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Exploiting formyl peptide receptor 2 to promote microglial resolution: a new approach to Alzheimer's disease treatment

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Running title: FPR2 to control microglial neuroinflammation

Abstract

Alzheimer's disease and dementia are among the most significant current healthcare challenges given the rapidly growing elderly population, and the almost total lack of effective therapeutic interventions. Alzheimer's disease pathology has long been considered in terms of accumulation of

amyloid beta and hyperphosphorylated tau, but the importance of neuroinflammation in driving disease has taken greater precedence over the last 15-20 years. Inflammatory activation of the primary brain immune cells, the microglia, has been implicated in Alzheimer's pathogenesis through genetic, pre-clinical, imaging and *post-mortem* human studies, and strategies to regulate microglial activity may hold great promise for disease modification. Neuroinflammation is necessary for defence of the brain against pathogen invasion or damage but is normally self-limiting due to the engagement of endogenous pro-resolving circuitry that terminates inflammatory activity, a process that appears to fail in Alzheimer's disease. Here we discuss the potential for a major regulator and promoter of resolution, the receptor FPR2, to restrain pro-inflammatory microglial activity, and propose that it may serve as a valuable target for therapeutic investigation in Alzheimer's disease.

Abbreviations

Aβ	Amyloid beta peptide
AD	Alzheimer's disease
CNS	Central nervous system
DAM	Disease-associated microglia
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
fAβ	Fibrillar Aβ
FPR1	Formylpeptide receptor 1 (human)
FPR2	Formylpeptide receptor 2 (human)
Fpr2	Formylpeptide receptor 2 (murine)
GWAS	Genome-wide association study
oAβ	Oligomeric Aβ
ROS	Reactive oxygen species
SPM	Specialised pro-resolving mediator
TBI	Traumatic brain injury

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The burden of Alzheimer's disease & dementia

Dementias are a considerable global health challenge. In 2016, the number of individuals living with dementia was estimated to be 44 million, a 50% increase compared to 1990 [1]. Of the different forms of dementia, Alzheimer's disease (AD) is by far the most common, affecting approximately 4% of individuals over the age of 65 [2] with a predicted prevalence of over 78 million people by 2050. [3]. These figures represent a significant burden on patients, their families and wider health care systems in society, with an estimated cost in 2015 of £27,450 per patient with moderate dementia, per year in the UK [4]. Moreover, while mortality rates due to heart disease, stroke and cancer have all steadily decreased in the last 20 years, AD associated death continues to rise [5,6], and there are still no effective therapies to slow down or halt disease progression, despite AD first being identified over a century ago. Strategies to address AD are thus an urgent public health priority.

Neuropathology of AD

AD is primarily associated with two characteristic pathologies: extracellular plaques consisting of fibrillar β-amyloid peptides (fAβ) and intraneuronal tangles of insoluble, hyperphosphorylated tau protein. The Aβ peptide is formed by sequential digestion of the ubiquitous transmembrane amyloid precursor protein by the enzymes β- and γ-secretase [7]. This generates soluble Aβ monomers, which can spontaneously aggregate into oligomers (oAβ) and subsequent insoluble fibrils (fAβ), which are the basis for plaque formation [8]. While plaques were initially suggested as the toxic moiety [9], opinion has shifted in recent years to focus on the detrimental actions of soluble oAβ and their potent pro-inflammatory and neurotoxic effects [10–13]. Under normal circumstances, tau protein is a regulator of microtubule formation [14], but for reasons that are still not fully understood, it undergoes hyperphosphorylation in AD, driving the formation of filamentous intraneuronal inclusions thought to impair trafficking and ultimately lead to neuronal death [15]. As with Aβ, soluble tau formulations appear to be sufficient to suppress neuronal activity [16], emphasizing the complexity of the pathological relationships between these disease associated proteins.

While much research has focused on the role played by these classical protein hallmarks in AD pathogenesis, there is increasing evidence for a role of neuroinflammation in the disease, driven by the principal brain immune cells, the macrophage-like microglia [17], aided, as we are increasingly realising, by the actions of astrocytes [18].

Neuroinflammation in AD

Although active brain inflammation has long been recognized as a feature of AD, for many years this was believed to be a response to dying neurons, and thus a secondary phenomenon. However, more recent human imaging studies and pre-clinical models indicate that progressive neuroinflammation may directly contribute to AD pathology. Furthermore, with the advent of genome-wide association studies (GWAS) investigating genetic risk elements for AD, the immune response itself has now taken centre-stage in our understanding of AD pathology [19–22]. Many immune system-related genetic loci have been identified as disease risk factors, and both human imaging studies [23,24] and pre-clinical models [25,26] have identified progressively increasing inflammatory activity in AD. It is worth examining the links suggesting inflammation may drive AD pathology, as this may offer new clues for intervention points and perhaps indicate novel targets for therapeutic development.

