Fighting fire with fire: the immune system might be key in our fight against Alzheimer's disease

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Abstract

The ultimate cause of Alzheimer's disease (AD) is still unknown and no disease-modifying treatment exists. Emerging evidence supports the concept that the immune system plays a key role in AD pathogenesis. This awareness leads to the idea that specific parts of the immune system must be engaged to ward off the disease. Immunotherapy has dramatically improved the management of several previously untreatable cancers, and could hold similar promise as a novel therapy for treating AD patients. However, before potent immunotherapies can be rationally designed as treatment against AD, we need to fully understand the dynamic interplay between AD and the different parts of our immune system. Accordingly, here we aim to review the most important aspects of both the innate and adaptive immune system in relation to AD pathology.

Short Summary

Emerging results support the concept that Alzheimer's disease is affected by the inability of the immune system to contain the brain's pathology. Here, we give a vision on how we can engage our immune system to fight this devastating disease.

Keywords

Alzheimer's disease; immune system; immunotherapy; innate immune system; adaptive immune system

Background

Alzheimer's disease (AD) is a devastating age-related neurodegenerative disorder which is characterized by the progressive and disabling deficits in cognitive functions, ultimately leading to impairment in daily life quality.[1] Worldwide, nearly 50 million people have AD or related dementia and it is estimated that this number will triple by 2050.[2] Moreover, the current estimated worldwide cost of dementia is 1 trillion US dollars a year, which is expected to double by 2030. The speed of disease progression is subjective to individual variability but AD is ultimately fatal.[3] Altogether, this makes AD a very burdensome disorder for patients, their family, caretakers and the health care system as a whole.[4]

Together with severe neuronal loss, it has been known for decades that typical characteristics of AD are the deposition of amyloid-beta (Aβ) peptides into senile plaques outside neurons and the formation of neurofibrillary tangles (NFT) composed of hyperphosphorylated Tau (p-Tau) protein inside neurons.[5] Importantly, over the past decade, it became increasingly clear that also neuroinflammation is an important early event in AD progression.[6,7] The steady progress in the understanding of the etiopathogenesis has led to the evaluation of therapies aiming to reduce pathological aggregates of Aβ and/or p-Tau or aiming to reduce neuroinflammation. Unfortunately, none of these strategies has led to clinical success.[8-13] As the number of AD patients is rising every year, we urgently need to rethink our way of designing novel therapeutic approaches to combat AD. This strategic shift can start with a better understanding of the interplay between our immune system and AD pathology.

As a person's age increases, so declines the overall immune system. This is exemplified by the weaker response to vaccination of elderly compared to younger individuals and increasing instances of disease and infection in elderly.[14] Since ageing is the primary risk factor for AD, a common theme in AD patients is a dysfunction of the immune system. Moreover, genome analyses link DNA variants in genes involved in the immune system to heightened Alzheimer's risk.[15,16] The lab of Michal Schwartz showed that progression of AD is associated with local suppression of immune cell trafficking to the central nervous system (CNS) via the choroid plexus.[17,18] Moreover, boosting monocyte-derived macrophage recruitment to sites of brain pathology is effective in arresting the disease in AD animal models.[19,20] This newer wave of results initiated the idea that the immune system might be key in our fight against AD. Consequently, research started looking into attempts to revive or modulate the body's own immune-based mechanisms. So far, this has mainly been focused on antigen-specific approaches, namely active and passive immunization. Next to these antibody-based immunotherapies, also other types of immunotherapy targeting other aspects of the immune system are recently being (pre)clinically evaluated. Immunotherapy is a powerful treatment approach that holds considerable promise for the future. This type of therapy has dramatically improved the management of several previously untreatable cancers[21], and it may similarly hold promise as a novel therapy to treat AD patients. However, before we can design powerful immunotherapies as treatment against AD, we need to fully untangle the interplay between the different facets of our immune system and AD pathology. In this review, we look into the dynamics of the innate as well as the adaptive immune system in relation to AD pathology. Moreover, we give a vision on how these new insights can form the basis of new AD immunotherapy approaches. We use the term

immunotherapy in the broad sense of the term. Meaning that we discuss all type of substances that stimulate or suppress the immune system in order to restore the ability of our body to fight against Alzheimer pathology.

The innate immune system and AD pathology

Over the past decade, it became clear that several innate immune pathways are involved in AD pathogenesis. Furthermore, multiple studies on AD patients have shown that neuroinflammation is not merely a response to pathological events, but that it significantly contributes to and exacerbates AD pathogenesis.[22]

The first evidence comes from ***post mortem* studies** on the brain and cerebrospinal fluid (CSF) of AD patients. It has been known for decades that clusters of reactive microglia and astrocytes accumulate in the brain of AD patients, particularly in the vicinity of Aβ plaques and NFTs.[23,24] Interestingly, astrocytic and microglial activation can precede Aβ deposition[25] and inflammatory changes can already be detected in the CSF of patients with mild cognitive impairment (MCI)[22], indicating that neuroinflammation is an early event in the disease course. Furthermore, the levels of pro-inflammatory mediators (e.g. cytokines, chemokines and complement proteins) are increased in the brain and CSF of AD patients.[26,27] Several of these studies were validated by protein and gene expression analyses, confirming the activation of inflammatory pathways in AD. For example, a comparative gene expression analysis of hippocampal samples from AD patients and healthy controls demonstrated that several pro-inflammatory mediators, such as COX-2, NF-κB, and interleukin (IL-) 1 precursor, were among the top upregulated genes.[28] Another large-scale study on *post mortem* brain tissues from late-onset AD patients highlighted an upregulated innate immune gene regulatory network as most highly associated with AD pathophysiology.[29]

Secondly, **epidemiological studies** have shown that several lifestyle events with an associated inflammatory component, *e.g*. systemic infection and obesity, increase the risk of AD development.[25] Conversely, long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) is linked to a reduced risk of AD.[30,31] NSAIDs generally inhibit cyclooxygenase 1 and/or 2, which are key inducers of inflammation via prostaglandin synthesis, but have many off-target effects. In addition, it has *e.g.* been demonstrated that NSAIDS can directly affect amyloid pathology by decreasing the levels of the 42 amino acid form of Aβ ($A\beta_{42}$).[32] Although numerous NSAID compounds have displayed efficacy in AD mouse models[31], large-scale clinical trials have failed to demonstrate a positive therapeutic effect or were too variable to be conclusive.[22] However, different reasons can explain their failure. Amongst others, the timing (*e.g.* pre-symptomatic or symptomatic patients), dosing and specificities of the administered NSAIDs could be inadequate.[26] Moreover, it is plausible that more specific anti-inflammatory pathway interference is needed than that by NSAIDs.[22]

Finally, **genome-wide association studies (GWAS)** conducted in large cohorts of AD patients and controls identified single-nucleotide polymorphisms and rare coding variants in genes implicated in innate immunity. More specifically, variants in the gene encoding complement receptor 1 (*CR1*), the main receptor for complement protein C3b, are associated with an increased AD risk.[33] Furthermore, the *CD33* locus has been identified as a risk factor for AD.[34] CD33 is a surface receptor expressed on microglia and other myeloid cells that has been shown to suppress pro-

inflammatory cytokine production, thus regulating innate immune responses. *TREM2* is another AD-susceptibility locus, as the rare R47H variant allele is associated with a two- to threefold higher predisposition to AD.[35] TREM2, short for 'triggering receptor expressed on myeloid cells 2', is expressed on microglia where it modulates inflammatory signaling and cell survival. In addition, it is thought that TREM2 has a role in suppressing Aβ oligomers (AβO) induced neurotoxicity.[36] Notably, it was recently shown that higher inflammatory reactivity is associated with the Apolipoprotein-E (ApoE) ε4 allele, the strongest genetic risk factor for AD, but the mechanism to this link is poorly understood.[36]

Next to the *post-mortem*, epidemiological and genetic studies on AD patients described above, a fourth line of evidence comes from experimental data from pre-clinical models where genetic or pharmacological manipulation of immune pathways impact AD pathology, which will be discussed further below. Taken together, increasing evidence underlines a key role for the innate immune system in AD development and pathology. These findings underscore the necessity for a finely tuned innate immune activation that can be achieved by a moderate and time dependent activation of different parts of the innate immune system. Below, we dig deeper into the current knowledge of different parts of the innate immune system and their effect on AD pathology. More precisely, we discuss the role of different pro-inflammatory cytokines, with a focus on tumor necrosis factor (TNF) and interleukin (IL-) 1, the complement system (**Figure 1**) and different innate immune cells (microglial cells,, granulocytes and dendritic cells (DCs)) (**Figure 2**). In table 1 and table 2 we give an overview of the discussed preclinical and clinical studies respectively. Although, we place the following cytokines under the innate immune system, we note that they can also be derived from the adaptive immune system.

Pro-inflammatory cytokines

A) TNF

The role of TNF in AD. TNF is a pleiotropic cytokine that was originally identified as a serum factor able to necrotize certain tumors.[37] It is a very potent pro-inflammatory protein that exerts an extreme spectrum of biological activities, with major roles in cell proliferation, differentiation, apoptosis, the acute phase response, fever and inflammation.[38] Importantly, multiple studies indicate that TNF is a key mediator in AD. The initial indication for this hypothesis was the elevated presence of TNF in the plasma, in the CSF and in proximity of Aβ plaques in the brains of AD patients.[39-41] Moreover, TNF serum levels of AD patients are associated with an increased rate of cognitive impairment, with up to a tenfold increase in decline rate in patients with high TNF levels compared to those with low baseline levels.[42] Evidence for the contribution of TNF in AD has also been provided by studies on different AD mouse models. Consistent with the findings in human AD patients, TNF levels in the CSF and around Aβ plaques are elevated in Tg2576[43], APP/PS1[44] and 3xTgAD mice[41]. It was demonstrated that TNF production is one of the earliest events after intracerebroventricular (icv) $A\beta_{40}O$ injection and that this further exerts neuronal damage by upregulation of inducible nitric oxide synthetase.[45] TNF was also identified as the upstream regulator of gene expression differences between AD patients and age-matched controls.[46] Moreover, TNF induces neurotoxicity via stimulation of microglia to release neurotoxic glutamate[47] and increase amyloidogenic processing of the Aβ precursor protein

(APP) in astrocytes.[48] Besides its (neuro)inflammatory roles, TNF has several physiological functions in the brain, including preservation of synaptic strength[49], modulation of synaptic scaling[50] and regulation of blood-brain barrier (BBB) permeability[41]. Thus, low levels of TNF are required for normal physiological functioning of the brain, whereas TNF concentrations that exceed the upper limit of the homeostatic range are believed to be neurodegenerative.[51]

TNF as therapeutic target. Chronic administration of a TNF-lowering agent (3,6'-dithiothalidomide) was shown to reduce multiple pathological hallmarks and memory deficits in 3xTgAD mice[52], supporting a role for TNF in disease progression. Moreover, *ex vivo* treatment of Tg2576, 5xFAD, and $A\beta_{42}$-treated wild-type mouse hippocampal slices with the TNF-inhibitor infliximab was shown to restore long-term potentiation (LTP) impairment.[53] Infliximab administration was also show to reduce the level of Aβ plaques, Tau phosphorylation and TNF in the APP/PS1 mouse model.[54] Another study showed that icv injection with an anti-TNF antibody rescues memory impairment induced by icv injection of $A\beta_{40}O$ in mice.[55] Moreover, blocking TNF/TNFR1 signaling using a TNFR1 blocking single domain antibody led to a reduction of the detrimental AβO effect upon icv injection in mice.[46] Contrarily, TNF overexpression exacerbates AD pathology both in 3xTgAD[56] and 5xFAD mice.[57] Finally, global genetic ablation of TNF signaling in 3xTgAD mice exacerbated pathogenesis[58], arguing against the therapeutic potential of TNF inhibitors in AD.

