

# Therapeutic targeting of neuroimmune mechanisms in neurodegeneration

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## Abstract

Effective treatments for age-related chronic neurodegenerative diseases such as Alzheimer’s disease remain limited, in part because the molecular drivers of cognitive decline are still not fully understood. Human genetic studies, together with detailed analysis of disease pathology, indicate that the immune system has an important influence on disease progression. Research to date has focused largely on microglia – specialized innate immune cells that reside within the central nervous system (CNS) – as functional studies combined with deep transcriptional profiling have improved our understanding of this innate immune cell type in neurodegeneration and have identified several potential therapeutic targets. Increasing evidence now shows that microglia coordinate diverse CNS and peripheral cell populations to shape disease outcomes. In this Review, we discuss these neuroimmune interactions, which reveal a more intricate framework for how the central and peripheral immune systems may influence neurodegeneration. These insights could redirect future drug discovery efforts towards immune targets that complement existing therapies aimed at core pathological features. We also outline how this knowledge suggests new therapeutic strategies and highlight a critical need for disease-specific neuroimmune biomarkers.

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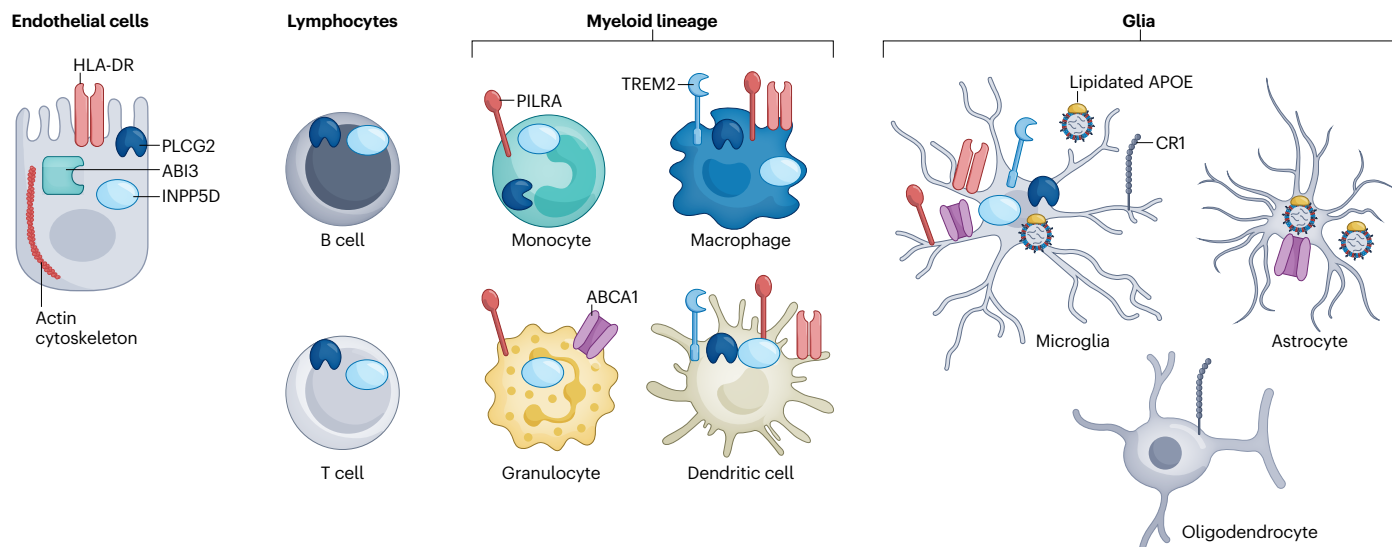
## Introduction

Activation of microglia – the resident innate immune cells responsible for surveillance and maintenance of homeostasis within the central nervous system (CNS) – has long been identified as a pathological hallmark of chronic neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD) and frontotemporal dementia (FTD). The consequences of this cellular immune response to pathology have been widely debated: some evidence suggests that it mitigates pathology, whereas other results suggest that it can exacerbate neuronal degeneration. In AD, genome-wide association studies (GWAS) have identified numerous risk-associated variants expressed in microglia, including in genes encoding triggering receptor expressed on myeloid cells 2 (*TREM2*), *CD33*, complement receptor type 1 (*CR1*), and Abelson interactor family member 3 (*ABI3*)<sup>1,2</sup>. Furthermore, AD heritability is enriched in open chromatin and active regulatory regions within microglia<sup>3,4</sup>. Although the genetic risk factors that contribute to PD, FTD and other chronic neurodegenerative diseases are distinct from those identified in AD, studies indicate that many of these variants also ultimately affect microglia function<sup>5–7</sup>. Indeed, emerging data indicate that microglia orchestrate complex and diverse functions, and the paradigm of 'resting versus activated microglia' has been replaced by identification of heterogeneous molecular profiles that can now be leveraged to determine which microglial states shape disease progression.

It is becoming increasingly clear that neuroimmune signalling and crosstalk mediated by various glial and peripheral immune cells may also contribute to AD pathogenesis<sup>8–10</sup>. Many AD risk genes expressed in microglia are also present in diverse peripheral immune cell populations (Fig. 1). For example, recent functional studies of *PLCG2* – a gene

encoding phospholipase C gamma 2 – have demonstrated that a rare coding variant that has been shown to be protective in AD<sup>11</sup> affects immune function in both the CNS and periphery. In addition, emerging evidence from studies examining AD pathology indicates that T cells can enter the brain parenchyma and act directly on microglia, promoting neurodegeneration in AD mouse models<sup>8</sup>. T cells have been detected in cerebrospinal fluid (CSF) of patients with AD<sup>9</sup>, further supporting this hypothesis. These central–peripheral interactions are actively orchestrated by diverse brain borders. The vascular blood–brain barrier (BBB) forms the principal interface between the CNS and the periphery, and it houses specialized immune niches that surveil and send signal to the brain through cells such as perivascular macrophages (PVM)<sup>12,13</sup>. Beyond the BBB, emerging data point to the involvement of other border regions in the neuroimmune interface<sup>14</sup>, including the dura<sup>15</sup>, leptomeninges, meningeal lymphatics<sup>16,17</sup> and choroid plexus<sup>18</sup>. Dysfunction of the BBB and other brain borders is evident early in disease<sup>19</sup> and may contribute to neurodegeneration. Supporting this view, several AD risk variants are expressed in border-associated cell types, wherein they can lead to dysregulated protein transport and immune interactions<sup>20–22</sup>. Together, these observations suggest that microglia may not act alone and underscore the need to consider how the peripheral immune system can influence CNS function.

In this Review, we will discuss recent advances in our understanding of neuroimmune interactions in the context of chronic neurodegenerative disease, particularly AD. We will focus on progress of the first wave of microglial targeting therapies that have been informed by human genetics, then describe emerging therapeutic approaches based on the rapidly developing understanding of microglial biology. This includes



**Fig. 1 | CNS-resident, vascular and peripheral immune cell types express AD risk factors.** Genome-wide association studies have linked Alzheimer's disease (AD) risk factors to peripheral immune cell types, vascular endothelium and central nervous system (CNS)-resident cells, including microglia, oligodendrocytes and astrocytes. These profiles suggest that multiple cell types beyond microglia may contribute to neurodegenerative disease and could be modulated by therapeutic strategies. Endothelial cells that form the blood–brain barrier in the cerebrovasculature can express many intracellular and extracellular factors, such as Abelson interactor family member 3 (*ABI3*). In the adaptive

immune system, lymphocytes express intracellular signalling mediators such as phospholipase C gamma 2 (*PLCG2*) and inositol polyphosphate-5-phosphatase D (*INPP5D*), whereas myeloid lineage cells in the periphery – such as monocytes, macrophages and dendritic cells – express a variety of receptors and their downstream signalling components such as triggering receptor expressed on myeloid cells 2 (*TREM2*) and paired immunoglobulin-like type 2 receptor alpha (*PILRA*). In the CNS, microglia show the broadest expression of AD risk factors whereas oligodendrocytes show robust complement receptor 1 (*CR1*) expression and astrocytes express apolipoprotein E (*APOE*).

approaches that target interactions between the CNS and peripheral immune systems, and how the brain vasculature acts as an important site of neuroimmune interactions. Finally, we highlight advances in the development of immune-based biomarkers which can be leveraged to enable accurate diagnosis, monitor disease progression, and evaluate efficacy in clinical trials.

## Microglia in health and neurodegeneration

Microglia are yolk sac-derived macrophages that reside in the CNS parenchyma and serve as its innate immune system. During development, microglia help maintain structural integrity during fetal morphogenesis<sup>23</sup> and coordinate the assembly of neuronal circuits<sup>24</sup>. Microglia show prominent spatiotemporal heterogeneity<sup>25,26</sup>, which is transcriptionally governed by the local composition of neuronal subtypes<sup>27,28</sup>.

