAE mouse model for MS, suggest that cell-based therapeutics may be a viable option [95]. Still in its infancy, cell-based therapies for AD have been discussed by researchers over the past few years, primarily focusing on the potential of using induced pluripotent stem cells (iPSCs) to replace lost neurons and the numerous pitfalls and limitations for these methods [106, 107]; however, other researchers have discussed the potentials for glial cell-based therapies as potentially safer alternatives [108]. We think that utilizing gene therapies to introduce properly functioning microglia early in disease is more likely to be successful than attempting to replace lost neurons using iPSCs after the damage has been done. Although a few potential treatments for AD have reached human clinical trials, more work will be necessary to identify therapies to effectively halt or slow disease progression. Extensive evidence suggests that successful AD treatment will need to be administered early in disease, and research has been underway to identify preclinical or prodromal AD. Studies thus far indicate that a combination of biomarkers and genetic risk scoring will provide the best predictive power to find presymptomatic patients who may benefit from treatment. Identification of these individuals will be invaluable for developing effective AD therapeutics.

AD research has progressively shown an important role of immune response and inflammation in disease pathology, so it is not surprising that TREM2 is such a promising target for early AD therapeutics. As we discuss in this manuscript, more research will be necessary to determine how TREM2 influences disease before we will know how to target TREM2 to effectively treat AD. Recent research has started to move in the right direction by studying specific AD-associated TREM2 mutations as well as the potential role of sTREM2. Results from these studies will prove valuable not only for developing TREM2-targeted therapeutics but for further understanding the underlying biology of disease and possibly revealing additional treatments.

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Article Highlights

- Vaccines targeting amyloid have reached phase 3 clinical trials but have currently shown little or no improvement in cognitive symptoms, leading researchers to search for alternative AD therapeutics.
- Since pathology appears years before cognitive symptoms, treatments for AD most likely need to be administered early in disease to be affective.
- TREM2 has been strongly associated with AD and plays a key role in innate immune response; however, the exact mechanisms are unclear. There is conflicting evidence about whether TREM2-targeted therapeutics should enhance or downregulate expression of TREM2.
- Context is important for understanding the role of TREM2 in AD; microglial activation state, presence of amyloid-mediated or tau-mediated pathology, and acute vs chronic injury can all have different effects that can be beneficial or harmful.
- Most research to-date has explored *Trem2* knockout/knockdown; however, it has been demonstrated that different *TREM2* mutations associated with disease influence sTREM2 levels differently. More research using transgenic models studying identified TREM2 mutations is necessary.