Next to the above preclinical evaluation of TNF as therapeutic target, different clinical studies in this regard were conducted or are ongoing. In 2006, a first prospective, single-center, open-label, pilot study was performed in which 15 patients with mild-to-severe AD were given the TNF blocker etanercept for 6 months via weekly perispinal administration.[59] Compared to the standard cognitive impairment expected in AD over 6 months, the study showed a significant improvement in three standard cognition measurements. One patient with late-onset AD even showed rapid cognitive improvement within minutes after administration.[60] Although encouraging, these results should be interpreted with care due to the limited study size, lack of blinding, and absence of placebo controls. Secondly, a nested-control study showed that anti-TNF therapy for rheumatoid arthritis is associated with a lower relative risk of AD[61], suggesting that lowering the neuroinflammatory TNF response could be beneficial for AD. Strikingly, a similar result was seen in a recent large scale retrospective case-control study of electronic health records from 56 million patients, in which the association between treatment with a TNF blocking agent and AD risk was examined.[62] More specifically, the study showed that inflammatory diseases involving TNF, such as rheumatoid arthritis and psoriasis, are associated with increased risk for AD, whereas treatment with an anti-TNF biologic, protein-based drug (further termed biological) was correspondingly associated with a decreased AD risk. Finally, a 2015 phase 2 trial on the effect of weekly subcutaneous injection of etanercept over a 24 week period showed that the drug is well tolerated in AD patients.[63] However, none of the cognitive, functional, and behavioral outcomes were statistically different between the etanercept and placebo group. Possible reasons for this outcome are the small sample size of the study, incapability of etanercept to cross the BBB, or the actual inefficiency of etanercept against AD.

One possible factor contributing to the divergent results of preclinical and clinical data is that cellular TNF responses are induced by binding to two distinct transmembrane receptors, namely TNF receptor 1 (TNFR1) and TNFR2.[64] For both receptors, binding of TNF leads to receptor

trimerization and recruitment of protein complexes to their intracellular domains. However, since TNFR1 contains an intracellular death domain whereas TNFR2 does not, their trimerization induces distinct signaling cascades and cellular responses.[65] In general, triggering TNFR1 leads to pro-inflammatory and neurotoxic activities, whereas activation of TNFR2 has homeostatic, immunomodulatory and neuroprotective roles. Accordingly, a more selective TNF counteracting approach might be more desirable for the treatment of AD. [41,66] This is exemplified by a study on brain samples from AD patients that demonstrated increased TNFR1 and decreased TNFR2 levels compared to non-demented brains.[67] Moreover, knock-down of TNFR2 in 3xTgAD mice results in TNFR1-mediated exacerbation of pathology[68], and this was confirmed by genetic deletion of the *Tnfr2* gene in APP23 mice[69]. In line with this, another study demonstrated that $A\beta_{40}$ induces neuronal apoptosis through TNFR1 signaling.[70] TNFR1 signaling is also described to increase the enzymatic generation of Aβ peptides by increasing the levels and activity of BACE1.[71] Conversely, TNFR2 but not TNFR1 is critical for nerve remyelination mediated by oligodendrocytes[72] and protection against glutamate-induced neurotoxicity.[73] Importantly, recent research has shown that signaling through TNFR1 is a key pathway contributing to neuroinflammation in two AD mouse models.[46] Furthermore, TNFR1 deficiency ameliorated amyloidosis and rescued the mice from induced cognitive impairments. Specific blocking of the TNF/TNFR1 axis has also been shown beneficial in other studies.[71,74,75] Strikingly, treatment of human TNFR1 (hTNFR1) transgenic AD mice in a mouse TNFR1 (mTNFR1) deficient background with an anti-hTNFR1 biological recapitulated the effects of TNFR1 deficiency.[46]

Last year, INmune Bio conducted a phase 1b open-label clinical trial of XPro1595 in patients with mild to moderate AD with elevated blood levels of the inflammatory biomarker CRP (NCT03943264). XPro1595 is a second-generation biological that sequesters soluble TNF without blocking signaling by transmembrane TNF through TNFR2, thus specifically inhibiting the TNF/TNFR1 axis. In January 2021, the company announced in a press release that the drug was well tolerated, decreased multiple neuroinflammatory markers in the CSF and, notably, led to significant changes in multiple AD-related pathways.[76] A following blinded, randomized, placebo controlled phase 2 trial can be expected in the coming year.

Taken together, blocking TNF or more specifically TNFR1 holds promising therapeutic potential against AD.

B) IL-1

The role of IL-1 in AD. IL-1β is a master cytokine of local and systemic inflammatory responses which was originally described in the 1940s as 'the endogenous pyrogen' due to its pronounced property to induce fever.[77] Subsequently, it was revealed that two forms of IL-1 exist: IL-1α and IL-1β. Whereas IL-1α remains mostly membrane anchored and functions in this way through autocrine or juxtracrine cell-to-cell signaling, IL-1β is secreted and acts in a paracrine or systemic manner.[78] Despite their different characteristics, both cytokines have identical biological activities, exerted by binding to IL-1 receptor type I (IL-1R). From here onwards, we will use IL-1 when both α- and β- forms are applicable. The initial evidence for a role of IL-1β in AD was mainly based on the increased concentration of this cytokine in the serum, CSF and *post mortem* brain of AD patients.[40,79,80] Moreover, AD patients show an increased expression of IL-1α in activated microglia and astrocytes, and this is regionally correlated with the distribution of Aβ plaques and Tau deposits.[81,82] Another study reported decreased intrathecal levels of IL-1R antagonist (IL-

1RA), suggesting a propensity towards IL-1 mediated neuroinflammation in AD patients.[83] Increased IL-1α and IL-1β levels have also been observed in the brain and CSF of several AD mouse models.[44,84,85] Furthermore, two studies demonstrated that the NLPR3 inflammasome is activated in and contributes to AD pathology[86] and Tau aggregation[87]. The NLPR3 inflammasome activates caspase-1 leading to downstream IL-1β release. This inflammasome has also been shown to mediate Aβ-induced secretion of IL-1β.[88] The same study demonstrated that IL-1β is essential for the microglial production of pro-inflammatory and neurotoxic factors, and the recruitment of microglia to Aβ plaques. Likewise, research has shown that AβO promote maturation of pro-IL-1β in microglia, which further enhances microglial neurotoxicity.[89] However, IL-1R signaling also plays a role in non-inflammatory brain functions. For example, IL-1β is involved in spatial memory[90], and modulates LTP in the hippocampus, a process considered to underlie certain forms of learning and memory.[91,92] Conversely, the buildup of IL-1β in the brain compromises LTP by the stimulation of mitogen-activated protein kinases and the disruption of brain-derived neurotrophic factor signaling.[93,94] Based on these data, it is likely that small amounts of IL-1β are required for physiological brain functioning, whereas an excess of IL-1β as occurs in AD leads to neurotoxicity and impairments in memory.

IL-1 as therapeutic target. Striking evidence for the therapeutic potential of IL-1 blockade comes from a 2011 study showing that chronic treatment of 3xTgAD mice with an IL-1 receptor blocking antibody rescues cognitive impairment, attenuates neuronal Tau pathology and partly reduces fibrillar and oligomeric Aβ disposition.[95] A similar result was seen in a recent study demonstrating that IL-1 blockade, either by IL-1R knockout or treatment with recombinant IL-1RA (anakinra), attenuates AβO-induced cognitive impairment and alterations in the levels of mitochondrial proteins.[96] In addition, the intrahippocampal injection of anti-IL-1β siRNA improves behavioral changes and neurodegeneration in 6 month old APP/PS1 mice.[97] Conversely, the slow release of IL-1β in the cerebral cortex increases immunoreactivity and hyperphosphorylation of Tau in rats[98], and the overexpression of IL-1β exacerbated Tau pathology and microglia activation in 3xTgAD mice.[99] Notably, the latter study also observed a reduction in Aβ load due to IL-1β overexpression, which the authors explain by microglial activation aiding in amyloid clearance. Other than that, pharmaceutical inhibition of upstream pathways of IL-1β, such as the NLRP3 inflammasome or caspase-1 activation, alleviates pathology in several AD mouse models.[100-106] Taken together, anti-IL1β therapy is surmised to be of potential benefit for treating AD.

As opposed to TNF, and despite the preclinical evidence for its involvement in AD pathology, no clinical trials that target IL-1β or its receptor have been described in the context of AD despite the availability of anakinra (Kineret®, Amgen Inc.), a recombinant, non-glycosylated human IL-1RA.[107] Since its approval for the treatment of rheumatoid arthritis in 2001, anakinra has been proven efficacious in a broad range of inflammatory diseases, such as gout and cryopyrin-associated periodic syndromes.[108] The drug owes its success to its safety, short half-life and good tissue penetration.[107] Of note, anakinra is able to enter the brain where it still exerts IL-1 inhibition after peripheral administration.[109] However, we note that this study was conducted in stroke patients, in which loss of BBB integrity has been described.[110,111] Accordingly, a large scale retrospective case-control study on the association between AD risk and anakinra treatment would be extremely valuable and could indicate whether or not a clinical trial is warranted.

C) Other cytokines

Although less extensively studied, other cytokines than TNF and IL-1β have also been implicated in AD. Importantly, the specific effects of these cytokines heavily depend on their levels, context and vary from patient to patient, indicating their multifunctional effects.[26]

The pro-inflammatory cytokine **IL-6** is increased in *post mortem* AD brains, and its signaling pathway is activated in the hypothalamus and hippocampus of APP/PS1 mice.[112] The same study showed that icv injection of an IL-6 neutralizing antibody alleviates memory impairment and metabolic alterations in this mouse model, suggesting that IL-6 may link cognitive decline and peripheral metabolic changes in the disease. The expression of the IL-6 cytokine is increased directly by Aβ, either by a direct or IL-β dependent mechanism.[113,114] The latter indicates that IL-6 could act as a secondary process that exaggerates the pro-inflammatory effects initiated by IL-1β.[115]

Also **IL-12/IL-23** signaling is crucially involved in amyloidosis and cognitive impairment, as genetic and pharmaceutical ablation of these cytokines has been shown to reduce amyloid burden and reverse cognitive decline.[116] Although the precise mechanisms of these cytokines in AD remain unclear, IL-12 blocking antibodies are an appealing candidate for an initial translational clinical trial, because of their clinical validation in other diseases such as Crohn's disease[117] and multiple sclerosis.[118]

Several data have shown that the multifunctional cytokine transforming growth factor beta **(TGF-β)** is upregulated in the CSF, serum and brain of AD patients.[119-121] TGF-β is also found in Aβ plaques and NFTs[122], and correlates with the degree of cerebral amyloid angiopathy in APP/PS1 mice and AD patients.[123] The multifaceted roles of TGF-β in AD have been reviewed in great detail elsewhere.[124] Briefly, it is hypothesized that microglia are altered by changes in brain TGF-β signaling in AD, triggering their pathogenic functions.[124,125] In addition, TGF-β was shown to facilitate Aβ fibrillogenesis in a TGF-β receptor-independent manner, indicating that increasing TGF-β may worsen AD pathology.[126] However, TGF-β signaling was also shown to exert protective effects on Aβ pathology[127,128], prevent Tau hyper-phosphorylation[129] and exert anti-inflammatory effects[130], suggesting that TGF-β could also be beneficial in AD.