In the healthy adult brain, microglia dynamically interact with neurons in their microenvironment, wherein they seem to be in constant surveillance<sup>29</sup>. For example, microglia respond to changes in neuronal activity to provide feedback regulation<sup>30</sup>, directly protect neurons and prevent neuronal calcium load via purinergic signalling<sup>31</sup>, promote spine formation through neurotrophic factor BDNF signalling<sup>32</sup>, and respond to neurotransmitter signalling including norepinephrine to help regulate sleep<sup>33</sup> and experience-dependent synaptic plasticity in the visual cortex<sup>34</sup>. A large body of data suggests that microglia can also affect neuronal function via synaptic engulfment. Studies from mouse brains, in which synapses become dysfunctional and are lost in a region-specific manner, suggest that microglia-synapse engulfment is a highly regulated process via specific molecular cues<sup>35–37</sup>. Disrupting synaptic engulfment leads to sustained neuronal hyperactivity, indicating that microglial phagocytosis of synapses has a protective role in maintaining proper neuronal function<sup>38</sup>. Apart from neurons, microglia can directly influence and respond to other CNS cells, including astrocytes<sup>39</sup>, oligodendrocytes<sup>40,41</sup> and PVM<sup>10</sup>, emphasizing the overarching role of microglia in regulating brain homeostasis.

In neurodegenerative disease, microglia undergo state transitions characterized by transcriptional changes<sup>42,43</sup>. The most well-studied state transition is often referred to as disease-associated microglia (DAM), which is defined by upregulation of genes involved in immune responses, phagocytosis and lysosomal biogenesis. Additional microglial states have been identified in mouse models and patients with AD, some related to the DAM state and other disease-specific states that probably underlie distinct, complex and adaptable microglial functions<sup>44,45</sup>. TREM2 is a key regulator of microglial state<sup>42</sup> that also modulates downstream processes such as lipid metabolism<sup>46</sup> and proliferation<sup>47</sup>. Additional genes associated with AD risk – including phosphatase-encoding genes *PLCG2* and *INPP5D* – are components of the TREM2 signalling pathway (Fig. 2a), providing further support that this receptor is a critical regulator of microglial function relevant to AD. Many other genetic risk factors have not been extensively studied owing to lack of clarity on the causative single-nucleotide polymorphism and low sequence homology between mouse and human orthologues.

Microglia also display region-dependent, age-dependent and sex-dependent heterogeneity in transcriptional states<sup>26,48,49</sup>. However, unlike neurons, in which subpopulations represent lineage identity, microglial heterogeneity reflects a dynamic process that enables diverse cellular functions from a single cell type<sup>44</sup>. Elucidating the effect of this dynamic cell type with spatiotemporal resolution has presented a challenge to the field. However, it also presents an exciting therapeutic opportunity to target specific disease-associated activities,

such as dampening secretion of the damage-inducing molecule osteopontin (SPP1)<sup>10,50</sup>, or enhancing protective functions of microglia through antagonism of paired immunoglobulin-like type 2 receptor alpha (PILRA)<sup>51</sup> or agonist activation of TREM2 (ref. 52). Furthermore, activation of TREM2 demonstrated distinct metabolic responses in microglia subpopulations based on low, mid or high levels of TREM2 expression, indicating that even levels of expression of certain genes can tune microglial responses to stimuli<sup>53</sup>.

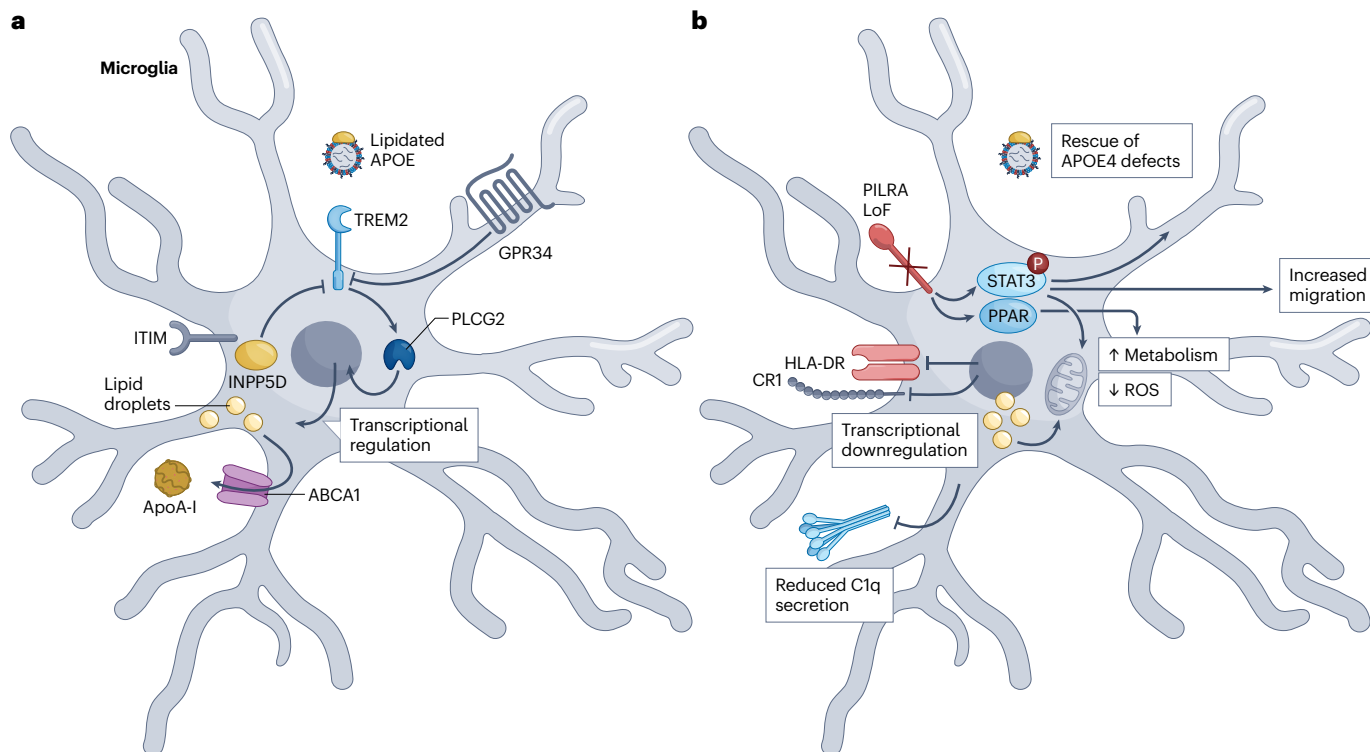
## Therapeutic approaches targeting microglia in AD

Drug development in AD has been dominated by approaches targeting hallmark pathologies such as amyloid plaques and tau pathology. However, the human genetic landscape in AD robustly implicates microglia and fortuitously revealed an entire new class of targets. Investment in this area has been further compelled based on data showing that targets with genetic evidence nearly doubles the rate of positive clinical outcomes<sup>54</sup>. This increased success rate is probably multifactorial in nature. First, genetic validation directly demonstrates that a gene contributes to disease rather than being a bystander. Second, genetic data can also provide confidence in determining the direction in which a potential drug should modulate a target based on how a coding variant affects target activity (for instance, loss-of-function variants that increase disease risk lend to a therapeutic strategy to activate a target). Last, a thorough understanding of the molecular genetics of human variants supports hypothesis-driven drug discovery, whereby screening cascades can be designed to identify a molecule with a mechanism of action that replicates or opposes human genetics based on the disease association. In some cases, such as *TREM2*, the genetic risk factor itself can be targeted, whereas in other instances, it is more straightforward to target pathways influenced by genetic variants based on either biological or technical limitations. Importantly, mechanistic data can also be used to identify non-genetically implicated targets, with the most compelling targets supported by multiple factors (such as biological activity, druggability and role in disease).

## Recent clinical advancements in targeting microglia: TREM2 therapies

The first wave of therapeutics targeting microglia directly via agonistic activation of TREM2 are now advancing in the clinic (Table 1). The therapeutic hypothesis for activating TREM2 is rooted in human genetic experiments, in which AD risk-conferring and loss-of-function coding variants in *TREM2* hinder microglia functions<sup>55</sup>. Increased levels of soluble TREM2 in CSF correlate with improved long-term outcomes in patients with AD, suggesting that promoting TREM2 signalling may have a beneficial effect<sup>56</sup>. On the basis of these results and of encouraging data in preclinical models, clinical trials have been initiated for agonistic TREM2 antibodies and small-molecule agonists in AD and adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), a disorder characterized by dysfunctional microglia that occurs as a result of loss-of-function mutations in colony-stimulating factor 1 receptor (CSF1R)<sup>57</sup>. The TREM2 agonist AL002 did not meet its primary end point in a phase II clinical trial for AD<sup>58</sup>, suggesting that either this mechanism of action may not be efficacious as a monotherapy or additional progress may be required to optimally target this receptor. Understanding the stage of disease in which TREM2 activation would be most effective and how frequently to dose are important clinical questions. Additional studies will be required to address these critical variables.