Neuroinflammation in AD: Evidence from human genetic analysis

While the strongest genetic risk factor for sporadic AD is the ε4 allelic variation of the apolipoprotein gene *APOE* (Liu et al., 2013), over twenty other genes have been associated with sporadic AD, many of which encode microglial proteins linked to inflammation (Table 1). Of these genetic risk factors, *TREM2* and *CD33* are of particular interest given the important roles they have been shown to play in microglial handling of Aβ [28,29]. TREM2 acts to control inflammatory responses, including suppressing pro-inflammatory cytokine production, stimulating phagocytosis, promoting biosynthetic metabolism and sustaining cellular energetics [30–33]. Importantly, allelic variants of *TREM2* have been shown to increase AD risk by up to three-fold [34,35] and have been

detected in a range of different human populations [19,20,36,37], underlining its role as a global risk variant for sporadic AD. The receptor CD33 has been implicated in a range of anti-inflammatory microglial functions including inhibition of cytokine release [38], regulation of inflammatory toll-like receptor 4 signalling [39] and suppression of Aβ phagocytotic clearance [40]. Notably, individuals with variants resulting in high CD33 expression experience significantly greater AD-related cognitive decline [41].

Interestingly, there appears to be a degree of overlap between the risk variants associated with sporadic AD and those with other inflammatory diseases. A GWAS accumulating data from more than 100,000 individuals in patient *vs.* control cohorts identified eight single nucleotide polymorphisms (SNPs) which were associated with both AD and immune-related conditions such as Crohn's disease and psoriasis [42]. Overall, the study of myeloid cell genomics has revealed significant over-representation of microglia in the populations of cells bearing AD risk genes [43], with notable AD risk allele enrichment in enhancers of microglial, macrophage and monocyte activity [44], strongly indicating an important role for microglial activity in AD development.

Influences of other inflammatory diseases upon AD risk

Many conditions known to drive neuroinflammation have been associated with AD, most notably in the case of traumatic brain injury (TBI) [45,46]. In particular, severe or repeated incidents of TBI have been directly linked to increased AD risk [47]: TBI increases soluble Aβ production in cortical tissue [48], and Aβ deposits and tau neurofibrillary tangles have been found at higher rates in TBI patients than controls [49].

Similarly, a wide range of chronic peripheral diseases have been linked with increased AD risk, including conditions as common as periodontitis [50], hypertension [51] and type 2 diabetes [52,53]. Whilst the mechanistic links underlying these associations are often poorly understood, it is notable that they share increased peripheral inflammatory activity as a common feature. More directly, increased plasma levels of the inflammatory markers lipopolysaccharide binding protein [54] and C-reactive protein [55] have been associated with an increased risk of AD development, again suggestive of a link between inflammation and AD.

While there is little evidence that AD has a direct infectious aetiology, several studies have indicated that microbes or microbial components may act to drive Aβ pathology. Aβ peptides have similar properties to the anti-microbial peptides of the peripheral innate immune response, in particular the human cathelicidin LL-37. Both peptides can activate the inflammation-associated receptor formyl peptide receptor 2 (FPR2) [56], and share an ability to bind and kill multiple different microbial species *in vitro* [57,58]. Moreover, transgenic mice over-expressing Aβ are relatively protected against experimental bacterial meningitis, whilst animals lacking the amyloid precursor protein are more susceptible to this infection [59]. These actions of Aβ may be relevant to human disease as several studies have found microbes in the brains of AD patients *post mortem* [60–63]. Whilst caution must be taken with such findings, as techniques for detection of microbes in the brain are highly susceptible to environmental artefact, the idea that microbial actors or their components could trigger Aβ production is of interest, and at the least provides further circumstantial evidence for an involvement of the immune response in AD pathogenesis.

Neuroinflammation in AD: Evidence from pre-clinical studies

Beyond the associative data obtained from human population studies, pre-clinical models have provided a second source of information suggesting a role for (neuro)inflammation in AD pathogenesis. Notably, single cell transcriptomic analysis of murine AD models have identified a significant population of so-called disease-associated microglia (DAMs) [64], a finding that has since been replicated in humans [65], although it is important to note that significant differences exist between DAMs across the two species. In general, however, DAMs are characterised by reduced expression of a variety of regulatory genes known to maintain microglial homeostasis, e.g. the fractalkine receptor *CX_3CR1*, alongside increased expression of genes associated with lipid metabolism and phagocytosis, notably including *TREM2*. Interestingly, DAMs were also reported for murine models of other neurodegenerative conditions [64,66], suggesting that the pro-inflammatory phenotype shift they represent may be a common response to disease processes.