Also type I and II interferons (**IFNs**) have been implicated in neuroinflammation in AD. In general, type I IFNs possess pro-inflammatory properties and are regarded as neurotoxic. For example, a recent study demonstrated that type I IFN signaling is upregulated in clinical AD. This is associated with amyloidosis and contributes to microglial activation and synapse elimination in several AD models.[131] A more extensive look on the neuroinflammatory and neurodegenerative roles of type I IFNs in AD can be found in the review of Taylor *et al*.[132] Despite the generally harmful effects of type I IFNs in AD, a double-blind, randomized, placebo-controlled, multicenter clinical trial was started in 2010 to evaluate the safety and efficacy of IFN-β1a (Rebif) administration in mild to moderate AD patients (NCT01075763). Strikingly, the study showed that the treatment was well tolerated and, although statistically not significant, resulted in a reduction in AD progression.[133] For IFN-γ, the majority of studies point towards a protective role of this type II IFN in AD. For instance, the intraperitoneal injection of IFN-γ in APP/PS1 mice decreases cognitive decline and Aβ accumulation, probably by restoring microglial autophagy.[134] Furthermore, IFN-γ overexpression was shown to enhance spatial learning and memory in old mice and the J20 AD mouse model[135], and suppress Aβ deposition through synergistic effects of activated glia,

complement upregulation and peripheral monocyte infiltration in TgCRND8 mice.[136] In addition, a study on Algerian AD patients revealed that IFN-γ plasma levels are decreased in moderate and severe AD patients compared to mild AD patients.[137] However, also opposing functions of IFN-γ have been described in AD. It has been shown that chronic intrahippocampal expression of IFN-γ increases the severity of Aβ pathology in 3xTgAD mice, while diminishing pTau pathology.[138] Another study suggested that release of IFN-γ from infiltrating T helper 1 cells accelerates disease marks, such as microglial activation, Aβ disposition and cognitive impairment, in APP/PS1 mice.[139] These seeming contradictions highlights our limited understanding of how type I and II IFNs function in AD.

Taken together, although the precise roles of these other cytokines are yet to be unraveled, it is clear that their modulation can influence disease progression, opening new therapeutic opportunities.

The complement system

The role of the complement system in AD. The complement system consists of a hub-like network that can be activated through the classical, lectin or alternative pathway. All three converge on the cleavage of the central complement protein C3, which may then lead to the formation of the membrane attack complex (MAC), enhancement of phagocytosis of the target via opsonization, and recruitment of immune cells by anaphylatoxins.[140]

Importantly, compelling evidence accumulates that complement activation occurs in AD. Multiple studies reported elevated levels of C3, C4 and C1q in the CSF and *post mortem* brains of AD patients[141-143], albeit with limited utility as diagnostic markers due to heterogeneity and narrow differences.[144] The C3 and C1q accumulation in AD brain tissue also correlates with Tau disposition.[145] Moreover, the protein levels of the complement defense protein CD59, which prevents MAC assembly, are significantly decreased in the hippocampus and frontal cortex of AD patients. Besides case-control studies measuring complement levels, additional support for complement involvement in AD is provided by GWAS. Polymorphisms in *CR1* (also known as *CD35*), the gene encoding for the main receptor of C3b and C4b, are associated with increased AD risk. This genetic linkage has been replicated in several independent datasets[33,146-150] and is linked with more rapid cognitive decline and increased amyloid plaque burden[147] and correlates with increased CSF Aβ levels[149]. A genetic follow-up in a Flanders–Belgian cohort suggested a duplication of an intragenic copy number variation that increases the number of C3b/C4b binding sites in CR1 as the explanation for the common AD risk association.[149,150] Finally, a tensor decomposition method of human monocytes and macrophages gene expression profiles found that AD-associated loci influence the expression of genes involved in complement.[151]

Multiple mechanisms how the complement system may play a role in AD have been put forward. In the 1990s, studies reported evidence of the binding of C1q with the Aβ peptide.[152-154] This binding may have dual pathologic significance, as it activates complement and promotes the aggregation of Aβ peptides. Furthermore, the binding of C1q to Aβ interferes with the phagocytosis of Aβ by microglia, either due to C1q-mediated enhancement of Aβ aggregation or steric hindrance of C1q with microglial Aβ receptors.[154,155] In addition, the E4 isoform of ApoEhas been implicated as a specific complement checkpoint inhibitor by high-affinity binding to C1q.[156] These C1q-ApoE complexes are observed in human AD plaques. Another study proposed a model where Aβ evokes astrocytic secretion of C3, leading to increased synaptic

excitation and disrupted dendritic morphology through C3/C3aR signaling and intraneuronal calcium dysregulation.[142] Importantly, the classical complement pathway has been shown to tag superfluous synapses for phagocytic clearance during development.[157] This process of synaptic pruning may become aberrantly reactivated in AD, leading to disrupted neuronal connectivity. Conversely, C3 and CR3 partake in microglial phagocytosis and clearance of fibrillar Aβ, indicating a possible benign role for the complement system in AD.[156] In addition, microglial C1q, together with IL-1α and TNF, induces a C3-producing A1 astrocytes, a subtype of reactive astrocytes that is abundantly present in the brain of AD patients.[158] Finally, complement has also been shown to interact with and be activated by Tau. Not only does Tau activate C1q through binding to the C1q A chain collagen tail antibody-independent binding site[159], it also induces microglial engulfment of excitatory synapses in a C1q-dependent manner.[145]

The complement as therapeutic target. A broad range of preclinical studies indicate the potential of complement modulation in AD. The absence of C1q in the APP and APP/PS1 mouse models has been shown to reduce the level of activated glia surrounding Aβ plaques, while total and fibrillar Aβ were unaltered.[160] Surprisingly, the decreased neuropathology in these C1q KO mice coincides with increased C3 levels, indicating both protective and detrimental roles of complement in the disease.[161] Likewise, administration of an anti-C1q antibody could prevent AβO - and Tau- induced synapse loss in wild-type and Tau-P301S mice, respectively.[145,162] Similar to C1q knockout mice, deficiency in the complement protein C3 ameliorates synapse loss and cognitive impairment in aged wild-type[163], young APP/PS1[162], and aged APP/PS1 mice[164], despite an increased Aβ plaque load in the latter. Thus, the classical complement pathway seems to mediate synapse loss early in AD pathogenesis and make neurons, particularly in the hippocampal CA3 region, more vulnerable to aging even in the abundant presence of Aβ plaques.[164] Moreover, C3 deletion has been shown to reduce plaque-associated synapse loss in the PS2APP mouse model and mitigate neuron loss and brain atrophy in Tau-P301S mice, improving cognitive impairment.[143] However, C3 deficiency in hAPP mice, either by genetic C3 knockout[165] or transgenic expression of the soluble complement receptor-related protein y (sCrry)[166], accelerated Aβ plaque deposition, neurodegeneration, and differential activation of microglia. This suggests that C3 activation can also protect against plaque accumulation and Aβ-induced neurotoxicity, arguing against complement inhibition as a potential therapeutic strategy. The conflicting results of C3 deficiency between APP/PS1 and PS2APP *versus* hAPP mice could be attributed to the presence of the mutant human presenilin gene in the former two. Nevertheless, it does demonstrate that not one pathway or complement protein is responsible for AD development, and that the effects are likely dependent on the timing, source, and level of activity. Therefore, targeting more downstream effector complement events, such as glial activation by anaphylatoxins, could prevent inhibition of protective complement effects. This is exemplified in a study where oral treatment of Tg2576 and 3xTg mice with the C5aR antagonist PMX205 resulted in substantial decrease of pathology and cognitive impairment.[167] Interestingly, a recent preclinical pharmacokinetic study of PMX205 in mice identified no detrimental effects of the compound and showed that repeated subcutaneous injection provides high BBB and blood-spinal cord barrier penetration, making this an ideal route for neurological diseases and clinical application.[168]

So far, no clinical trials targeting complement in AD patients have been reported. This can be attributed to the low amount of clinically approved agents that target the complement, and the inadequate insights in how complement activation contributes to AD pathogenesis. The design of effective therapeutic strategies that inhibit the detrimental events of complement, without perturbing protective functions, will require a better understanding of the exact role, source and interactions of each complement component in the disease.[169,170] With the increasing studies on the role of complement in neurodegenerative disorders over the past decade, this knowledge gap can be expected to close in the near future. Furthermore, the large quantities of complement compared to other mediator systems such as cytokines, and the high pharmaceutical tractability of C3aR and C5aR as G protein-coupled receptors, make the complement an attractive target for intervention in AD.[171] Of note, long-term complement modulation, as may be required for the treatment of a chronic disease such as AD, in elderly patients with a weaker immune system should be considered with caution.[170] However, increased infectious complications could be avoided by blocking terminal complement proteins downstream of C3. This is illustrated by the well-tolerated long-term treatment with the anti-C5 antibody eculizumab in patients with paroxysmal nocturnal hemoglobinuria .[172,173] Finally, Amyndas' peptidic complement inhibitor AMY-101 has successfully advanced to human studies, with good safety and tolerability profiles in a phase I study in healthy male volunteers (NCT03316521) and safe prolonged treatment in non-human primates.[174,175]

Innate immune cells

A) Microglial cells

The role of microglial cells in AD. Microglia are long-lived, resident macrophages that compromise approximately 10% of the CNS cell population. They are the primary immune surveillance cells for pathogens and cellular debris and are the main source of pro-inflammatory mediators in the brain. Moreover, microglia have physiological housekeeping functions, such as neuronal support, synaptic remodeling and maintenance of myelin homeostasis.[176] In the onset of AD pathology, oligomeric forms of Aβ are removed by microglia and microglial cells are recruited upon Aβ plaques formation.[177] Moreover, by forming a physical barrier, microglia prevent outward plaque expansion and in this way control plaque spreading, composition and toxicity.[178] However, chronically activated microglia produce proinflammatory cytokines, such as the above described TNF and IL-1β, that can induce neuroinflammation and neurotoxicity in the brain.[27] The phagocytic activity of microglia drops and the production of proinflammatory cytokines and neurotoxic molecules increases in the course of AD pathogenesis. Based on gene expression profiles, different activation states of microglial cells have been identified. This can explain the distinct roles of microglia in the development and progression of AD. More specifically, single cell RNA sequencing of the brain immune cells in 5xFAD mice uncovered a disease-associated microglia (DAMs) subtype that have the potential to restrict neurodegeneration. The study also showed that DAMs are located in proximity to AD plaques and that they are present in human AD *post mortem* brains.[179] Van Hove *et al.* made a single-cell atlas of mouse brain macrophages and showed that the appearance of brain macrophages strongly vary depending on their anatomical niche. [180]

Recently, large-scale GWAS made clear that the risk of developing late-onset AD is increased in persons with rare variants of certain immunoreceptors expressed in microglia, such as CD33g[181] and TREM2.[35,182] As described above, TREM2enables microglia to mature to a DAM profile and ultimately sustaining the microglial response to Aβ plaque-induced pathology. The R47H variant of this latter protein blunts binding with its ligand and is linked with an approximately threefold increased risk of AD.[183] Moreover, overexpression of TREM2 by microglia improves cognitive decline in mouse models of AD[184] and an altered TREM2 function decreases microglial response to Aβ plaques and consequently neurodegeneration and plaque deposition.[185]
The above findings indicate that genetic polymorphisms of microglial immunoreceptors add to the onset and/or progression of neurodegeneration. This makes microglia potential target cells for therapeutic interventions. However, the exact contribution of the different reactive microglia subtypes to AD is currently unclear and subject of intense researches.[22] This discordance is recently nicely reviewed by Tejera et al.[23]