One of the challenges of the first generation of therapeutic antibodies targeting TREM2 is that target engagement may be insufficient



**Fig. 2 | Cellular interactions of AD genetic risk factors define disease-relevant pathways.** Alzheimer's disease (AD) risk factors that are co-expressed in microglia interact either via direct signalling mediators or through transcriptional regulation, revealing convergent pathways. Two examples are shown. **a**, TREM2 interacts with other AD risk factors including APOE, a putative ligand for TREM2. This interaction is inhibited by INPP5D by an ITIM-domain receptor, whose identity is unknown. GPR34 shows a genetic interaction with TREM2, as GPR34 loss of function (LoF) rescues deficits in Trem2 KO mice, and its tonic signalling limits the ability of microglia to transition to a responsive

state. PLCG2 mediates signalling downstream of TREM2 and is required for transcriptional regulation of many genes, including ABCA1, which mediates cholesterol efflux from lipid droplets. **b**, PILRA LoF has broad effects on AD risk genes and is associated with reduced risk in APOE4 carriers. Mechanistically, PILRA LoF increases STAT3 phosphorylation and PPAR activity, which promotes downstream signalling that enhances microglial migration and metabolic activity, respectively. PILRA LoF also reduces transcription of AD risk genes, such as HLA-DR and CR1, and reduces secretion of C1q, a complement component involved in synaptic pruning. ROS, reactive oxygen species.

owing to poor CNS penetration. Preclinical studies in an amyloid mouse model have shown that TREM2 antibodies engineered to cross the BBB using a transport vehicle – which comprises a monovalent transferrin receptor (TfR) binding site in the Fc domain – display substantially improved CNS exposure and biodistribution, and enhance TREM2 receptor clustering and microglial metabolism<sup>47</sup>. This finding suggests that activating TREM2 may rescue brain hypometabolism observed in patients with AD<sup>59</sup>.

### Microglial metabolism: the next wave of therapeutic targets

The growing number of AD-associated genes that regulate microglial metabolism – including TREM2, PILRA<sup>51</sup>, APOE (apolipoprotein E)<sup>60</sup> and PLCG2<sup>61</sup> – highlights metabolic function as a critical node in microglial function. Evidence that metabolic alterations can influence microglial behaviour<sup>62</sup> and downstream disease outcomes further supports the therapeutic potential of these pathways. Differences in microglial immunometabolism have also been linked to sex-specific phenotypes observed in AD mouse models<sup>63</sup>, and in humans, females have a higher risk of developing AD than males<sup>64</sup>. These observations have prompted exploration of several candidate drug targets within this metabolic axis.

Hexokinase 2 (HK2)<sup>65</sup> and prostaglandin E2 receptor (EP2)<sup>66</sup> have been identified as important regulators of myeloid cell metabolism and inflammation. However, given their pleiotropic expression across cell types, targeting these pathways would not specifically modulate microglial metabolic activity. Although HK2 and EP2 are not ideal drug targets, these studies confirm the critical role of metabolism in regulating immune cell state and function in microglia. In oncology, the interplay of metabolic activity and immune cell function is well-understood and has provided a paradigm shift in therapeutic approaches; this principle may also apply to microglia. In particular, lipid and glucose metabolic pathways are emerging as critical regulators of beneficial microglial responses to disease pathology through maintenance of high metabolic capacity<sup>67</sup> to avoid dysfunction<sup>68</sup> and support responses to mounting pathologies.

Small-molecule agonists of Liver X receptor (LXR) promote lipid efflux in glia, resulting in marked improvement of disease pathologies including reduced neuroinflammation, tau accumulation and neurodegeneration in a tauopathy mouse model carrying an APOE4 allele<sup>69</sup>. LXR agonists, however, are not therapeutically viable owing to safety liabilities, including hepatic lipogenesis and hypertriglyceridemia<sup>70</sup>. The lipid transporter ABCA1, a downstream target of LXR, can ameliorate

disease phenotypes when overexpressed approximately twofold in transgenic mice<sup>69</sup>. Predicted loss-of-function variants in *ABCA1* increase AD risk<sup>71</sup>, providing human genetics support for *ABCA1* agonist activation as an alternative therapeutic approach. However, directly targeting *ABCA1* remains challenging; agonist peptides show no activity in CSF, probably owing to restricted brain exposure<sup>72</sup> and small molecules designed to upregulate *ABCA1* expression have not succeeded clinically<sup>73</sup>, potentially owing to indirect effects of their mechanism of action. Therefore, CNS-penetrant small-molecule agonists that specifically increase *ABCA1* cholesterol efflux activity in the brain represent a promising avenue for further drug discovery.

GPR34 is a G-protein-coupled receptor (GPCR) expressed in homeostatic microglia that senses lysophospholipids and may represent an alternative strategy to modulate lipid metabolism. It is an attractive small-molecule target given the druggability of GPCRs<sup>74</sup>. Tonic GPR34 signalling is thought to maintain microglia in a quiescent, low metabolic state. Therefore, inhibiting GPR34 in the presence of pathology may allow microglia to transition to disease-resolving states. Loss-of-function studies have recently demonstrated improved cognitive impairment in an amyloid mouse model and reduced neuroinflammation potentially via ERK signalling<sup>75</sup>. Studies in human iPSC-derived microglia (iMG) have shown that CRISPR-mediated knockout (KO) of *GPR34* is sufficient to rescue lipid dysregulation in *TREM2* KO iMG, indicating that GPR34 and *TREM2* signalling pathways converge<sup>76</sup>. *GPR34* KO iMG also show enhanced mitochondrial function independently of *TREM2* KO, suggesting that loss of *GPR34* is sufficient to modulate

microglial metabolism. In both healthy animals and AD mouse models, *GPR34* KO accelerated microglial state shifts from homeostatic to responsive states (such as DAM)<sup>76</sup>. Therefore, GPR34 represents a novel disease-relevant and putatively druggable target for modulating microglial state and metabolism.

A loss-of-function coding variant in the gene encoding *PILRA* abrogates ligand binding<sup>77</sup> and reduces AD risk<sup>1,2</sup>. Additional genetic analyses indicate that a *PILRA* variant also modifies AD risk in *APOE4* carriers, adding a new dimension to the human genetics of this receptor<sup>51,78</sup>. *PILRA* is a cell surface inhibitory immune receptor with an extracellular IgV ligand binding domain that adopts the fold characteristic of sialic acid-binding immunoglobulin-like lectins (SIGLEC), as well as two intracellular immunoreceptor tyrosine-based inhibitory motifs (ITIM)<sup>79</sup>. Mechanistic studies of *PILRA* KO in human iMG have shown rescue of *APOE4*-driven immunometabolic defects and revealed distinct regulation of lipid metabolism via PPAR<sup>51</sup>. In a chimeric AD model, mice transplanted with *PILRA* KO iMG showed reduced amyloid pathology and improved detection of synaptic markers that are reduced in disease. A *PILRA* antagonist antibody phenocopied *PILRA* KO iMG<sup>51</sup>. Together, these findings position *PILRA* as a novel drug target for AD that regulates immunometabolism in microglia (Fig. 2b).

### Targeting microglial-synapse interactions

Synaptic dysfunction and neuronal network disturbance are early pathologies in neurodegenerative diseases<sup>80</sup>. A key developmental pruning mechanism involving the complement cascade was found to

**Table 1 | Targets and clinical development status for therapeutics that modulate the neuroimmune axis**

Target	Drug	Company	Molecule	Mechanism of action	Clinical stage	Clinical trial number	Indication	Ref.
TREM2	AL002	Alector	Antibody with PSEG Fc mutations	TREM2 stalk binding agonist with enhanced effector function	Phase II	NCT04592874	AD	Wang et al. <sup>229</sup>
TREM2	VGL101	Vigil	Antibody	TREM2 stalk binding agonist	Phase II	NCT05677659	ALSP	Larson et al. <sup>230</sup>
TREM2	VG-3927	Vigil	Small molecule	Proposed 'molecular glue' properties to activate TREM2 via DAPI2 interactions	Phase I	NCT06343636	AD	Alzforum
C1q	ANX005	Annexon	Antibody with IgG4 Fc	Inhibits C1q binding to block complement cascade activation	Phase III (GBS) *Phase IIb/III (HD/ALS)	NCT04701164	GBS, HD/ALS	Kumar et al. <sup>231</sup>
Fibrinogen	THN391	Therini Bio	Antibody	Fibrinogen cleavage by thrombin exposes a cryptic epitope termed P2, which is distinct from the coagulation epitope on fibrin THN391 binds the P2 epitope without interfering with the clotting process	Phase I	NCT06701721	AD, diabetic macular oedema	Kantor et al. <sup>232</sup>
TYK2	A-005	Alumis	Small molecule	Allosteric brain-penetrant TYK2 inhibitor	Phase I (1H 2024)	NCT05223832	MS, PD	ClinicalTrials Arena
RIPK1	DNL788/SAR443820	Denali and Sanofi	Small molecule	Brain-penetrant kinase inhibitor	Phase II	NCT05237284	MS	Hincelin-Mery et al. <sup>233</sup>
BTK	SAR442168	Sanofi	Small molecule	Brain-penetrant kinase inhibitor	Phase III	NCT04411641	MS	Fox et al. <sup>215</sup>
NLRP3	NT-0796	NodThera	Small molecule	Brain-penetrant inflammasome inhibitor	Phase Ib/phase IIa	ACTRN12621001082897	PD	Harrison et al. <sup>234</sup>
NLRP3	VENT-02	Ventus	Small molecule	Brain-penetrant inflammasome inhibitor	Phase I	Not available	PD, epilepsy, AD, ALS	Tengesdal et al. <sup>235</sup>

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ALSP, adult-onset leukoencephalopathy with axonal spheroids and pigmented glia; GBS, Guillain-Barré Syndrome; HD, Huntington's disease; MS, multiple sclerosis; PD, Parkinson's disease; TREM2, triggering receptor expressed on myeloid cells 2; TYK2, tyrosine kinase 2; \*Planned clinical studies not yet initiated based on company disclosure.