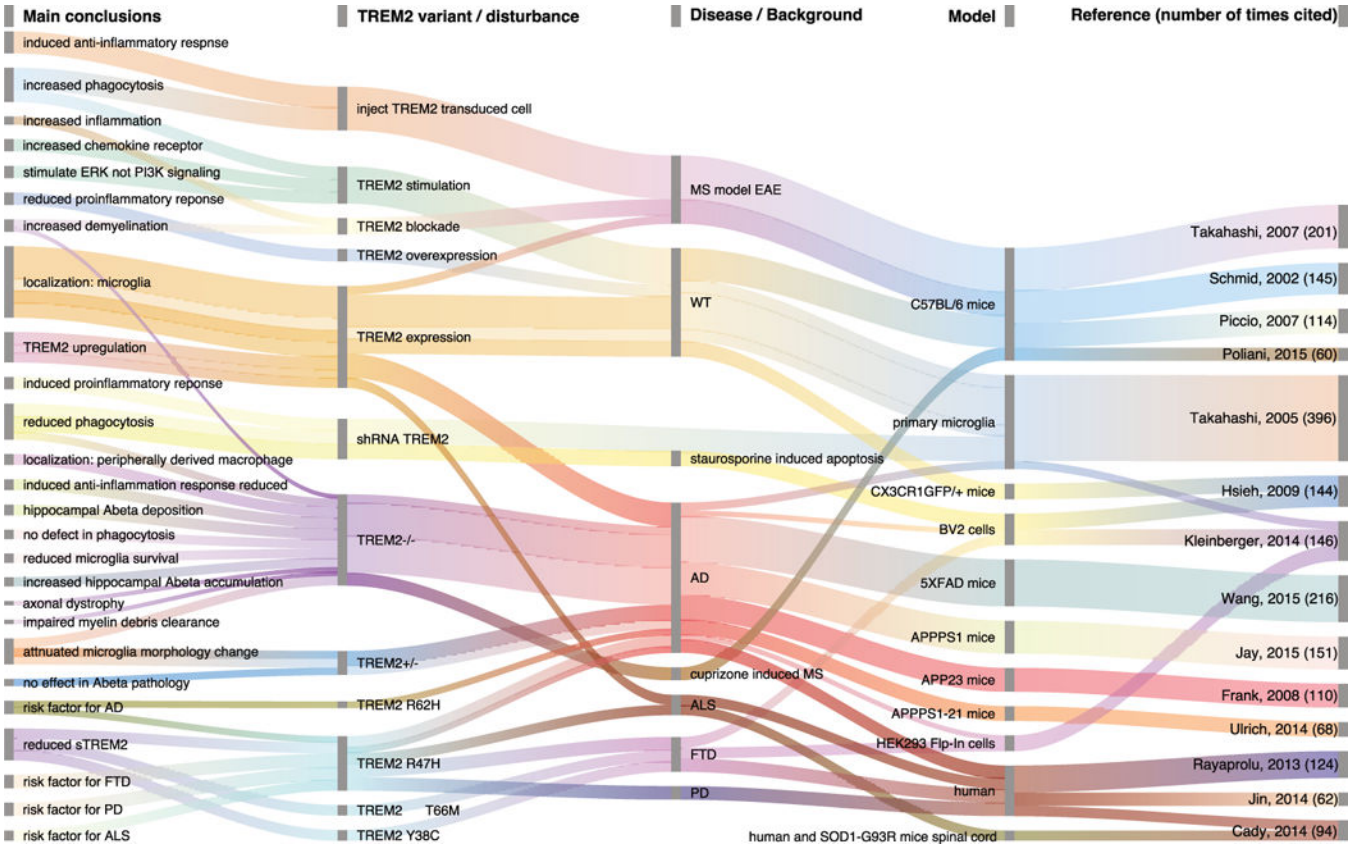

Figure 1.

Sankey plot depicting the 14 most cited articles in a literature review of TREM2 and microglia research. Columns show the main conclusion, related TREM2 variants or disturbance, disease background, research model, and reference (the number of times the reference was cited at time of literature review is in parentheses). Wavy lines depict the main conclusions that were reported in different studies and the different conclusions reported in one reference.