Microglial cells as therapeutic target. From a therapeutic view, a potential approach is to shift the inflammatory state of microglia from an inflammatory M1 state to a phagocytic M2 phenotype. Zhang *et al.* showed that jujuboside A, an anti-inflammatory drug component, inhibits abnormal activation of microglia and enhance microglial uptake of $A\beta_{42}$ and cognitive decline in APP/PS1 mice.[186] Next, also other anti-inflammatory drugs (a.o. metformin and 5-aryloxypyrimidine) have shown to, among others, suppress the inflammatory microglial functions and improve cognitive functioning in mouse models of AD.[187,188] The inflammatory state in microglia can also be controlled by interfering with the transcription factor NFAT: APP/PS1 mice that lack the NFATc2 isoform show less cytokines and lower amount of severe microgliosis compared to normal APP/PS1 mice.[189]
Wang and colleagues interfered with TREM2 expression on microglial cells. For this, they used a mouse model that expresses the common or the R47H variant of TREM2 and tested the effect of an anti-human TREM2 agonist monoclonal antibody (AL002c).[190] The authors were able to show microglial proliferation upon systemic administration of the monoclonal antibody. Moreover, prolonged administration reduced filamentous plaques and neurite dystrophy, impacted behavior, and tempered microglial inflammatory response.[190]
An alternative way of tackling the detrimental effect of microglial cells is by cell-based therapies in which the proinflammatory microglia are replaced with genetically edited autologous or allogeneic microglial cells. Similar strategies are nowadays used in the onco-immunotherapy field as recently reviewed by Anderson *et al.[191]* Danielyan and colleagues tested the intranasal delivery of bone marrow-derived mesenchymal stem cells, macrophages, and microglia to the brain in the APP/PS1 model of AD.[192] Although additional work is needed, they could show that the procedure led to effective microglia delivery to the brain in naive BL/6 mice. Another study transplanted adipose-derived mesenchymal stem cells into the hippocampus of APP/PS1 mice via an automated infusion pump and could show a reduction in Aβ deposition and restored learning function. [193] A possible explanation for the beneficial effects of mesenchymal stem cells is that these cells limit the expression of proinflammatory factors and up-regulate expression of alternative activation markers and Aβ-degrading enzymes by microglial cells. Moreover, increased levels of Aβ degrading enzymes, more specifically matrix metalloproteinase 9 and insulin-degrading enzyme, and the anti-inflammatory cytokines IL-10 and TGF-β, and reduced levels of

the pro-inflammatory cytokines IL-1β and TNF were detected in mesenchymal stem cell-injected mice compared to control mice. Furthermore, mesenchymal stem cell treated mice had lower level of Aβ plaques and were better at spatial learning than untreated mice.[194]
So far, only preclinical studies have been performed that target microglia in order to alter AD development. Only one phase 2 clinical trial (NCT04592874) has been submitted to clinical.gov and this trial is enrolling 265 patients with early AD since end 2020 to evaluate efficacy and safety of AL002, a monoclonal antibody that binds to the microglial receptor TREM2 and activates signaling.
Next, also metabolic reprogramming of activated microglia can be a possible therapeutic avenue. In the onco-immunotherapy field, metabolic reprogramming of tumor-associated macrophages is already in a more advanced stage as recently reviewed by Puthenveetil *et al.[195]* In macrophages in general, pro-inflammatory stimuli induce a metabolic switch from oxidative phosphorylation to glycolysis, a phenomenon similar to the Warburg effect well characterized in tumor cells. Recently, Baik and colleagues showed that the exposure of microglial cells to Aβ results into acute microglial inflammation that is accompanied by metabolic reprogramming from oxidative phosphorylation to glycolysis.[196] This shift in metabolism depends on the mTOR-HIF-1α pathway. Once activated, microglia reach a chronic tolerant phase as a result of broad defects in energy metabolisms and subsequently diminished immune responses, including cytokine secretion and phagocytosis. Moreover, the same authors showed that metabolic boosting with recombinant interferon-γ treatment reversed the defective glycolytic metabolism and inflammatory functions of microglia, thereby mitigating the AD pathology of 5xFAD mice. Lauro *et al.* recently nicely reviewed the metabolic reprogramming of microglia upon inflammatory triggers and the effect on the regulation of the innate inflammatory response.[197] Taken together, modulating metabolism of microglial cell might be a new therapeutic strategy for AD.
To make the step to clinical test microglial targeting therapies, it is of utmost importance to better understand the role of the different disease-specific microglial phenotypes during AD pathology. This knowledge is necessary to design an immunotherapy that boosts or tempers the right microglia type depending on the precise disease stage.

B) Infiltrating innate immune cells

Next to microglial cells, also peripheral innate immune cells can regulate the inflammatory status of the brain by infiltrating from the periphery into the CNS. Vascular inflammation and a dysfunctional BBB and blood-CSF barrier have been reported in AD pathology.[198,199] Blood-derived leukocyte populations are reported in the brains of AD animal models and patients.[200-203] The role of innate immunity is frequently seen as a Yin and Yang situation, meaning that the outcome of the infiltrating immune cells can be either determinantal or beneficial depending on the timing in the disease course and the used preclinical disease model. Below, we look closer into the role of neutrophils, circulating monocytes and DCs in AD and their potential as therapeutic targets.

The role of neutrophils in AD. Neutrophils are the first line of defense against invading pathogens, but are simultaneously responsible for tissue destruction during inflammation.[204,205] Recent preclinical studies show that changes in cognition may be mediated by the adhesion of neutrophils to cerebral small vessels.[206,207] In addition, lymphocyte function-associated antigen (LFA-1)

controls neutrophil arrest on inflamed endothelium in mice with AD pathology. Neutrophil activity and levels of related oxidative stress and neutrophil extracellular traps (NETs) have also been associated with AD pathology in humans.[208,209]

Neutrophils as therapeutic target. Different studies show that endothelial ICAM-1 engagement by neutrophil LFA-1 may induce changes in the cytoskeleton of brain endothelial cells to increase permeability, an event already observed in brains affected by AD.[198,210,211] The blockade of LFA-1 or the depletion of neutrophils in the beginning of AD pathology, reduce neuropathological hallmarks and memory deficits.[207] More importantly, Zenaro *et al.* further stringent these result by showing that the temporary inhibition of neutrophils during AD onset, have a beneficial long-term effect in older animals.[207] This research suggests that neutrophil-directed therapy may also benefit AD patients. However, so far it is hard to develop an effective neutrophil-based intervention to treat AD as the differences in neutrophil characteristics between patients with AD and healthy elderly is not yet sufficiently understood.

Neutrophils play diverse roles in various disease processes, including infection, pulmonary diseases and cardiovascular diseases, making them also in these clinical settings an attractive therapeutic target. Németh *et al.* recently reviewed the potential of neutrophils as emerging therapeutic target.[212] Also in the onco-immunotherapy field, neutrophils have recently gained interest as potential treatment target. However, also in this field it became clear that neutrophils are kind of double-edged sword and that strategies should be developed not only to disrupt pro-tumor neutrophils but also reinstate anti-tumor neutrophils. The current state of neutrophils as cancer treatment is recently reviewed by Zhan *et al.[213]*

Several aspects have limited prior interest in the development of neutrophils targeting therapies. For example, there are far too many uncertainties and controversies related to various aspects of neutrophils; e.g. their lifespan, transcriptional activity, specific roles in the disease settings and the potential existence of neutrophil subpopulations. . Consequently, our first priority should be to learn more about neutrophils in AD pathology and the development of immunotherapy treatments targeting neutrophils in order to rationally design effective therapies that target them.

The role of circulating monocytes in AD. Monocytes play important roles in the peripheral clearance of Aβ which diffuses from the brain into the periphery.[214-216] The defective capacity of peripheral monocytes to engulf Aβ resulted in higher $A\beta_{40}$ and $A\beta_{42}$ levels in AD mouse models. However, the reported changes of peripheral blood monocytes in AD patients are conflicting and confusing.[217,218] This discrepancy across studies in literature may be explained by the fact that monocytes are a very heterogenous population of different subsets. In humans, three circulating monocyte subsets are classified based on relative expression levels of CD14 (co-receptor for toll-like receptor 4 (TLR4) and mediates lipopolysaccharide (LPS) signaling) and CD16 (Fc gamma receptor IIIa). Flow cytometric phenotyping has identified three different populations of monocytes, namely classical ($CD14^{++}$, $CD16^{-}$), intermediate ($CD14^{+}$, $CD16^{+}$), and non-classical ($CD14^{+}$, $CD16^{++}$) monocytes.[219] The three monocyte subsets are phenotypically and functionally different.[220] Contrary, in mice there are two subtypes of monocytes, namely the pro-inflammatory subset ($CX3CR1^{low}$ $CCR2^{high}$ $Ly6C^{high}$) which is involved in inflammatory responses, and the anti-inflammatory subset ($CX3CR1^{high}$ $CCR2^{neg}$ $Ly6C^{low}$) that establishes the resident patrolling monocyte population.[19] Pro-inflammatory monocytes can infiltrate into the brain and subsequently differentiate into activated macrophages that are involved in phagocytosis of toxic

elements, including Aβ. Moreover, these monocyte-derived macrophages can more efficiently clear Aβ deposits than resident microglia.[221] The Ly6C^{low} monocyte population internalizes Aβ and efficiently eliminates Aβ microaggregates.[222] Moreover, a reduction of non-classical CD14^{+} CD16^{+} monocytes is seen in AD patients compared to MCI patients or age-matched healthy controls.[223]

Circulating monocytes as therapeutic target in AD. The depletion of monocytes reduces cell crawling inside Aβ^{+} veins and increases Aβ deposition in APP/PS1 mice.[224] Recent independent preclinical studies have shown that infiltration of monocyte-derived macrophages to sites of brain pathology resulted in reduced pathology and reduced plaque burden.[215,221,225,226] Moreover, boosting the recruitment of monocyte-derived macrophages to sites of brain pathology in AD animal models is effective in arresting the disease. Taken together, these studies highlight the potential of an early recruitment and/or activation of monocytes in AD. However, it should be noted that monocytes from AD patients show a reduced ability to clear Aβ from the brain.[227] As the mechanisms behind this dysfunctionality to clear Aβ are not yet fully understood, we currently do not have the necessary knowledge to design a therapy that interferes with it. However, a future therapeutic approach might be to transplant bone marrow derived progenitor cells from healthy individuals into AD patients to replenish the malfunctioning monocytes. In this regard, a lot can be learned from the extensive bench of knowledge gained in the cancer field regarding antigen-loading of monocyte, purification processes and dose.[228,229]

The role of dendritic cells in AD. DCs form the connection between the innate and the adaptive immune system. These cells constantly sample the interfaces between the blood and the interstitium of the brain and between the blood and the CSF. Because of their connective role, DCs are strategically located (e.g. on the surface of the cortex and on the surface of the choroid plexus).[230,231] However, evidence of the presence of DCs in the brain parenchyma is missing. Butovsky and colleagues have shown by using green fluorescent labelled DCs in the APP/PS1 mouse model that DCs are associated with Aβ plaques in the brain parenchyma.[214] These results hint to the idea that peripheral DCs are recruited to the brain and participate in plaque clearance. This is supported by the observation that AD patients have less DC precursors in their peripheral blood.[232]. Wu *et al.* showed that this may be the case in multiple sclerosis[233], but the recruitment of DCs to the brain in other neurodegenerative disorders has not been conclusively proven. Consequently, it is not yet clear if the decline in DCs or its precursors in AD is a pathological cause, consequence, or combination of the two.

Dendritic cells as therapeutic target. The reduction in number and functionality of DCs in AD patients may aggravate the disease pathogenesis. Consequently, a DC-based therapy, similar to what is used in the cancer field[234,235], may be an alternate approach to fight AD. Cao *et al.* were the first to publish on DC-based vaccination in a mouse model for AD, namely the APPSwe mice.[236] Vaccination with bone marrow derived DCs that were sensitized to $A\beta_{42}$ peptide generates an antibody responses without the adverse induction of excessive inflammation. Another study vaccinated with $A\beta_{42}$-sensitized DCs together with splenocytes and could constrict learning and memory deficits in APPswe/PSEN1dE9 mice.[237] Despite the above described research, the data on DC vaccination as therapy against AD is still limited. However, extensive

knowledge on *ex vivo* and *in vitro* based platforms for proliferation and generation of mature DCs is available from research in the cancer field and could be used to take a big leap in the AD field.