## Box 1 | Drug delivery strategies to improve BBB transport and biodistribution in the CNS

The blood–brain barrier (BBB) limits therapeutic access and is a major challenge for central nervous system (CNS) drug delivery. Technologies that leverage the native transcytosis capacity of receptors expressed at the BBB to deliver cargos such as the iron-carrier transferrin receptor (TfR) have shown potential to overcome this barrier in preclinical studies<sup>163</sup> and recent clinical trials. Data from early-stage clinical trials show that an anti-amyloid antibody engineered to bind TfR demonstrated rapid and robust plaque clearance in patients with Alzheimer's disease, suggesting that TfR-mediated brain uptake remains efficient in disease<sup>162</sup>. Nonetheless, a further understanding of the factors that affect TfR-mediated transport and the identification of other transcytosis receptors could inform brain delivery options. Moreover, new BBB targets are emerging, as the amino acid transporter CD98hc was shown to mediate delivery of antibodies into the brain with preferential binding to glia<sup>164</sup>. Dual TfR and CD98hc targeting platforms are being investigated that could potentially enable tuning of brain uptake and exposure<sup>236</sup>. Additionally, insulin-like growth factor 1 receptor (IGF1R) is being targeted for BBB transport of alpha-synuclein antibodies<sup>237</sup> to tackle this Parkinson's disease pathology. Thus, a new generation of BBB targets and engineered approaches for CNS delivery may improve therapeutic targeting in the CNS.

be reactivated in a region-specific manner in models of neurodegenerative diseases<sup>81</sup>. In the periphery, the complement cascade functions as key arm of the innate immune system to attack and destroy invading pathogens<sup>82</sup>. In the CNS, components of the complement pathway, such as C1q, are upregulated and secreted by microglia and deposited on synapses. This initiating step leads to C3 activation and glial-mediated synapse elimination<sup>81,83</sup>. Microglial synaptic engulfment has been observed in multiple disease models, including amyloidosis<sup>81,84</sup>, tauopathy<sup>84,85</sup> and progranulin deficiency<sup>86</sup>. Therefore, complement pathway activation may be an underlying mechanism driving synapse loss in neurodegenerative disease<sup>87</sup>.

Blocking complement either genetically or pharmacologically in AD models ameliorates synaptic function and cognitive impairment<sup>81,84</sup>. These studies support a role for microglial-synapse engulfment in disease and implicate complement factors as potential therapeutic targets, an approach that has been successful in other disease areas such as neuromyelitis optica spectrum disorder<sup>88</sup> and age-related macular degeneration<sup>89</sup>. Indeed, antibodies that block C1q, the active form of C1s, or other components of the complement cascade are advancing in the clinic for multiple diseases<sup>90</sup> (Table 1), with interesting results in mouse models of AD. Other targets of interest in the pathway include CR1, which is expressed on glia<sup>91</sup> and PVM<sup>20</sup>, and C7, which can be inhibited with a blocking antibody<sup>92</sup>.

Several additional regulators of microglia-synapse engulfment have been described, including TREM2 (refs. 38,93) and other receptors via binding to cell surface exposed phosphatidylserine<sup>94,95</sup>, CX3CR1 (ref. 96), SPP1 (ref. 10) and neuronal pentraxin (NPTX2)<sup>97</sup>. TREM2 detects damaged synapses by externalized phosphatidylserine on cell membranes following localized caspase-3 activation<sup>98–100</sup>. Microglia lacking TREM2 were unable to phagocytose synapses in AD mouse models,

leading to neuronal hyperactivity<sup>38</sup>. NPTX2 binds C1q at the synapse wherein it is released by excitatory neurons in an activity-dependent manner<sup>101</sup> and inhibits downstream microglial-synapse engulfment<sup>97</sup>. By contrast, SPP1 is upregulated and secreted by PVM as amyloid accumulates in the perivascular space, leading to aberrant activation of C1q and synapse loss<sup>10,102</sup>. These observations propose additional therapeutic avenues to intervene with microglial-mediated synaptic pruning.

## Brain borders

The unique anatomical and physiological properties of brain borders shape how peripheral cues reach the CNS. The meninges<sup>103</sup>, choroid plexus<sup>104</sup> and the BBB<sup>105</sup> each contribute to this regulation through their characteristic combination of endothelial, mural, stromal and resident immune cell types. Other immune cells within brain borders<sup>106</sup>, beyond microglia in the parenchyma, suggests an evolved arrangement to allow restricted sensing of peripheral challenges while maintaining a delicate CNS environment for optimal neuronal function. These border regions, particularly in the dura matter, subdural meninges<sup>107</sup>, meningeal lymphatics<sup>15,17</sup> and choroid plexus<sup>108,109</sup>, act as active sites for neuroimmune interactions. Mapping where these interactions occur will be critical to determine how new therapies could affect disease progression.

## Brain vasculature

Unique amongst brain borders, the brain vasculature is distributed across the brain parenchyma, at most microns away from any individual neuron<sup>110</sup>. The brain vasculature consists of continuous endothelial cells with specialized properties – such as paracellular tight junctions, regulated transcytosis and downregulated immune adhesion receptors – induced by signals from enveloping pericytes, astrocyte end-feet and neurons. These properties define the specialized biology of the BBB<sup>111</sup>, which has historically been a limitation for development of effective CNS therapies (Box 1). In addition to acting as a barrier to protect the CNS, the brain vasculature has an essential role in transporting key nutrients and signalling molecules, clearing waste and antigens from the brain, and controlling cerebral blood flow, and it is emerging as an important regulator of neuroimmune interactions in health and disease.

Vascular dysfunction is now recognized as an early pathological change associated with neurodegeneration<sup>19</sup>. Disruptions in cerebral blood flow and molecular changes in the BBB<sup>112</sup>, can precede clinical symptoms of disease and midlife vascular risk factors predispose for later-life amyloid deposition and neuroinflammation. In AD, amyloid accumulates not only in parenchymal plaques but also along the vasculature forming cerebral amyloid angiopathy (CAA), with 80% of post-mortem AD brains exhibiting considerable vascular pathology in addition to amyloid plaques<sup>113,114</sup>. Although it is difficult to conclusively determine whether vascular pathologies directly contribute to neurodegeneration, the presence of CAA correlates with an increased rate of cortical microbleeds<sup>115</sup>. Brain vascular cells express AD risk genes<sup>1</sup>, which may contribute to vascular dysfunction<sup>20</sup>. Conversely, microglia also regulate cerebrovascular amyloid pathology. In an AD mouse model, depletion of microglia results in profound CAA via redistribution of parenchymal amyloid to blood vessel walls leading to early lethality<sup>116</sup>. Moreover, *APOE* variants specifically expressed in microglia and *PICALM*, which is expressed in both microglia and vascular cells, have also been linked to increased CAA<sup>117,118</sup>. Large GWAS studies to identify CAA risk factors hold promise to more clearly determine genes linked to this neuropathological feature of AD.