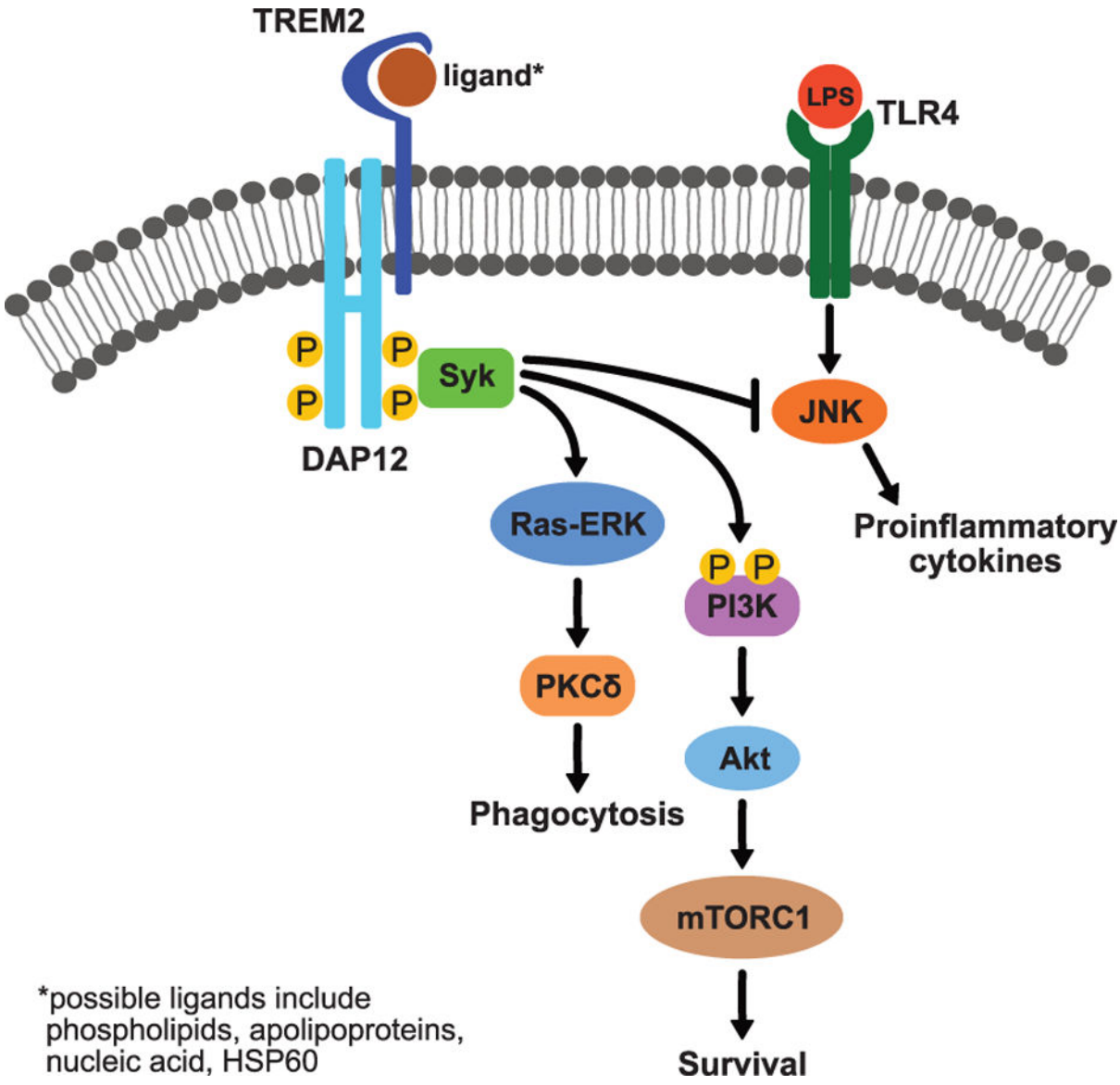

Figure 2.

TREM2 molecular signaling in microglia, initiating phagocytosis and microglial survival or modulating proinflammatory response, is not well characterized so only validated components are displayed. *In vitro* studies have suggested possible ligands for TREM2, which bind TREM2 to initiate signaling. TREM2 associates with DAP12, which is phosphorylated to activate signaling through recruitment of spleen tyrosine kinase (Syk). Syk activates the Ras/extracellular signal-regulated kinase (ERK)/protein kinase C (PKC) pathway to initiate phagocytosis. Microglial survival is initiated by the activation of the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin complex 1 (mTORC1) pathway. TREM2 is thought to influence inflammatory response by inhibiting the c-Jun N-terminal kinase (JNK) pathway which can be activated when ligands like lipopolysaccharide (LPS) bind toll-like receptor-4 (TLR4), initiating the production of proinflammatory cytokines.