The adaptive immune system and AD pathology

As discussed above, the innate immune system is strongly implicated in AD pathogenesis. In contrast, the current knowledge about the role of the adaptive immune system in healthy and diseased CNS is more scarce. This can be explained by the fact that the CNS has long been seen as immune privileged. Recent advances have adapted this view and led to a better understanding of the role of adaptive immune cells within the CNS.[238] To show that the adaptive immunity influences AD pathogenesis, Marsh *et al.* generated an immune-deficient AD mouse model that lacks T, B and natural killer cells; namely Rag-5xFAD mice.[239] This model exhibits an increase in Aβ pathology and also neuroinflammation is exacerbated. Furthermore, Sanchez and colleagues showed that restoration of the adaptive immunity in RAG-5xFAD mice via bone marrow transplantation led to a corresponding reduction in Aβ plaques and a significant increase in microglia in the brain parenchyma.[240] All in all, these preclinical studies strongly suggest the role of adaptive immune cells in AD pathology. Several small studies in AD patients have reported changes in the distribution[201,241-243], function and cytokine secretion[244-246] of peripheral adaptive immune cells. More recently, a study on multiple large AD patient cohorts reported that an adaptive immune response occurs in the blood and CSF of individuals with AD.[247] However, whether and in which degree the adaptive immune cells enter the brain to maintain neuroinflammation in AD patients is still largely unknown.

Taken together, the current knowledge about the interplay between adaptive immunity and AD pathology is limited. But recent available research does suggest a therapeutic opportunity to interfere with the adaptive immune system in order to alter AD development (Figure 3). Below, we dig deeper into the current knowledge of lymphocytes, their role in AD and their potential therapeutic window.

A) T cells

The role of T cells in AD. In the last years, it became clear that the lymphatic system of the brain carries immune cells from the CSF and connects to the deep cervical lymph nodes, enabling peripheral immune cells to respond to brain antigens.[248] We now know that peripheral T cells are needed for life-long brain plasticity[249] and maintaining cognitive and behavioral capacity[250]. Moreover, already back in 1997, scientist detected T cells specific for Aβ in the blood of AD patients.[244]

Next to the role of peripheral T cells in AD pathology, it is now becoming clear that T cells can also infiltrate into the brain. In this regard, Sanchez *et al.* recently observed T cells adjacent to plaque-associated microglia in the brain of 5xFAD, PS19 and PS19-5xFAD mice as well as in wild-type mice.[240] This study hints that $CD8^+$ T cells, also known as cytotoxic T cells, respond to the inflammatory AD environment by infiltrating the brain and directly interacting with microglia. Next to $CD8^+$ T cells, also $CD4^+$ T cells can infiltrate into the brain. Similar to $CD8^+$ T cells, infiltrating $CD4^+$ T cells can be destructive[251] but, depending on the subtype of these T cells, they can also limit neuronal damage and neurodegeneration[252]. Studies in AD mouse models and patients suggest that certain subsets of $CD4^+$ T cells can have a positive impact on AD pathology.[18,201,246,253] For example, Fisher *et al.* showed that icv injected T helper 1 (Th1) cells can target Aβ plaques and

reduce innate inflammation.[254] A third type of T cells, namely regulatory T cells (Tregs), can also infiltrate into the brain. Multiple groups provided evidence for an overall protective role of Tregs in restoring memory deficits, reducing plaque load and decreasing microglia activation in AD models.[253,255,256]

In a clinical study, Gate and colleagues have identified a specialized T cell type in the blood, CSF and brain tissue of AD patients, adding clinical evidence of the adaptive immune system's role in AD.[247] More precisely, the study shows that in the blood of people with MCI or AD more $CD8^+$ T cells are present than in cognitively unimpaired controls. Especially, a subset of T effector memory cells expressing CD45RA turned up in AD and MCI. These cells are also known as T-EMRA cells and are characterized by a high killing efficiency, rapid detachment from any cell they recognize, and secretion of multiple proinflammatory cytokines upon activation. This study also reported on an increase in $CD8^+$ T cells in hippocampal parenchyma and adjacent leptomeninges in the brain of seven AD patients compared to the brain of healthy controls. Remarkably, numerous $CD8^+$ T cells were associated with the blood vessels affected by cerebral amyloid angiopathy (CAA) in three AD patients, whereas almost none were seen around the vasculature of controls. Thus, an active pathogenetic role of $CD8^+$ T cells in the progression of AD may be assumed. T cells were also detected in the CSF of AD patients. Surprisingly, 20% of the detected T cells were $CD8^+$, and of those again 20% were T-EMRA. An important question that arises from this observation is: Are these T cells just passing through or do they carry out an immunological function? There is some first evidence in favor of the last option as clonal expansion of these T cells was shown by Gate *et al*. Clonal expansion indicates that the T cells have encountered their cognate antigen.[247]

The contradictory outcomes of the above preclinical and clinical studies regarding the role of T cells in AD pathology underlies the fact that the different subsets of T cells may have conflicting effects on pathology when infiltrating the brain; from a protective role of Tregs to a disruptive effect of infiltrating cytotoxic $CD8^+$ T cells.

T cells as therapeutic target. Adoptive cell therapy, also known as cellular immunotherapy, has not fully entered the field of AD yet in contrast to the onco-immunotherapy field[257]. However, this type of therapy is extensively explored in the cancer field. Therefore, lessons from onco-immunotherapy can be learned and are likely to accelerate the development and the clinical acceptance of T-cell based immunotherapy treatments for AD and other dementias. Importantly, as emphasized above, the specific subtype of T cells that is recruited to the brain is of utmost importance for the clinical outcome of the therapy. The preferred subset of T cells in the AD-immunotherapy field will likely be different compared to the onco-immunotherapy setting. In the latter, the goal is to specifically kill cancer cells meaning that recruiting $CD8^+$ T cells can be beneficial. In contrast, based on the present preclinical and clinical data, it may be speculated that $CD8^+$ T cells recruited from the periphery contribute to AD progression by directly acting on neurons/neurites, but also by indirectly affecting the functional properties of microglia. Consequently, these observations may serve as rational for the development of therapeutic interventions targeting $CD8^+$ T cells; effector and/or memory and/or T-EMRA $CD8^+$ cells to moderate AD severity.

A clinical trial (NCT04070378) is currently recruiting AD patients to evaluate whether Daratumumab have a clinical effect in patients with mild to moderate AD. Daratumumab is a

human antibody that targets CD38 and is able to cross the BBB. CD38 is expressed on activated $CD8^+$ T cells and is significantly increased in early AD patients. By using Daratumumab the cytotoxic $CD8^+$ T cells may be reduced.

Next to therapies focusing on reducing $CD8^+$ T cells, therapies to restore Tregs function can also be explored as a mean to modulate the inflammatory status of AD. It has been shown that the suppressive function of Tregs on responder T cell proliferation is compromised at the AD stage, compared with MCI and healthy controls.[258] Currently, BHT Lifescience Australia is recruiting mild to moderate AD patients for their phase 1 clinical trial (NCT03865017) in which they will isolate $CD4^+$ $CD25^+$ Tregs from patients, expand them, and inject them back in the patient. Of note, Tregs have been shown to suppress microglia-mediated inflammation as well.[259] So, the role of Tregs in ameliorating the proinflammatory immune response in AD requires further investigation in order to properly design a T cell-based immunotherapy.

B) B cells

The role of B cells in AD is not fully understood. B cells produce immunoglobulins (Igs) that target Aβ in peripheral blood and CSF of patients[260,261] and mice[182,262] with AD. Consequently, a lot of effort has been put into the development of passive and active immunization targeting Aβ and more recently also targeting Tau.[263] However, B cells may contribute to AD pathogenesis beyond merely the production of Igs. Recently, Kim and colleagues showed in different murine transgenic models that there is an accumulation of activated B cells in circulation and increased infiltration of B cells into the brain parenchyma of AD patients. Surprisingly, the study of Kim *et al.* provides evidence that B cells enhance AD-like symptoms.[264] Moreover, the depletion of B cells alone is sufficient to reduce Aβ plaque burden and DAMs in 3xTgAD mice.[265] From this point of view, the inactivation of B cells can benefit AD patients. This is in shear contrast with the established view that B cells would be benign in AD via the production of beneficial Aβ plaque-reducing Ig and express AD ameliorating cytokines.

B-cells as therapeutic target. In the AD field, immunotherapy has mainly focused on antigen-specific approaches, namely active and passive immunization. For active immunization, e.g. Aβ is administered to induce humoral and cellular immunity. On the other hand, for passive immunization pre-formed antibodies are intravenously injected Although only a small fraction of intravenously administered antibodies passes the brain barriers and eventually enter the brain, their significant effects indicate the potential of this type of therapeutic approach.[266] Based on the two major pathogenic hypotheses of amyloidosis and tauopathy, AD-immunotherapy has mainly focused on passive and active vaccination against Aβ and Tau, respectively. Over 1000 papers have been published on these topics and over 100 immunization procedures against Aβ and Tau have been reported. Nonetheless, only one passive antibody therapy is recently approved by the Food and Drug Administration (FDA). Aducanumab, a high-affinity monoclonal antibody against a conformational epitope found on Aβ was recently FDA approved. However, the necessary caution is advised as so far only the clearance of Aβ is shown while uncertainty remains about aducanumab's clinical benefit. A confirmatory trial to show efficacy is still needed.*[267,268]* Passive immunotherapies are beyond the scope of this review and are reviewed extensively by Vander Zanden *et al.[269]* and Cacabelos *et al.*[270]. Initially, active immunization was seen as a

promising strategy, as a small number of relatively inexpensive treatments might induce long term protection. Evaluation of the first widely tested human anti-Aβ vaccine (NCT00021723), however, was stopped in 2002 because of a high rate (6%) of meningoencephalitis. Nonetheless, a follow-up study of the long-term effect of this vaccine showed a significant reduction in Aβ volume, but this was without improved dementia symptoms.[271] Followed by this, second-generation Aβ-active immunotherapies, anti-Aβ monoclonal antibodies targeting different Aβ epitopes, and anti-Tau immunotherapies have dominated active AD vaccines during the past decade.[272-274] Some dual vaccines demonstrated a capacity to reduce both Aβ and Tau aggregation and accumulation in transgenic animal models.[275,276] Despite excellent preclinical studies, all clinical trials so far have failed, probably due to (i) deficient pathogenic targets, (ii) inappropriate preclinical models, (iii) defective immunotherapeutic procedures and (iv) inadequate clinical trial design. However, CAD 106 and Vanutide cridificar (ACC-001) finished phase II clinical trials with promising results[277-279] and a phase II/III clinical trial of CAD106 (NCT02565511) is currently underway. The current preclinical and clinical state of active AD vaccination is nicely reviewed in.[270,280]

As discussed above, B cells also contribute to immune regulation or act as potent antigen-presenting cells. Despite their multiple diverse effector functions, the potential of B cells for cellular therapy is still largely underestimated, also in other research areas. In order to rationally develop a B cell-based immunotherapy against AD, a better understanding of the detrimental and/or beneficial roles of B cells in the disease pathology will be required. Once this knowledge gap has been closed, we can learn from the onco-field for the design and generation of good manufacturing practice-produced B-cell immunotherapies.

Conclusions

In the last ten years, over 100 AD drugs have been abandoned in development or during clinical trials. Consequently, effective or disease-modifying therapies against AD are still lacking. Ultimately, as proposed by Selkoe, the combination of Aβ clearing agents with therapies that enhance the clearance of Tau and modulate neuroinflammation might be the most beneficial.[281]

As discussed in this review, the innate as well as the adaptive immune system has a dynamic role in relation to AD development and progression, as they can play both detrimental and beneficial roles. A major hurdle on our road to effective AD-immunotherapies is to fully understand the different facets of the immune system on the different stages of AD. For example, different molecules that are proposed in this review as possible target for immunotherapy are also expressed by other cell types. This may possibly lead to harmful off target effects or additional beneficial effects. E.g. interfering with TREM-2 expression will not only affect microglial cells but also the survival and proliferation of other peripheral myeloid cells.[282] We can only start with the rational design of new immunotherapy-based approaches when we have a better understanding of the different facets of the immune system. An important point we need to keep in mind is the interspecies differences in immune responses between humans and the animal models we typically use to study the immune system.[283] We have learned much from genetically manipulated and inbred animal models, but instances in which these findings have been successfully translated to human immunity have been rare. During the last years we got a more detailed picture of the human immune system and we can build more sophisticated models to better reflect this complexity. Nevertheless, human specific studies are imperative before we

can go to large-scale clinical trials. Luckily, we can count on the huge amount of knowledge regarding the development of different onco-immunotherapies to take a significant leap in this process. Considered the different critical roles of the innate and adaptive immune system in AD pathology, we propose that a multidimensional immunotherapy would be most effective. Such multidimensional immunotherapy, rather than a monotherapy, could be able to (re-)engage the full power of the immune system to stop or slow down AD, and can also be extended to many other neurodegenerative diseases. Moreover, chronic progressive disorders usually require two or more drugs to effectively slow down the disease progression. The proposed shift from a mono- to a combination therapy is comparable with the current change in the cancer field where different therapies are combined, including immunotherapies, to increase treatment efficacy. However, such a combinatorial immunotherapeutic approach can only be designed if the clinical trials of different mono-specific immunotherapies are successful. Finally, the long-term effects of immune system modulation need to be evaluated, particularly the safety, because AD is chronic and continuous treatment will probably be required.