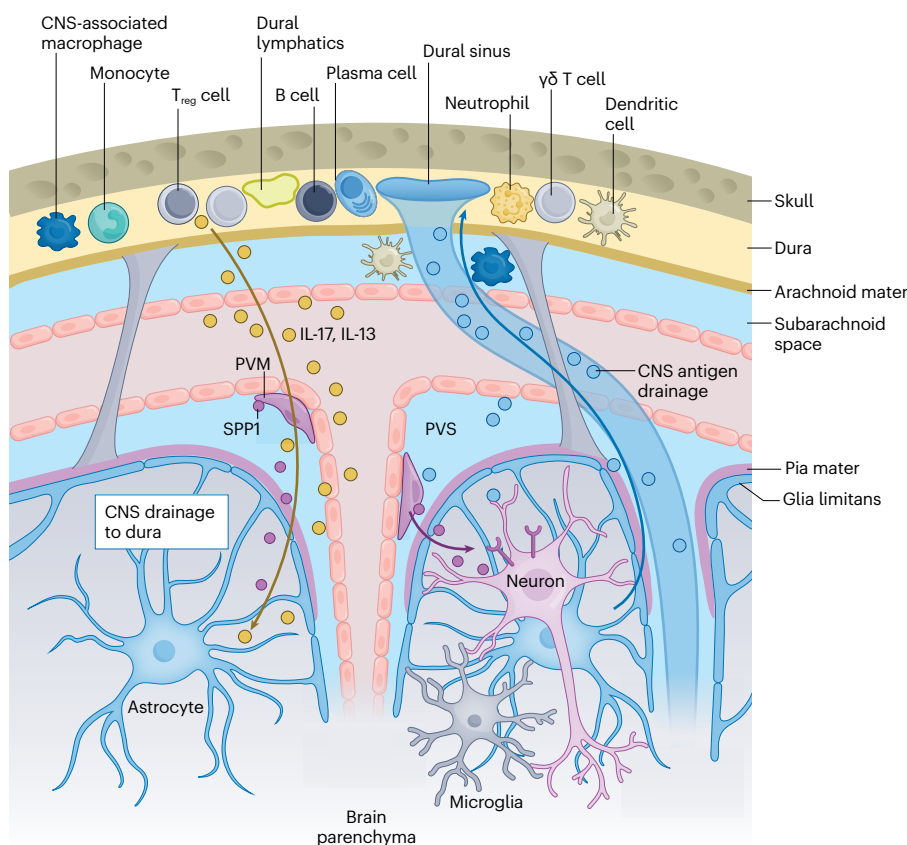
The potential for BBB breakdown has been reported in AD<sup>119</sup>, while other more subtle alterations in brain vascular function can lead to changes in neuroimmunity. Compromised mechanisms for amyloid- $\beta$  (A $\beta$ ) efflux from the CNS can lead to aggregation and glial activation, such as those observed upon loss of function of the receptor LRP1<sup>120</sup>. Changes in expression of *PICALM* have also been shown to compromise endothelial clearance of amyloid in preclinical models<sup>121</sup>. Additionally, the brain vasculature may facilitate peripheral immune cell infiltration in ageing and AD<sup>8,9,122</sup>. The brain vasculature harbours resident immune cells that can communicate with microglia and other parenchymal cells<sup>10</sup>, such as border-associated macrophages (BAMs) (Fig. 3), which can drive cognitive impairment and neuroinflammation in AD via oxidative stress<sup>123,124</sup>. BAMs within the perivascular space regulate A $\beta$  removal and, thus, are key contributors of CAA clearance, and BAM depletion or dysfunction is sufficient to increase CAA burden<sup>123,125</sup>. Consistent with these observations, BAMs have been linked to adverse events with anti-amyloid therapies, such as neuroinflammation and amyloid-related imaging abnormalities (ARIA)<sup>126</sup>, and may act as antigen-presenting cells to initiate CD4<sup>+</sup> T-cell responses<sup>127</sup>. Together, these studies highlight the role of immune cells residing within the cerebrovasculature to mediate neuroimmune crosstalk and regulate disease pathologies with important therapeutic considerations.

## Brain border structures: meninges, skull bone marrow and choroid plexus

Although the brain parenchyma lacks a standard lymphatic network, a sophisticated ‘peri-brain’ system has been described in which

CNS drainage routes carry solutes into the CSF and lymphatics<sup>15,17,128</sup>. Immune cells are present in the dura and skull<sup>129–131</sup>, and conduits link brain interstitial fluid (ISF) to CSF in these distal brain border sites. CSF, thus, functions as an immunologically relevant biofluid that carries antigens from the parenchyma to border sites for immune surveillance. Therefore, although physically separated from the brain parenchyma, immune cells in the CSF, meninges, dura and skull can monitor the health of the brain from a distance.

Each brain border site exhibits a distinct immunological niche (Fig. 3). The choroid plexus, located within the ventricles of the brain, consists of secretory, barrier epithelial cells that support mesenchymal, fenestrated endothelial cells and macrophages<sup>132</sup>. The choroid plexus epithelium is the principal source of CSF<sup>133,134</sup>, which may intermix with ISF before resorption by arachnoid villi<sup>135,136</sup>, classical lymphatics beneath the cribriform plate<sup>137</sup>, or meningeal lymphatics in the dura<sup>16,17</sup>. These routes drain to cervical lymph nodes or enter systemic circulation<sup>135,138</sup>. CSF flow along the meningeal lymphatics can bring antigens to the dural sinuses<sup>131,139</sup>, which are formed by stromal and vascular cells that express adhesion molecules (VCAM-1) and chemokines, such as CXCL12 (ref. 131) to support immunological processes. Dural immune cells originate not only from circulation but also from nearby skull bone marrow<sup>130,140</sup>, and they show dampened inflammatory responses to brain injury compared with their blood counterparts<sup>130</sup>. How the CNS communicates with immune cells in the dura and skull when they reside on opposite sides of the arachnoid barrier has been a longstanding question<sup>141</sup>. Addressing this paradox, a recent study has identified



**Fig. 3 | Immune cells at brain barriers coordinate surveillance and signalling.** Diverse communities of immune cells residing in defined brain border niches, enabling ‘immunity in orbit’ – surveillance of the brain from a distance – while sending signals back to parenchymal cells. At the brain vasculature, perivascular macrophages (PVMs) – a subset of border-associated macrophages residing in the perivascular space – sense antigens such as amyloid- $\beta$ . In response, PVMs secrete SPP1 to parenchymal microglia to upregulate endolysosomal activity and phagocytosis of neuronal synapses. In the meninges,  $\gamma\delta$  T cells residing in the dura (the outermost layer of the meninges) secrete IL-17a, which is detected by neurons, affecting glutamatergic synapse plasticity and cognition, and regulating anxiety-like behaviour. Dural T cells reside along the sinuses, which are immunological sites that drain central nervous system (CNS) antigens and host antigen-presenting cells. Thus, CNS-specific adaptive immune responses can be mounted at distal sites that can communicate to the parenchyma. Beyond surveilling the adult brain at steady-state, dural immune cells may shape brain development: a subset of innate lymphoid cells (ILC2s) in the dura secrete IL-13 to modulate inhibitory synapse development and social behaviour. PVS, perivascular space.

discontinuities in the arachnoid barrier created by bridging veins that enable CSF efflux into the dura and potentially connect the brain to immune cells in the dura and skull<sup>142</sup>.

Impaired clearance of aggregate-prone proteins, such as amyloid, from the brain is a hallmark of AD. A series of studies put forth different models of waste clearance from the brain, including via the glymphatic system<sup>143,144</sup> versus other pathways<sup>145,146</sup>, as well as the nature and degree of CSF and ISF mixing before exiting the brain. A key contention between these models rests on the degree of convective flow (glymphatic hypothesis) versus diffusion (classical hypothesis) that mediates CSF–ISF mixing in capillaries<sup>147</sup>. Biophysical considerations, such as the high resistance of the interstitial extracellular matrix of the brain to convective flow, remain to be reconciled with the glymphatic hypothesis<sup>148</sup>. Despite the controversy, slower waste clearance has been consistently documented in ageing and neurodegeneration<sup>149,150</sup> and altered lymphatic flow has been reported to aggravate amyloid burden in the brain<sup>21,151</sup>. In humans, some studies report amyloid accumulation in the dura<sup>150</sup>, whereas others report no changes in meningeal lymphatic vessels. Immune cells in the dura and skull bone marrow probably sense and respond to the shifts in CSF composition arising from impaired waste drainage in AD, suggesting that impaired lymphatic flow and waste clearance could alter the neuroinflammatory state of the brain.

## Therapeutics strategies targeting brain borders

Although still an emerging area, our expanded understanding of the brain vasculature beyond its barrier function suggests that the vasculature should be considered as part of therapeutic development for AD. For instance, approaches to attenuate CAA-induced vascular dysfunction and neuroinflammation are important elements of treatment strategies<sup>152,153</sup>. In addition, peripheral delivery of engineered Wnt7a signalling ligands that bind to the GPR124–RECK receptor complex on brain endothelial cells have been shown to promote restoration of BBB properties in brain tumours and ischaemic stroke models<sup>154</sup>, suggesting that vascular repair may be feasible after damage is incurred. Intriguingly, diverse disease models converge on a core set of gene expression changes in the brain endothelium<sup>155</sup>, with pathways related to leukocyte trafficking, extracellular matrix and aberrant angiogenesis linked to changes reported in AD<sup>20,156,157</sup>. Therefore, rather than general ‘BBB breakdown’, it seems that specific phenotypic and molecularly defined changes occur in the BBB during disease that are potentially therapeutically reversible. Indeed, partial reversal of transcriptional ageing signatures in brain endothelial cells has been demonstrated using various approaches, including a GLP-R agonist<sup>158</sup> and an inhibitor of ALPL (also known as TNAP) which restored tight junction barrier properties and receptor-mediated transcytosis of proteins, such as transferrin<sup>159</sup>.

Conversely, the ability to cross the BBB must be considered for the development of any AD therapeutic. The restricted BBB permeability to standard antibodies is preserved in disease<sup>160</sup> and recent preclinical data show that anti-amyloid antibodies targeting BBB-permeable transferrin receptor enhance brain delivery and reduce ARIA-like lesions and vascular inflammation<sup>161</sup>. Ongoing clinical trials have demonstrated that trontinemab, a BBB-penetrating anti-amyloid antibody, achieved similar results characterized by more rapid and extensive plaque clearance compared with standard IgGs<sup>162</sup>. Therefore, the BBB remains a key regulator that restricts CNS access for AD therapeutics that can be overcome with engineering approaches for large molecules<sup>163,164</sup>.