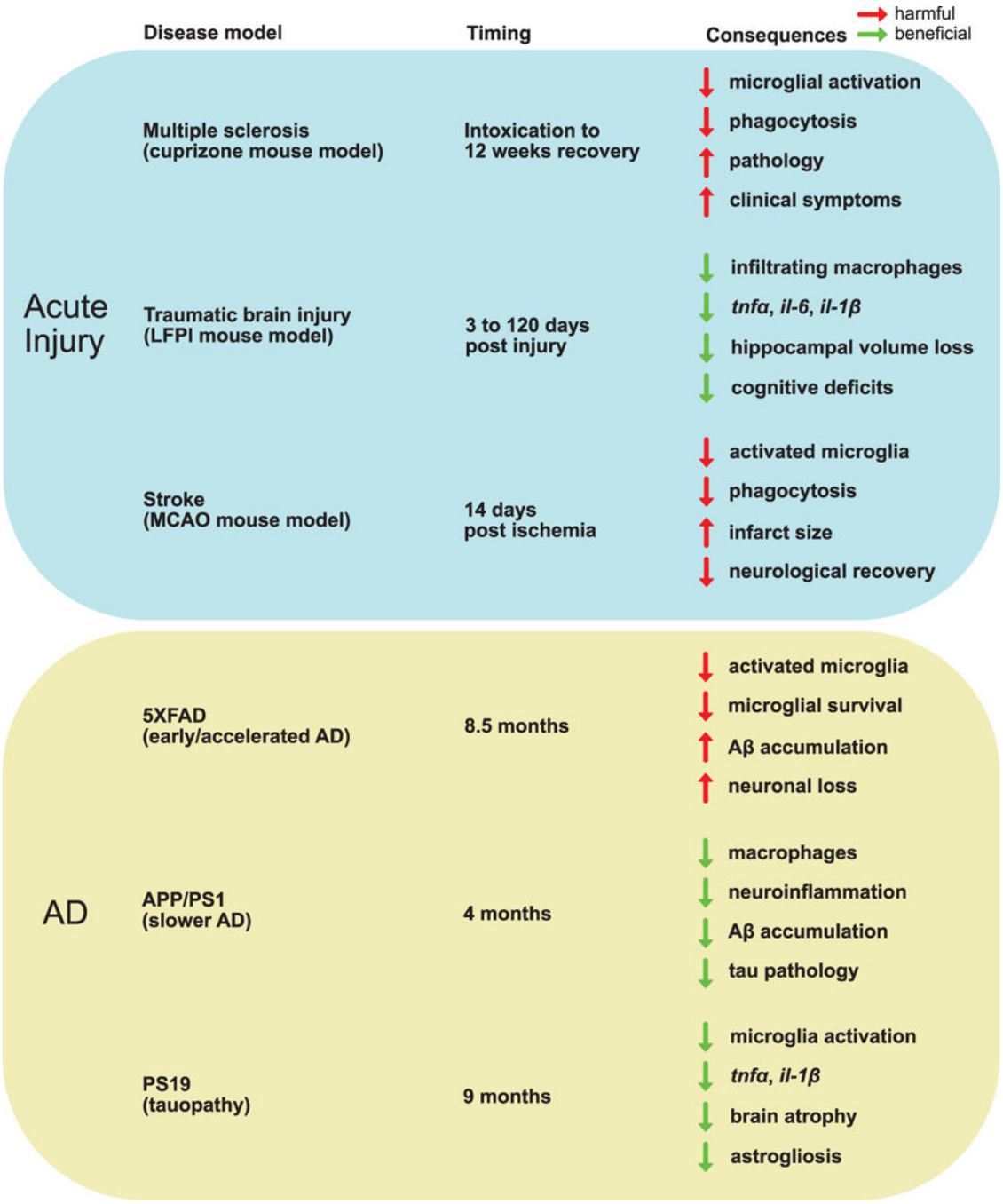

Figure 3.

Summary of key findings in TREM2 knockout models. The top box (blue) shows three studies representing acute injury: a cuprizone intoxication mouse model for demyelination observed in multiple sclerosis (Cantoni et al, 2005), a lateral fluid percussion model for TBI (Saber et al, 2017), and an experimental stroke mouse model using permanent MCAO (Kawabori et al, 2015). The lower box (yellow) shows three studies of AD mouse models crossed with *Trem2−/−* representing different disease pathology: the 5XFAD mouse model which develops cognitive deficits and amyloid accumulation by 6 months (Wang et al,

2015), the APP/PS1 mouse model which develops amyloid accumulation 6–9 months and cognitive decline by 12 months (Jay et al, 2015), and the PS19 mouse model which is a model for tauopathy and has no amyloid pathology (Leyns et al, 2017). The timing column represents when the researchers observed the consequences/effects shown in the right-hand column, which represents the difference in effect of *Trem2−/−* compared to WT. The arrows represent whether the effect on the described observation to the right of the arrow is increased (pointing up) or decreased (pointing down) and the arrow color represents whether the effect is considered harmful (red) or beneficial (green).