List of abbreviations

AD	Alzheimer's disease
ApoE	apolipoprotein-E
APP	amyloid-beta precursor protein
Aβ	amyloid-beta
AβO	Aβ oligomers
BBB	blood-brain barrier
CAA	cerebral amyloid angiopathy
CNS	central nervous system
CR1	complement receptor 1
CSF	cerebrospinal fluid
DAM	disease-associated microglia
DC	dendritic cell
GWAS	genome-wide association studies
icv	intracerebroventricular
IFN	interferon
Ig	immunoglobulin
IL	Interleukin
IL-1R	Interleukin 1 receptor type I
IL-1RA	Interleukin 1 receptor type I antagonist
LFA-1	lymphocyte function-associated antigen
LTP	long-term potentiation
MAC	membrane attack complex
MCI	mild cognitive impairment
NETs	neutrophil extracellular traps
NFT	neurofibrillary tangles
NSAID	non-steroidal anti-inflammatory drugs
PILRα	paired immunoglobulin-like type 2 receptor α
p-Tau	hyperphosphorylated Tau
sCrry	soluble complement receptor-related protein y
T-EMRA	T effector memory cells expressing CD45RA
TGF-β	transforming growth factor beta
Th1	T helper 1
TNF	tumor necrosis factor
TNFR	tumor necrosis factor receptor
Tregs	regulatory T cells
TREM2	triggering receptor expressed on myeloid cells 2

Tables

Table 1: Overview of discussed preclinical studies. This table summarizes the target, strategy, approach and used animal model in the discussed preclinical studies. Moreover, the outcome of the study is indicated with a '↓' or '↑' symbol meaning a decrease or an increase of the assessed outcome respectively. Abbreviations: AD: Alzheimer's disease; TNF: tumor necrosis factor; TNFR: tumor necrosis factor receptor; APP: *amyloid*-beta *precursor protein*; Aβ: *amyloid*-beta; pTau: *phosphorylated tau;* SNAP25: synaptosomal-associated protein 25kDa; LTP: long-term potentiation; Tg: transgene; $A\beta_{40}O$: *amyloid*-$beta_{40}$ oligomer; APP/PS1 mice: mice containing human transgenes for both APP bearing the Swedish mutation and PSEN1 containing an L166P mutation, both under the control of the Thy1 promoter; 3xTgAD mice: mice containing three mutations associated with familial Alzheimer's disease (APP Swedish, MAPT P301L, and PSEN1 M146V); 5xFAD mice: mice expressing human APP and PSEN1 transgenes with a total of five AD-linked mutations: the Swedish (K670N/M671L), Florida (I716V), and London (V717I) mutations in APP, and the M146L and L286V mutations in PSEN1; APP23 mice: mice bearing a 7-fold overexpression of mutant human APP bearing the pathogenic Swedish mutation; J20 mice: mice overexpressing human APP with two mutations linked to familial Alzheimer's disease (the Swedish and Indiana mutations); TgCRND8 mice: transgenic mice overexpressing mutant human APP at levels approximately 5-fold higher than endogenous murine APP; McGill-R-Thy1-APP rat: rat expressing human APP_{751} with the Swedish and Indiana mutations, under the control of the murine Thy1.2 promoter. APP^{NLGF} mice: APP overexpression by using a knock-in approach to express APP at wild-type levels and with appropriate cell-type and temporal specificity; Tau-P301S mice: tauopathy model; BACE1: beta-secretase 1; IL: interleukin; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; TGF-β: *transforming growth factor* beta; IFN: interferon; C1: complement 1; C3: complement 3; DC: dendritic cell; LFA-1: lymphocyte function-associated antigen *1.*

Target	Strategy	Approach	Animal model	Outcome	Reference
TNF signaling	Pan-TNF inhibition	Intraperitoneal 3,6'-dithiothalidomide injection	3xTgAD mice	APP ↓ Aβ peptide and Aβ plaque numbers ↓ pTau ↓ memory function ↓ SNAP25 and synaptophysin ↑	[52]
		TNFR1 and -2 knock-out	3xTgAD mice	Aβ and Tau-related pathology ↓ microglial $A\beta_{42}$ phagocytosis ↑	[58]
		Infliximab treatment (*anti-TNF-α*)	Hippocampal slices of Tg576, 5xFAD and $A\beta_{42}$-treated wild type mice	Improved LTP	[53]
		Intracerebroventricular Infliximab injection (*anti-TNF-α*)	APP/PS1 mice	levels of TNF, Aβ plaques and pTau ↓ CD11c-positive dendritic-like cells ↑	[54]
		Intracerebroventricular anti-TNF antibody injection	$A\beta_{40}O$ intracerebrove	memory impairment ↓	[55]

			ntricularly injected mice		
	Increasing TNF levels	Chronic neuron-specific TNF overexpression	3xTgAD mice	Aβ and pTau levels↑ microglial activation ↑ peripheral cell infiltration↑ neuronal death ↑	[56]
		3'-modified human TNF-globin transgene (Tg197 transgenic mouse)	5xFAD mice	amyloid deposition ↓ neuronal integrity ↓ neuroinflammation ↑	[57]
	TNFR1 inhibition	TNFR1 knock-out	APP/PS1 mice and $A\beta_{42}O$ intracerebroventricularly injected wild type mice	amyloidosis ↓ neuroinflammation ↓ cognitive impairment ↓	[46]
			APP23 mice	Aβ plaque formation ↓ BACE1 levels and activity ↓ microglial activation ↓ learning and memory ↑	[71]
		Intracerebroventricular TNFR1 single-domain antibody (TROS) injection	$A\beta_{42}O$ intracerebroventricularly injected wild type mice	neuroinflammation ↓ memory impairment ↓	[71]
		Chronic infusion of soluble TNF inhibitor (XENP345), TNFR1 knock-out	3xTgAD mice	Aβ accumulation ↓	[74]
		Subcutaneous injection of soluble TNF inhibitor (XPro1595)	5xFAD mice	Aβ plaques ↓ activated immune cells ↓ LTP impairment ↓	[75]
	TNFR2 inhibition	Intrahippocampal injection of adeno-associated virus vector-delivered TNFR2 siRNA	3xTgAD mice	Aβ and Tau pathology ↑	[68]
		TNFR2 knock-out	APP23 mice	plaque formation ↑ BACE1 levels and activity↑ microglial activation ↑	[69]
IL-1 signaling	IL-1β inhibition	Intrahippocampal IL-1β siRNA injection	APP/PS1 mice	cognitive decline ↓ neuronal injury ↓	[97]

	IL-1R inhibition	Intraperitoneal IL-1R blocking antibody injection	3xTgAD mice	oligomeric and fibrillar Aβ forms↓ tau ↓ neuroinflammation ↓ cognitive decline ↓	[95]
		Anakinra (IL1R blocking Ab) treatment	$A\beta_{40}O$ treated mouse primary hippocampal cultures	loss of mitochondrial membrane potential and fusion proteins ↓	[96]
		Subcutaneous Anakinra (IL1R blocking Ab) injection	McGill-Thy1-APP rats	synaptic plasticity deficits ↓	[101]
		IL1R knock-out	$A\beta_{42}O$ intracerebroventricularly injected mice	memory impairment ↓ expression of mitochondrial fission and fusion proteins ↓	[96]
	Increasing IL-1β levels	Cerebral implantation of IL-1β impregnated pellets	Sprague-Dawley rats	immunoreactivity and hyperphosphorylation of Tau ↑	[98]
		Sustained hippocampal IL-1β overexpression ($IL\text{-}1\beta^{XAT}$ mice)	3xTgAD mice	Aβ load ↓ Tau pathology ↑ microglia activation ↑	[99]
	NLRP3 inflammasome inhibition	Intraperitoneal JC-124 injection (NLRP3 inflammasome inhibitor)	TgCRND8 mice	Aβ deposition ↓ microglial activation ↓ astrocytosis ↑ oxidative stress ↓ neurodegeneration ↓	[100]
		Intraperitoneal MCC950 injection (NLRP3 inhibitor)	McGill-Thy1-APP rats	synaptic plasticity deficits ↓	[101]
		Intraperitoneal MCC950 injection (NLRP3 inhibitor)	APP/PS1 mice	Aβ accumulation ↓ inflammasome activation ↓ microglial activation ↓ neuronal deterioration ↓	[103]
		Intraperitoneal mefenamic acid administration	$A\beta_{42}O$ intracerebroventricularly injected wild type rats and 3xTgAD mice	microglial activation ↓ memory deficits ↓	[104]
		Intraperitoneal artemisinin injection	APPswe/PS1dE9 mice	neuritic plaque burden ↓ neuroinflammation ↓	[105]
		Intraperitoneal dihydromyricetin injection	APP/PS1 mice	Aβ clearance ↑ number of activated microglia ↓	[106]

				memory and cognition deficits ↓	
	Caspase-1 inhibition	Intraperitoneal VX-765 injection (a caspase-1 inhibitor) and caspase-1 knock-out	J20 mice	Aβ deposition ↓ neuroinflammation ↓ spatial memory impairment and hyperactivity ↓ synaptophysin levels ↑	[102]
IL-6 signaling	IL-6 inhibition	Intracerebroventricular anti-IL-6 antibody injection	APP/PS1 mice	memory impairment ↓ peripheral glucose intolerance ↓ plasma IL-6 levels ↓	[112]
IL-12/23 signaling	IL-12/23 inhibition	Knock-out of IL-12/IL-23 subunits (p19, p35, p40)	APP/PS1 mice	Aβ plaque load ↓	[116]
		Intraperitoneal anti-p40 antibody injection	APP/PS1 mice	Aβ plaque load ↓	[116]
		Intracerebroventricular anti-p40 antibody injection	APP/PS1 mice	behavioral deficits ↓	[116]
TGF-β signaling	TGF-β inhibition	Intracerebroventricular SB431542 injection (an inhibitor of the TGF-β/Activin/NODAL pathway)	$A\beta_{42}O$ intrahippocampal injected rats	Aβ toxicity ↑	[129]
	Increasing TGF-β levels	Intracerebroventricular TGF-β injection	$A\beta_{42}O$ intracerebroventricularly injected mice	cognitive impairment ↓ synapse loss ↓	[127]
		Intracerebroventricular/ intranasal TGF-β administration	$A\beta_{42}O$ intrahippocampal injected rats	neurodegeneration ↓ neuroinflammation ↓	[128]
Type I IFN signaling	IFNAR inhibition	Intracerebroventricular anti-IFNAR antibody injection	5xFAD mice, APP^{NLGF} mice	microglial activation ↓ ↓ synapse loss ↓	[131]
Type II IFN signaling	Increasing IFN-γ levels	Intraperitoneal IFN-γ injection	APP/PS1 mice	Aβ clearance ↑ microglial autophagic dysfunction ↓ cognition ↑	[134]
		Neuronal IFN-γ overexpression (SJL mice)	J20 mice	neurogenesis ↑ spatial learning and memory ↑	[135]
		Intrahippocampal injection of adeno-associated	TgCRND8 mice	Aβ deposition ↓ activated glia ↓ complement activation ↑	[136]