## Role of the peripheral immune system in the CNS

Emerging data from mouse models and human pathology suggest that the peripheral immune system may be more involved in brain homeostasis and disease than previously thought. Numerous AD risk factors are not exclusively expressed in microglia but are also detected in peripheral immune cells such as monocytes, neutrophils, natural killer cells, T cells and B cells. Moreover, genetic signals in the HLA region suggest that antigen-presenting cells, such as macrophages and dendritic cells, could play an important part in regulating adaptive immunity in AD. Recent studies have found T cells and B cells residing within the brain or brain borders<sup>14</sup>, wherein they are thought to modulate neuroimmune functions. This observation raises intriguing questions of whether, and if so, how, these dynamic cellular interactions could become dysfunctional with ageing and in disease. Notably, peripheral immune dysregulation was detected in the CSF of aged and cognitively impaired individuals<sup>165</sup>, whereas epigenetic changes in peripheral immune cells resulting in increased inflammatory gene expression was recently reported in AD<sup>166</sup>. Therefore, upon revisiting human genetics signals in the context of these findings, targeting peripheral immune populations may be an important aspect or potential outcome of therapeutic strategies for CNS diseases when leveraging human genetics for target selection.

## T cells in the CNS

T cells monitor the body to eliminate cancer or pathogen-infected cells by engaging with specific antigens via T-cell receptors (TCRs)<sup>167,168</sup>. Under normal conditions, T cells are largely excluded from the brain parenchyma by the glia limitans. Although the signals underlying CNS-homing are not fully understood, known routes of T-cell entry include the vascular BBB<sup>169</sup>, leptomeninges<sup>170</sup> and choroid plexus<sup>171,172</sup>. These T cells can undergo apoptosis<sup>173</sup>, differentiate into central memory or tissue-resident T cells in the CSF and brain borders<sup>9,174</sup>, or exit the CNS. Single-cell studies have shown that T cells in the CSF are distinct from those in blood<sup>122,175</sup>, suggesting that they encounter CNS-specific antigens. Brain resident CD4<sup>+</sup> T cells can contribute to microglial synaptic pruning during development<sup>176</sup>. In the healthy adult brain, T cells are sequestered in brain borders and CSF yet influence neuronal development and function from afar (Fig. 3). For example, T cells in the meninges secrete cytokines such as IL-17, IL-4 and IFN $\gamma$  to regulate synaptic plasticity, short-term memory and social behaviour<sup>177–179</sup>. Depletion of T cells results in cognitive dysfunction, which is reversible via T-cell restoration<sup>180</sup>. These and other findings indicate the dependency of neuronal function on lymphocytes within and beyond brain borders. Indeed, neurons express various cytokine receptors enabling detection and response to immune modulators<sup>181</sup>.

In ageing and neurodegenerative diseases, T cells infiltrate the brain and undergo clonal expansion, with cytotoxic CD8<sup>+</sup> T cells present in mouse models of disease<sup>8</sup> and ageing<sup>182</sup>, as well as in human ageing<sup>183</sup> and AD<sup>9,184</sup>. Helper CD4<sup>+</sup> T cells respond to alpha-synuclein pathology in patients with PD and mouse models<sup>185,186</sup>. Lymphocytes can exert either protective or detrimental effects depending on the context. In an amyloid model, immunodeficiency exacerbated amyloid pathology whereas bone marrow transplantation partially rescued these effects<sup>187</sup>. By contrast, in a *APOE4* tauopathy model, T cells recruited by microglia clonally expanded and triggered neurodegeneration<sup>8</sup>. These divergent findings could reflect differential roles of distinct T-cell subsets or differences between pathology models. Microglia express MHC class II which functions as

antigen presentation machinery<sup>188</sup>, suggesting that these cells could potentially contribute to T-cell activation in AD.

Regulatory T cells (T<sub>regs</sub>) have a potential neuroprotective function, suppressing inflammation in the hippocampus, and have shown functional deficiencies in human AD<sup>189,190</sup>. In mouse models of AD, enhancing T<sub>reg</sub> activity – either through expansion or adoptive transfer – mitigated amyloid pathology, reduced neuroinflammation and improved cognitive function<sup>191,192</sup>, although transient depletion of T<sub>regs</sub> can also mitigate AD pathology<sup>193</sup>. These findings highlight the complex roles of T cell subsets in the brain, and although it is increasingly evident that T cells can gain access to the brain parenchyma in mouse models of neurodegenerative disease, the relevance to human disease remains an outstanding question.

Several molecular pathways govern T-cell activation and infiltration in the AD, which suggest potential therapeutic targets. The CXCL16–CXCR6 and CXCR3–CXCL10 axes may mediate the recruitment and residency of activated T cells into the parenchyma<sup>194,195</sup>. Expression of the PD-1–PD-L1 immune checkpoint pathway, which functions to preserve immune tolerance, may potentially be altered in peripheral immune cell types in patients with AD<sup>196</sup>. Immunotherapies targeting this pathway could be repurposed to investigate their potential for efficacy in AD. Expansion of T<sub>regs</sub> with low-dose IL-2, a master lymphocyte regulatory cytokine, were safe and well tolerated in a phase I trial for ALS and require larger trials to determine efficacy<sup>197</sup>. This approach has not yet been examined for AD. Although many questions remain about the precise roles of T cell subsets in AD, their involvement in shaping the neuroinflammatory milieu indicates further study is needed to determine their therapeutic potential.

## Novel therapeutic targets with peripheral and CNS impact

The wealth of genes linked to AD risk that are expressed in microglia within the CNS has driven substantial amount of research into how this cell type affects disease. However, many of these genes are also expressed in the peripheral immune system, and any alterations in expression or function associated with genetic variation may just as readily affect peripheral immune cell populations. This, along with the emerging functional data described above, suggests a more holistic view of how therapeutically modulating immune function and its impact in the CNS is warranted.

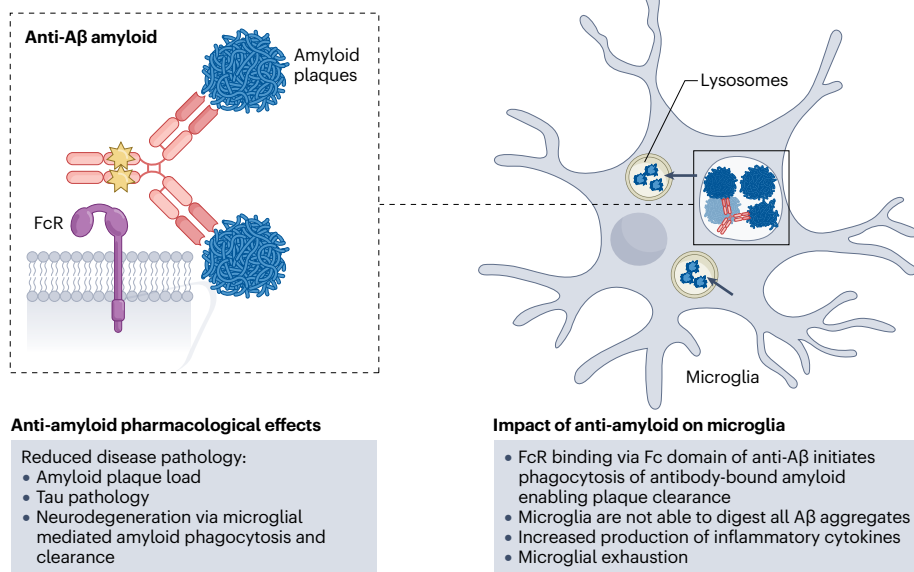
**PLCG2.** PLCG2 is a potential immunomodulatory drug target that is expressed in both innate and adaptive immune cells such as microglia, macrophages, T cells and B cells. It functions as a signalling mediator downstream of multiple immune receptors including Toll-like receptors and TREM2 to regulate inflammation, phagocytosis, lipid metabolism and cell survival<sup>61</sup>. On the basis of its intracellular localization and phospholipase enzymatic activity, PLCG2 is a candidate small-molecule drug target. A mild hypermorphic *PLCG2* variant P522R has been shown enriched in a cohort of cognitively healthy centenarians<sup>198</sup> and confers protection in AD<sup>11</sup>. The emerging role for the *PLCG2* P522R variant in promoting immune cell function has been shown in both peripheral B cells<sup>199</sup>, macrophages and microglia<sup>200</sup>. These findings raise the possibility that the peripheral immune system, in addition to activity in CNS resident microglia, could contribute to the neuroprotective effects of *PLCG2* P522R. Reduced PLCG2 activity via the M28L variant worsens disease in an AD mouse model<sup>201</sup>, however the effect of this variant on the peripheral immune system has not been investigated. Notably, the evidence linking the M28L variant to increased AD risk is less established than for P522R and AD protection. By contrast, strong hypermorphic

variants of *PLCG2*, such as S707Y and M1141K, are associated with autoimmunity and hematopoietic malignancies<sup>202</sup>. Together, the genetics of *PLCG2* suggest that therapeutic modulation would need to achieve the correct threshold of optimal activity and potentially act via signalling bias (such as promoting TREM2 yet not inducing pro-inflammatory pathways<sup>61</sup>). Efforts to identify small-molecule PLCG2 agonists are in the preclinical discovery stage. Although previously considered a liability, mild activation of PLCG2 is an intriguing approach based on human genetics and functional data indicating potential beneficial effects from both peripheral and CNS immune cells.