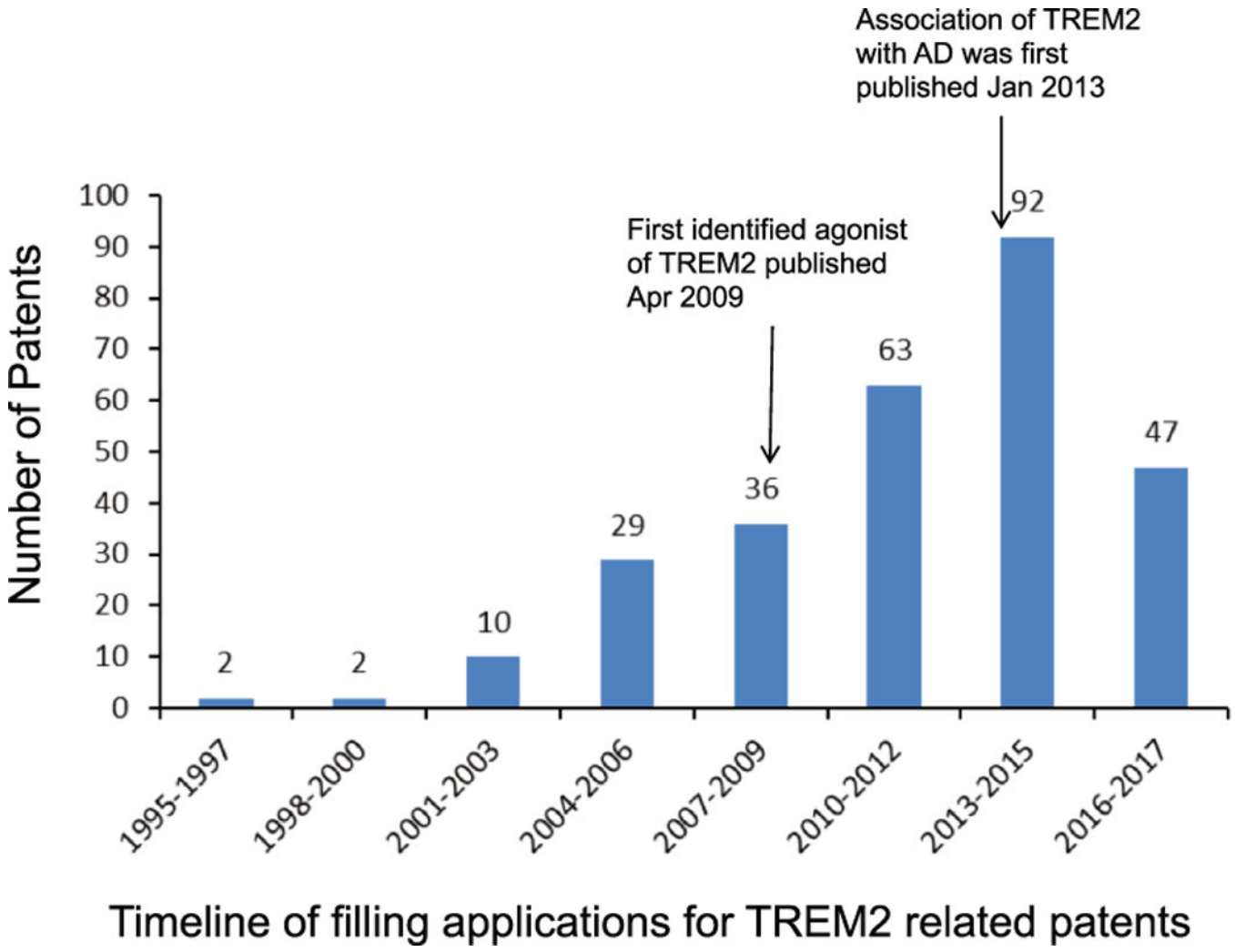

Figure 4.

The number of TREM2-related patent applications every 2 years starting from 1995, which was the oldest record found, to near the end of 2017. Found in a Google Patents (https://patents.google.com) search performed on 15 November 2017. Numbers at the top of each bar are the number of patents reported within the 2-year span.