		virus vector-delivered IFN-γ			
		Neonatal intracerebroventricular injection of adeno-associated virus vector-delivered IFN-γ	3xTgAD mice	amyloid pathology ↑ pTau ↓ microglial activation ↑ neurogenesis ↑	[138]
Complement system	C1q inhibition	C1q knock-out	Tg2576 mice, APP/PS1 mice	activated glia ↓ synaptic markers decrease ↓	[160]
		Intrahippocampal anti-C1q antibody injection	Tau-P301S mice	microglial synapse removal ↓ synapse density ↑	[145]
		Intracerebroventricular anti-C1q antibody injection	$A\beta_{40}O$ intracerebroventricularly injected mice	synapse loss ↓	[162]
	C3 inhibition	C3 knock-out	Aged wild type mice	synapse loss ↓ cognitive impairment ↓	[163]
			APP/PS1 mice	Aβ plaques ↑ neuroinflammation ↓ cognition ↑ loss of synapses and neurons ↓	[164]
			PS2APP mice	plaque load ↑ plaque-proximal synapse loss ↓	[143]
			Tau-P301S mice	brain atrophy and neuronal loss ↓ behavioral abnormalities ↓	[143]
		C3 knock-out, sCrry overexpression	hAPP mice	Aβ plaque deposition ↑ microglial activation ↑ neurodegeneration ↑	[166]
	C5aR inhibition	Oral PMX205 delivery (a C5a receptor peptide antagonist)	Tg2576 mice	Aβ deposition ↓ activated glia ↓ cognitive decline ↓	[167]
			3xTgAD mice	Aβ plaques ↓ pTau ↓ neurodegeneration ↓	[167]
Microglia	Shift from inflammatory to anti-inflammatory phenotype	Administration of jujuboside	APP/PS1 mice	$A\beta_{42}$ uptake ↑ microglial activation ↓ cognitive decline ↓	[186]
		Administration of metformin	APP/PS1 mice	amyloid plaque ↓ cognitive decline ↓	[188]
		Administration of AL002c	R47H-KO-5XFAD mice	filamentous plaques ↓ microglial proliferation ↑	[190]
	Cell-based therapy	Administration of bone marrow-	APP/PS1 mice	effective microglia delivery to the brain	[192]

		derived mesenchymal cells, macrophages and microglia			
		Administration of adipose derived mesenchymal stem cells	APP/PS1 mice	Aβ levels ↓ learning function ↑	[193]
		Administration of human placenta amniotic membrane derived mesenchymal stem cells	APPswe mice	Aβ plaques ↓ spatial learning ↑	[194]
		Reactivation of glycolytic metabolism by IFN-γ treatment	5xFAD mice	reversion of inflammatory state	[196]
Neutrophils	Reduction of neutrophils	Neutrophil depletion or inhibition of neutrophil trafficking via LFA-1 blockade	5xFAD and 3xTgAD mice	cognitive decline ↓	[207]
Monocytes	Recruitment of monocyte derived cells	Injection of grafted $CD115^{+}$ monocytes	APPSWE/PS1 mice	cognitive decline ↓	[215]
Dendritic cells	Cell-based therapy	Injection of bone marrow derived DCs sensitized to $A\beta_{42}$ peptide	APPswe mice	antibody responses against Aβ ↑	[236]
		Injection of DCs sensitized to $A\beta_{42}$ peptide	APPswe/PSEN1d9 mice	cognitive decline ↓	[237]

Table 2: Overview of discussed clinical studies. This table summarizes the target, approach and outcome in the discussed clinical studies. Moreover, the NTC number and phase of the clinical trial is indicated. Abbreviations: TNF: tumor necrosis factor; IFN: interferon; AD: Alzheimer's disease; CRP:C-reactive protein; ADAS: Alzheimer's Disease Assessment Scale; Cog: Cognitive Subscale, SIB: severe impairment, MMSE: mini-mental state examination; TREM: triggering receptor expressed on myeloid cells.

Target	Reference/ NTC number/phase	Approach
TNF signaling	[59] Prospective pilot	Weekly perispinal administration of the TNF inhibitor Etanercept for 6 months in patients with mild to severe AD
	NCT01716637 Phase 1	Weekly perispinal administration administration of the TNF inhibitor Etanercept for 6 weeks in patients with mild to severe AD
	[63] NCT01068353 Phase 2	Weekly subcutaneous Etanercept injection for 24 weeks in patients with mild to moderate AD
	[76] NCT03943264 Phase 1b	Specific inhibition of TNF/TNFR1 axis by XPro1595 in patients with mild to moderate AD with elevated CRP blood levels
Type I IFN signaling	[133] NCT01075763 Phase 2	Subcutaneous IFN-β1a injection 3 times per week for 28 weeks in patients with early-onset AD
Complement system	[175] NCT03316521 Phase 1	Single ascending dose and multiple doses using subcutaneous or intravenous administration of C3 inhibitor AMY-101 in healthy males
Microglia	NCT04592874 Phase 2	AL002 (anti-TREM2 antibody) in participants with early AD
T cells	NCT04070378 Phase 2	Daratumumab (anti-CD38 antibody) in participants with mild to moderate Alzheimer's disease
	NCT03865017 Phase 1	Multiple intravenous infusions of CD4+CD25+ Tregs in participants with mild to moderate AD

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Figure legends

Figure 1: Schematic representation highlighting the interplay between complement-, TNF-, IL-1α, and IL-1β- mediated events in AD pathology and corresponding potential therapeutic strategies. Amyloid-beta (Aβ) aggregation triggers the activation of complement (C) 1q, which in turn induces Aβ aggregation in a feedforward loop, decreases microglial Aβ phagocytosis, and stimulates microglia to become more reactive. Activation of the microglia, either by complement or directly by Aβ, can then lead to aberrant synaptic pruning of C1q- and C3-tagged synapses. Reactive microglia also secrete tumor necrosis factor (TNF) and interleukin (IL)-1β, exerting neurotoxicity via TNFR1 and IL-1R, respectively. The secreted TNF can also promote microglial glutamate release in an autocrine manner, inducing excitoneurotoxicity through N-methyl-D-aspartate receptor (NMDAR) signaling. Furthermore, IL-1α, TNF and C1q secreted by activated microglia polarize astrocytes toward a pro-inflammatory phenotype that produces excess C3. The latter astrocytic release of C3 can then induce intraneuronal calcium dysregulation, contributing to the alteration of neuronal function. Finally, C1q can also be activated by Tau, inducing microglial engulfment of excitatory synapses. Preclinical studies indicate the therapeutic potential of the TNF inhibitors etanercept and infliximab, and the more specific TNFR1 inhibitors TROS and Xpro1595. Etanercept and Xpro1595 also showed therapeutic potential in clinical studies. For IL-1, preclinical studies with anti-IL-1β antibody, IL-1β siRNA, and the IL-1R receptor antagonist anakinra showed potential benefit as AD treatments. Also complement is a potential therapeutic target, as indicated by preclinical studies with C1q antibody, the C3 antagonist sCrry, and the C5aR antagonist PMX205. Figure created with BioRender.com.

Figure 2: Schematic overview of the interplay between innate immune cells and AD pathology and potential therapeutic strategies. Microglial cells: The phagocytic activity of microglia decline, while the production of proinflammatory cytokines escalates during Alzheimer's disease (AD). The inactive R47H variant of triggering receptor expressed on myeloid cells 2 (TREM2) is expressed on microglial cells of AD patients. (1) Anti-inflammatory drugs can be used to skew microglia from an inflammatory phenotype to a more anti-inflammatory type. Next, also AL002 can be used as a therapy. (2) AL002 is a monoclonal antibody that binds to the microglial receptor TREM2 and activates signaling. (3) Finally, genetic edited autologous or allogenic microglia can be given to AD patient as therapy to replace proinflammatory microglia. **Neutrophils:** Lymphocyte function-associated antigen (LFA-1) controls neutrophil infiltration in the brain of mice with AD pathology. Neutrophil activity causes tissue destruction, oxidative stress and neutrophil extracellular traps (NETs) formation. (1) Depletion of neutrophils or (2) blocking LFA1 binding can be examined as potential therapy. **Circulating monocytes:** Monocytes from AD patients show a decrease in phagocytic Aβ capacity in the periphery and a reduction in number of $CD14^{+}CD16^{+}$ monocytes. Therapeutic options focusing on monocytes can be (1) the recruitment of monocyte derived macrophages to the brain or (2) transplanting bone marrow derived progenitor cells from healthy individuals into AD patients. **Dendritic cells (DCs):** There is less association of DCs with Aβ plaques in the brain parenchyma of AD patients compared to healthy controls. Moreover, there is a decrease in number and functionality. Vaccination of AD patients with DCs sensitized to Aβ42 peptide is a potential therapeutic strategy. Figure created with BioRender.com.

Figure 3: Schematic overview of the interplay between adaptive immune cells and AD pathology and potential therapeutic strategies. T cells: The different subsets of T cells exert different functions in Alzheimer's disease (AD) pathology. $CD8^+$ T cells adjacent to plaque-associated microglia in the brain induce cytotoxic effects. $CD4^+$ T cells can also be destructive but can also reduce innate inflammation, limit neuronal damage and neurodegradation. Treg cells may restore memory deficits, reduce plaque load and decrease microglia activation in AD models. (1) Daratumumab targets CD38 that is expressed on activated $CD8^+$ T cells. This antibody may reduce the toxic $CD8^+$ T cells. (2) Phase 1 clinical trial (NCT03865017) will isolate $CD4^+$ $CD25^+$ Tregs from patients, expand them, and inject them back in the patient in order to suppress inflammation. **B cells** produce immunoglobulins (Igs) that target amyloid-beta (Aβ) or phosphorylated Tau (pTau). (1) Passive immunization relies upon the intravenous injection of pre-formed antibodies to boost resistance to the aggregation of Aβ or phosphorylated Tau (pTau) (2) For active immunization, e.g. Aβ or pTau is administered in order to stimulate a response of both humoral and cellular immunity. Figure created with BioRender.com.