**INPP5D.** Inositol polyphosphate-5-phosphatase D (INPP5D) is genetically implicated in AD<sup>203</sup> and emerging as a druggable target readily amenable to small-molecule modulation based on its structure and function. *INPP5D* encodes the protein Src homology 2 (SH2) domain-containing inositol 5'-phosphatase 1 (SHIP1), which is expressed in microglia and peripheral immune cells<sup>204</sup>. As a lipid phosphatase signalling mediator, it inhibits numerous immune pathways by functioning downstream of ITIM-domain containing receptors and suppressing ITAM receptors such as TREM2. *INPP5D* resides within a major AD GWAS risk locus, and it is highly expressed in AD brains. Recent data suggest that INPP5D could regulate the NLRP3 inflammasome<sup>205</sup>, suggesting that increased SHIP1 can have a pro-inflammatory effect in the CNS. Specific targeting of SHIP1 in immune cells is challenging owing to homology with SHIP2, which is expressed ubiquitously. However, pan-SHIP1 and SHIP2 inhibitors can increase microglial functions in mouse models of AD<sup>206</sup>, although the safety profile of this approach requires further investigation. SHIP1 is known to have phosphatase-dependent and independent effects mediated by binding interactions, therefore, strategies to modify both enzymatic activity and binding partners need to be considered. Moreover, the directionality of modulating this lipid signalling node requires further elucidation as selective SHIP1 agonists<sup>207</sup> have been investigated as part of a strategy to dampen immune cell function at late stages of disease, in which chronic neuroinflammation is thought to be a disease driver.

## Non-genetically implicated targets with immune pathway potential.

The cyclic GMP-AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway detects pathogen or self-DNA released into the cytoplasm wherein it can trigger innate immune responses in macrophages, dendritic cells and T cells. Signalling via the STING pathway induces type I interferons and pro-inflammatory cytokines to coordinate innate and adaptive immune responses. STING activity is required to control pathogenic infections; however aberrant sterile activation leads to numerous human diseases. cGAS–STING has been implicated in Aicardi–Goutières syndrome<sup>208</sup> and AD<sup>209</sup>, and STING deficiency or inhibition can be protective in neurodegenerative and inflammatory mouse models<sup>210</sup>. Small-molecule cGAS inhibitors have been identified<sup>211</sup> that engage the catalytic pocket or block ligand binding, which have provided starting points to therapeutic development. Peripherally restricted cGAS inhibitors are in early clinical development for inflammatory indications, whereas brain-penetrant compounds are in preclinical development. Small-molecule STING inhibitors that prevent ligand binding or bind covalently have also been identified although have not yet reached the clinic. Finally, a protein degradation approach has been explored for reducing STING activity using proteolysis-targeting technology (PROTAC)<sup>212</sup>. In neurodegeneration, inhibiting the cGAS–STING pathway would most probably affect subpopulations of microglia that predominantly express a type I interferon



**Fig. 4 | Mechanism of action for anti-amyloid antibodies and impact on microglia.** For amyloid plaque clearance, anti-amyloid antibodies require effector function in the Fc domain (orange stars) that bind Fc receptors (FcRs) expressed on microglia. FcR engagement directs microglia cells to phagocytose antibody-bound amyloid which leads to internalization and lysosomal degradation. However, microglia cannot digest all amyloid- $\beta$  ( $A\beta$ ) aggregates, and FcR engagement can promote inflammatory cytokine production. With long-term chronic dosing, the burden anti-amyloid antibodies place on microglia could lead to exhaustion and ineffective efficacy.

signature<sup>213</sup>, and peripheral inhibition of this pathway could provide an added benefit worth further exploration.

Cytokines are key coordinators of immune responses and drivers of neuroinflammation, and therapeutic approaches to inhibit their production may be beneficial in AD. Tyrosine kinase 2 (TYK2) is a Janus family tyrosine kinase that mediates STAT signal transduction downstream of IL-6, IL-10, IL-23 and type I interferon receptors that are broadly expressed in immune cells. These cytokines regulate macrophage activation and T-cell responses involved in autoimmunity and protection against invading pathogens, and they may have an important role in the CNS. Mutations in TYK2 protect from psoriasis<sup>214</sup> and a peripherally restricted inhibitor was recently approved for moderate-to-severe psoriasis. Meanwhile brain-penetrant inhibitors are in preclinical stages and probably slated for clinical trials in multiple sclerosis. The utility of TYK2 inhibition as an approach for AD requires further investigation, however given the recent expansion of our understanding of the neuroimmune axis in these diseases, it represents an attractive therapeutic avenue. A brain-penetrant small-molecule inhibitor of receptor-interacting serine/threonine-protein kinase 1 (RIPK1) (DNL788/SAR443820), an intracellular kinase known to drive inflammatory responses and necroptotic cell death, was pursued based on similar rationale, but recently failed to meet the primary end points in phase II ALS and multiple sclerosis trials, suggesting that this specific pathway may not be a primary driver of neuroinflammation in these diseases. Tolebrutinib, a brain-penetrant Bruton's tyrosine kinase (BTK) inhibitor was designated a breakthrough therapy by the FDA given positive phase III results in multiple sclerosis<sup>215,216</sup>. Finally, brain-penetrant NLRP3 inflammasome inhibitors (VENT-02 and NT-0796) are in early clinical trials to evaluate safety and efficacy in PD, AD and ALS (Table 1).

**Pleiotropic immune modulation.** Advances in immuno-oncology provide an intriguing guide for broadly modulating the immune system to 'reset' pathological immune populations or expand potentially neuroprotective T cell subsets. A small population of  $T_{regs}$  reside within the brain parenchyma presenting an opportunity for IL-2-mediated

immune modulation<sup>217</sup>. Alternatively, inhibition of IFN $\gamma$  could be explored based on the potential of this pro-inflammatory cytokine to prime microglia by stimulating antigen presentation, and promote cytotoxic T-cell function. Surprisingly, peripheral administration of an IFN $\gamma$ -blocking antibody reduced tau-mediated brain atrophy in tau/*APOE4* mice<sup>8</sup>. Additional studies to determine whether blocking IFN $\gamma$  centrally, peripherally or both in tandem are necessary and would inform therapeutic development. Finally, introducing genetic circuits into T cells for more sophisticated function modulation and engineered  $T_{regs}$ <sup>218</sup> could be future therapeutic approaches once these mechanisms are better understood.

Our ability to fully leverage the potential of modulating the CNS and peripheral immune systems for neurodegeneration will depend on the ability to address numerous outstanding aspects of neuroimmune interactions such as determining the CNS antigen-presenting cells, identifying the immunodominant antigen(s) driving T-cell responses, and determining which brain border routes peripheral immune cells transmute in diseased versus healthy settings.

## Translating neuroimmune axis therapies into the clinic

Despite exciting recent discoveries linking the immune system to AD, our understanding of the effect of specific therapeutic strategies targeting the neuroimmune axis on human disease remains largely unknown. Several key factors must be considered to enable the effective selection of optimal targets and translation of these approaches to the clinic, including ensuring that there is adequate data to support species translatability of findings from preclinical models, especially given the divergence in immune-related genes across species. Examples of this are AD risk genes *CD33* and *PILRA*<sup>1,2</sup>, for which lack of homology between mouse and human has made translational preclinical drug development challenging. Another key element is the development of biomarkers detectable in biofluids such as plasma or CSF, or imaging-based approaches that enable measurement of the pharmacodynamic impact of therapeutics on microglia and/or other immune cells in patients. Last, understanding the impact immune modulation in combination

with recently approved therapies targeting amyloid pathology will be essential to their clinical implementation.

## Identifying biomarkers to support clinical development

Although there have been important advances in biofluid-based detection of AD pathologies to enable AD staging<sup>219,220</sup>, there are few biomarkers available for neuroimmune monitoring. Soluble TREM2 and SPP1 are both increased in biofluids of patients with AD to varying degrees<sup>56,221,222</sup>. These biomarkers have been monitored in clinical trials as a measure of pharmacodynamic effect of TREM2 antibodies, along with soluble CSF1R<sup>223</sup>. How to interpret changes in soluble TREM2, CSF1R and SPP1 in CSF is not yet fully understood yet will be crucial for linking these shifts to therapeutic response and disease mechanisms. Efforts to expand the panel of biomarkers that monitor microglial activity and neuroimmune interactions are actively in progress. Recent findings identified FABP3, MDH1, GDI1, CAPG, CD44 and GPNMB<sup>224</sup> as putative biomarkers of microglial metabolic and lysosomal activities. FABP3, GDI1 and MDH1 were found to be substantially increased in AD CSF<sup>224</sup>. Recent PET imaging studies examining the use of a radiolabelled TREM2 antibody engineered with a transport vehicle to detect microglial activation in mouse models of AD<sup>225</sup> are encouraging and could be utilized for numerous clinical applications in humans.