Figure 1

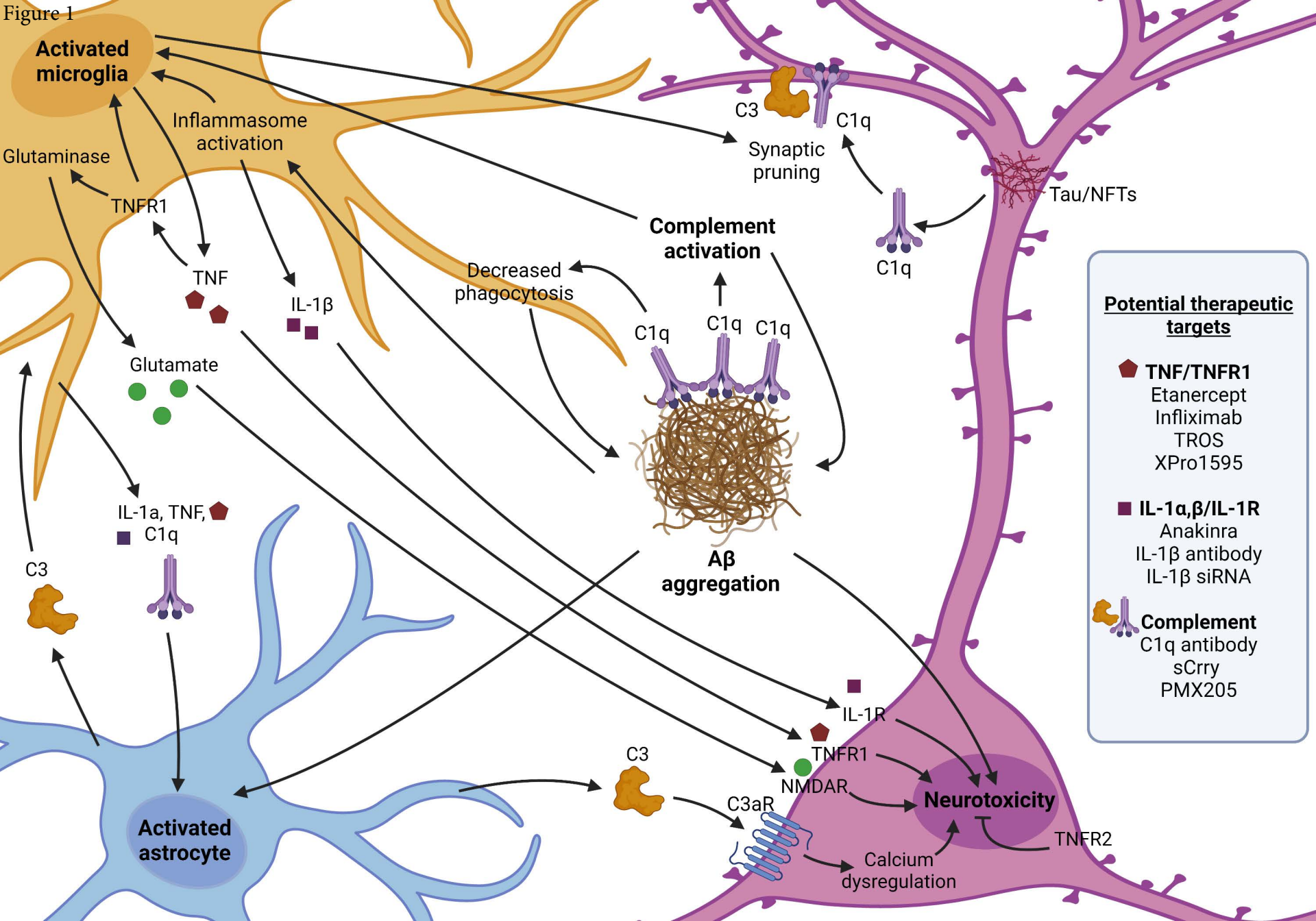

Activated microglia
Inflammasome activation
Glutaminase
TNFR1
TNF
IL-1β
Glutamate
IL-1a, TNF,
C1q
C3
Activated astrocyte
C3
C1q
Synaptic pruning
Tau/NFTs
C1q
Complement activation
Decreased phagocytosis
C1q
C1q
C1q
Aβ aggregation
IL-1R
TNFR1
NMDAR
C3
C3aR
Calcium dysregulation
Neurotoxicity
TNFR2
Potential therapeutic targets
TNF/TNFR1
Etanercept
Infliximab
TROS
XPro1595
IL-1α,β/IL-1R
Anakinra
IL-1β antibody
IL-1β siRNA
Complement
C1q antibody
sCrry
PMX205

Figure 2

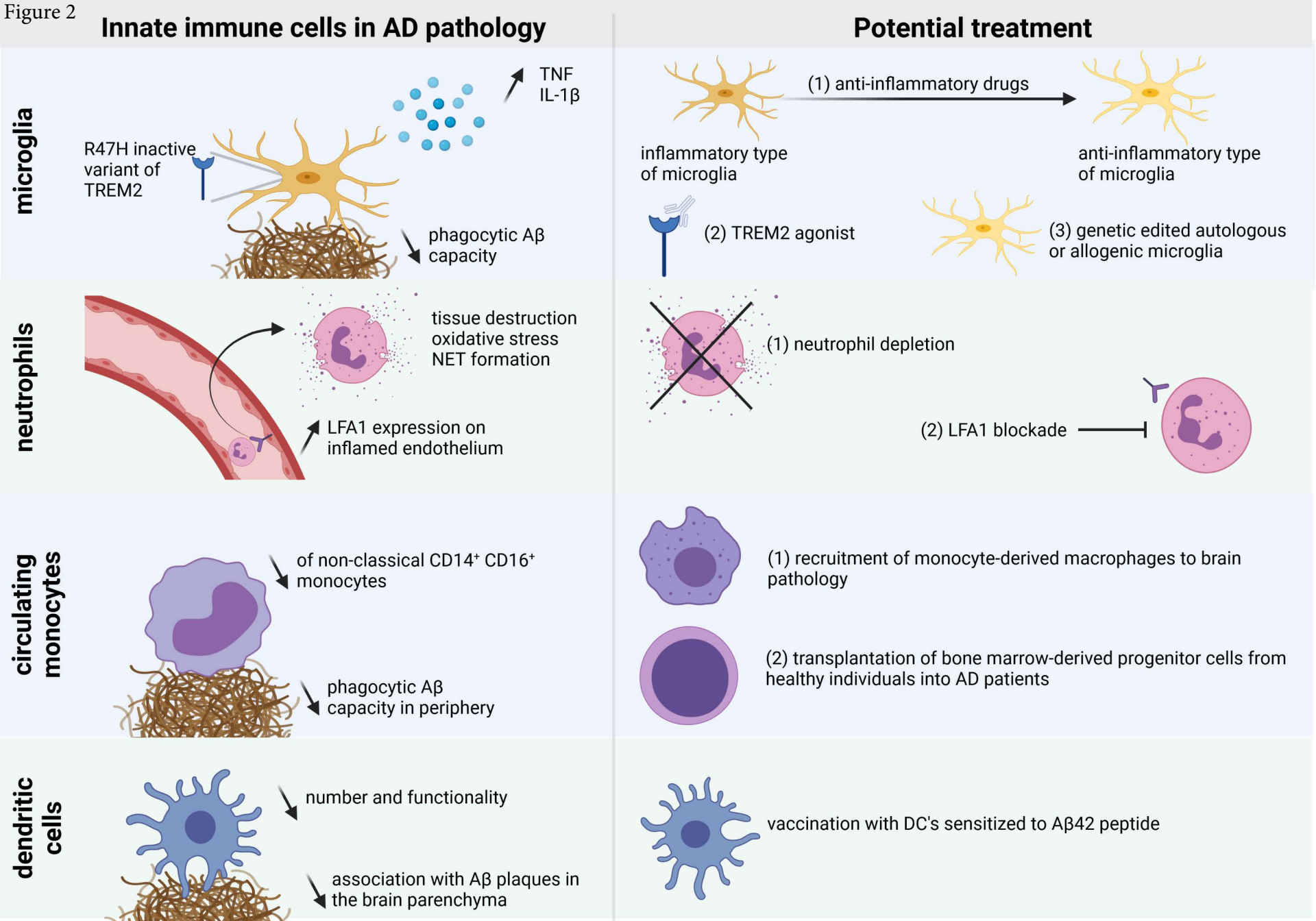
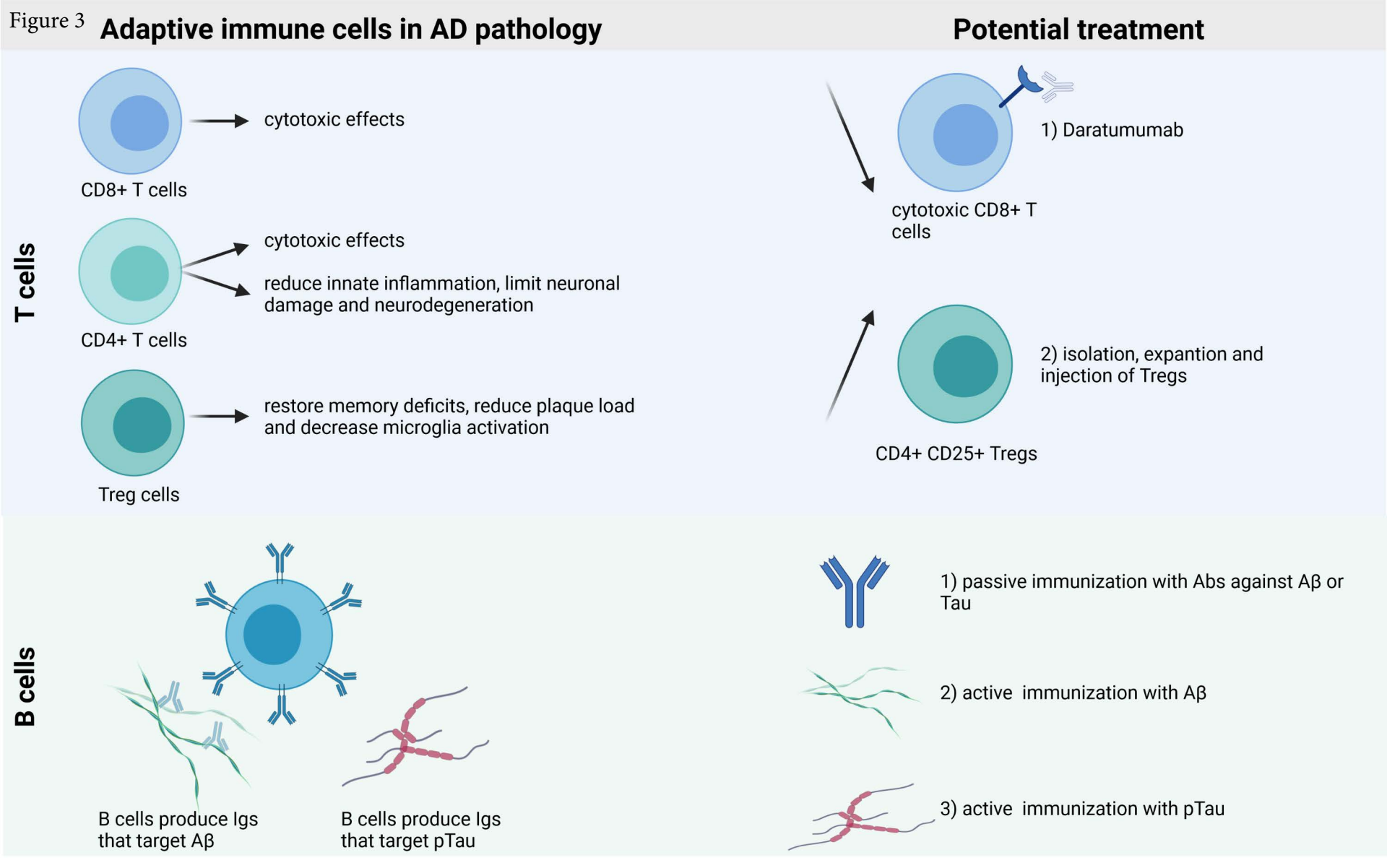

Innate immune cells in AD pathology
Potential treatment
microglia
TNF
IL-1β
R47H inactive variant of TREM2
phagocytic Aβ capacity
(1) anti-inflammatory drugs
inflammatory type of microglia
anti-inflammatory type of microglia
(2) TREM2 agonist
(3) genetic edited autologous or allogenic microglia
neutrophils
tissue destruction
oxidative stress
NET formation
LFA1 expression on inflamed endothelium
(1) neutrophil depletion
(2) LFA1 blockade
circulating monocytes
of non-classical CD14+ CD16+ monocytes
phagocytic Aβ capacity in periphery
(1) recruitment of monocyte-derived macrophages to brain pathology
(2) transplantation of bone marrow-derived progenitor cells from healthy individuals into AD patients
dendritic cells
number and functionality
association with Aβ plaques in the brain parenchyma
vaccination with DC's sensitized to Aβ42 peptide

Figure 3


Adaptive immune cells in AD pathology
Potential treatment
T cells
cytotoxic effects
CD8+ T cells
cytotoxic effects
reduce innate inflammation, limit neuronal damage and neurodegeneration
CD4+ T cells
restore memory deficits, reduce plaque load and decrease microglia activation
Treg cells
1) Daratumumab
cytotoxic CD8+ T cells
2) isolation, expantion and injection of Tregs
CD4+ CD25+ Tregs
B cells
B cells produce Igs that target Aβ
B cells produce Igs that target pTau
1) passive immunization with Abs against Aβ or Tau
2) active immunization with Aβ
3) active immunization with pTau