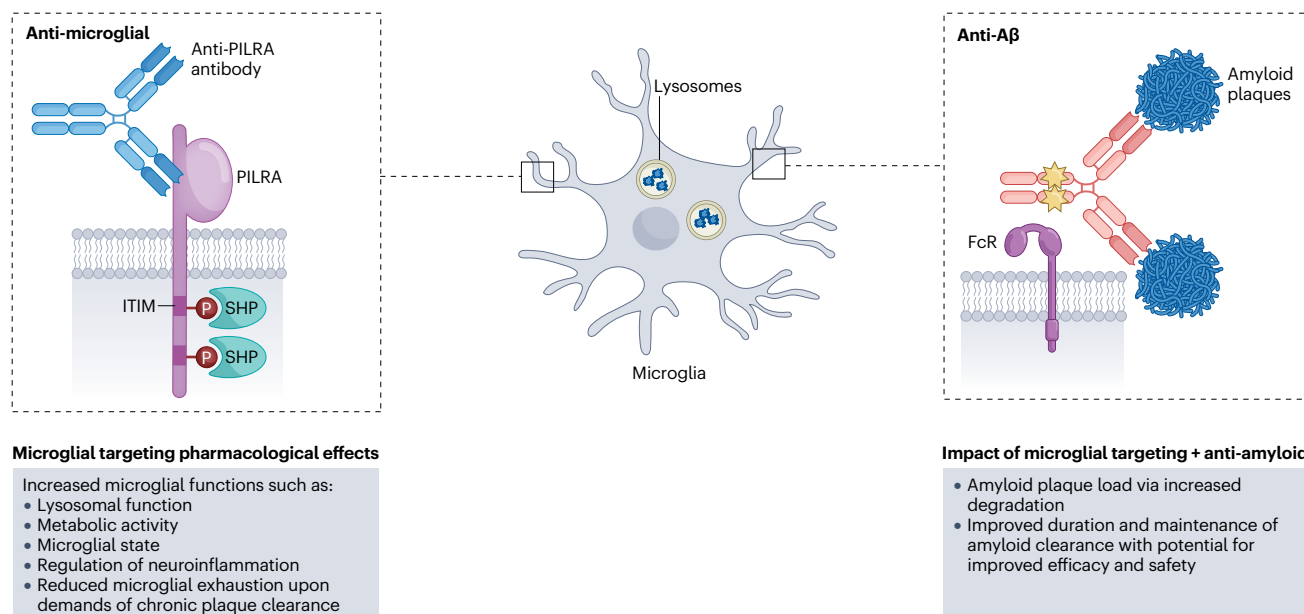
Another source of biomarker candidates is the brain vasculature given its anatomical exposure to brain and blood, as well as its tight coupling with CNS immunity. Highly sensitive biofluid biomarkers of vascular function and BBB integrity would be clinically valuable in diagnosing CAA and stratifying patients with AD for ARIA risk before anti-amyloid therapy. Additionally, longitudinal profiling of immune cells in CSF and

blood may also identify biomarker candidates and inform therapeutic strategies<sup>226</sup>.

## Combination therapies

Therapies targeting the neuroimmune axis may have the greatest utility when used in combination with therapeutics targeting other pathologies given the multifactorial nature of neurodegenerative diseases. This is particularly relevant in AD following the recent demonstration that anti-amyloid antibodies, such as lecanemab and donanemab, reduce amyloid plaque and slow the rate of cognitive decline. Although these clinical results represent a major advancement for patients, the effects on slowing disease progression were modest, and safety remains a concern as a subset of patients exhibit cerebral microhaemorrhages with varying severity<sup>227</sup>. Therefore, strategies to improve efficacy and safety of anti-amyloid antibodies are necessary, yet to date, there are few studies in preclinical models aimed at understanding the effect of combining therapeutic approaches targeting microglia or other immune regulators in the context of anti-amyloid therapy.

Anti-amyloids clear plaque by engaging Fc receptors expressed on microglia, recruiting these cells to phagocytose and degrade amyloid plaques (Fig. 4). Interestingly, recent preclinical studies suggest that amyloid clearance occurs upon initial dosing, yet diminished over time<sup>228</sup>. These findings, along with data demonstrating that these anti-amyloids can elicit a potentially detrimental inflammatory response, leads to a therapeutic hypothesis whereby combination dosing could support critical microglial functions while targeting amyloid pathology for clearance to improve efficacy for AD. For example, co-dosing regimens such as anti-TREM2 plus an anti-amyloid could simultaneously promote microglia phagocytic activity, increase the



**Fig. 5 | Therapeutic rationale of combination dosing of anti-amyloid and microglia-targeting mAbs.** Combining therapies with complementary mechanisms of action could support effective disease management under conditions in which anti-amyloid treatments place high demands on microglia as the primary effector cells. Microglia-targeting antibodies, such as those directed against TREM2 or PILRA, may improve the efficacy amyloid-targeting antibodies by enhancing amyloid clearance and

degradation, while supporting the ability of microglia to return the brain to homeostasis and halt disease. Pharmacological modulation of these pathways can promote microglial migration to the site of plaque, improve metabolic fitness to prevent exhaustion under chronic stress and pathology burden, increase lysosomal degradation of pathological proteins, and modulate neuroinflammatory responses triggered by FcR engagement of anti-amyloid antibodies.

## Glossary

### Aicardi–Goutières syndrome

A genetic leukodystrophy in which the immune system damages the myelin sheaths that protect neurons in the brain and spinal cord; symptoms include neurological defects such as developmental regression, seizures, microcephaly and poor feeding behaviour.

### Amyloid mouse model

A mouse strain that develops amyloid plaque deposition in the brain, a hallmark pathology of the Alzheimer's disease (AD), driven by genetic modification of amyloid precursor protein (APP) with one or more mutations found in human disease.

### Amyloid-related imaging abnormalities

(ARIA). Defined using MRI and caused by disruption of blood vessels in the brain with amyloid deposition; the risk of ARIA is increased with some anti-amyloid antibody therapies.

### Astrocyte end-feet

Processes that extend from astrocytes that ensheath blood vessels and provide structural integrity to the vasculature in the brain.

### Cerebral amyloid angiopathy

(CAA). A type of cerebrovascular disease characterized by amyloid deposition with cerebral blood vessels that can lead to cognitive impairment, microbleeds and other neurological symptoms.

number of microglia clearing plaque, and promote microglial states that enable a beneficial response to pathology (Fig. 5). Sequential dosing paradigms could be used to maximize this effect, either by using a TREM2 agonist to prime microglia before anti-amyloid treatment, or after dosing of an anti-amyloid to boost microglial functions and metabolic capacity, and reprogramme these cells from a potentially exhausted state when pathology reemerges. The potential value of these sequential dosing regimens are supported by a recent study that suggests that microglia fail to respond to plaque reaccumulated months after Aducanumab dosing<sup>228</sup>. Whether pharmacological intervention can promote microglia to become more responsive and function to clear amyloid after chronic anti-amyloid treatment remains a critical question that must be addressed to determine potential for long-term efficacy.

### Glia limitans

The outermost barrier of the CNS parenchyma, formed by astrocyte end-feet and a basement membrane that ensheathes the brain surface and lines perivascular spaces wherein it functions as a secondary checkpoint behind the endothelial blood–brain barrier.

### Neuromyelitis optica spectrum disorder

An autoimmune disease in which optic nerve and spinal cord are damaged by autoantibodies; symptoms include vision loss, pain, numbness, weakness and paralysis that can worsen over time.

### Pericytes

Cells that wrap around blood vessel walls and contribute to blood–brain barrier integrity and regulate blood flow.

### Synaptic engulfment

The selective removal of synapses that mediate neuronal signalling; this process is mediated by microglia via the complement pathway during normal development of the CNS and during disease.

### Tauopathy mouse model

A mouse strain that recapitulates tau pathology that occurs in neurodegenerative diseases including frontotemporal dementia (FTD) and AD; tangles of tau protein form in neurons and interfere with their health and function.

## Conclusions and future outlook

The past decade has been marked by important progress in our understanding of how immune system function contributes to AD, and insights into these mechanisms continue to evolve. Human genetic studies have provided initial clues towards specific pathways and cell types that contribute to disease, which has been complemented by robust mechanistic work and deep phenotyping of microglia and other immune cells. These studies have fundamentally changed how the field views neuroimmune interactions, which has translated to the development of a range of therapeutic approaches. Although the most advanced programmes are in early clinical studies, most are still at the preclinical stage with several impactful candidate therapeutics set to enter the clinic in the near term. Clinical evidence of modulating genetically validated targets, such as TREM2, will provide further biomarker, efficacy and safety data. These initial clinical trials will provide important landmarks in how recent advancements in our understanding of the role of the neuroimmune axis in neurodegenerative disease may translate to clinical benefit.

Regardless of outcome, the lessons learned from these studies will provide important insights into which findings in preclinical models translate clinically and shed light on the path for the next generation of candidate therapeutics. These advances will be predicated on robust translational studies and biomarker discovery that enables an understanding of how specific mechanisms of action impact the immune system and neurodegeneration in patients. Much work is still needed, particularly in determining the dynamic and diverse immune cell changes occurring in the CNS and systemically during disease, and there is currently a wealth of therapeutic potential to be brought forth in targeting the neuroimmune axis. Important advances have transformed AD from what seemed to be an unsolvable public health crisis to one in which therapeutic intervention may slow disease progression. We now can leverage this knowledge and momentum to follow the science towards even more meaningful impact for patients.

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## Author contributions

K.M.M. researched data for the article and contributed substantially to the discussion of the content. All authors wrote and reviewed and/or edited the manuscript before submission.

## Competing interests

K.M.M. and J.W.L. are full-time employees and shareholders of Denali Therapeutics Inc. S.H. has been a paid consultant for Eisai Ltd, Novo Nordisk and Alnylam; receives research funding from AstraZeneca and Eisai Ltd; and collaborates with Ionis Ltd.

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