Inflammatory pathways themselves appear intrinsically tied to the development and worsening of AD pathology. For example, whilst components of the complement pathway are

required for synapse refinement by microglia during development [67], accumulation of the same proteins has been linked to both amyloid and tau pathology in the murine PS2APP and TauP301S models, respectively [68–70]. Notably, microglial derived C1q is sufficient to activate reactive astrocytes, reducing their ability to promote neuronal survival and instead promote neuronal death [71]. Microglia to astrocyte communication is not unidirectional however, as astrocytes have been shown to drive microglial phenotype in return. For example, using APP/PS1 mice, Stat3-driven astrogliosis has been shown to associate with increased Aβ levels and plaque burden, suppression of the microglial Aβ clearance proteins CD33 and neprilysin, and increased production of pro-inflammatory cytokines, leading to impaired spatial learning and memory [72]. The relationship between astrocytes and AD progression is complex and incompletely understood however, as attenuation of astrocyte activity both enhanced Aβ plaque burden and dystrophic neurite number in APP/PS1 mice [73], and increased levels of pro-inflammatory cytokines and soluble Aβ in APP23 animals [74]. It seems likely that the role astrocytes play in AD will change according to the stage of disease progression, and is likely to be linked to different microglial activation states [71], but a detailed consideration of their function lies beyond the scope of this review.

Overall, neuroinflammation has been reported in at least seven independent animal models of AD and associated disease, including both Aβ and tau transgenics [75–80], and reducing inflammation through use of anti-inflammatory agents has successfully restored memory function in many of these models [76,80,81]. While the involvement of neuroinflammation in AD models is clear, further research is required to decipher the role of different glial (sub)-populations in disease, enabling us to fully understand the dynamic and complex roles of microglia and astrocytes during disease development, and to permit their translation to human disease.

The role(s) of microglia in AD

Inflammation in the central nervous system (CNS) differs markedly from that in the periphery with a relatively limited role for circulating leukocytes, their place largely being taken by central cells including astrocytes [71,82], perivascular macrophages [83], and probably most importantly the microglia [84,85]. Microglia are cells of myeloid origin that migrate into the brain tissue early in

development and remain there, monitoring and maintaining the CNS environment [86]. These cells play a number of critical roles in tissue maintenance and response to injury [87], pathogen defence [88], removing damaged tissue [89] and synaptic plasticity, learning and memory [90,91]. For reasons that are still unclear however, microglia tend to become hyper-reactive with increasing age, exhibiting stronger responses to stimuli and failing to return completely to their baseline status after threat elimination [92].

As suggested above, several cell types have been implicated in driving the neuroinflammatory response, including astrocytes [71,82] and perivascular macrophages [83], but the primary actors are thought to be microglia [84,85]. These cells play critical roles in tissue maintenance and response to injury [87], alongside pathogen defence [88], synaptic plasticity and consequently learning and memory [90], and are thus in a position to exert beneficial or detrimental effects on all of these AD-associated processes.

Depending on brain region, microglia compose approximately 5-20% of the total cells in the brain [93,94]. Their complexity and dynamicity are evidenced by transcriptional analysis of murine microglia, wherein at least nine distinct cell states were identified [95]. Greatest diversity was seen in prenatal and infant mice, with cells gradually becoming more uniform across the brain into adulthood. This uniformity declined upon advancing age and following induction of multiple sclerosis-like injury [95]. In human AD and control patients, single-nucleus RNA-Seq (snRNA-Seq) was able to identify four subclusters of microglia based on their transcriptomes, with at least one being over-represented in AD brain samples [96]. Notably, and unlike the previous murine studies, the presence of AD-associated cell populations was greater in women than men, possibly aligning with the increased incidence of AD in this sex [96]. Interestingly, of the 229 DAM genes previously identified to be upregulated in 5XFAD mice [64], only 28 were observed in the upregulated microglial cluster, including *APOE* and *SPP1* [96]. A further 49 genes upregulated in this human cohort had not previously been identified in mouse models, including *CD14* and the complement receptor *C1Qb* [96]. Thus, differential microglial phenotypes likely exist between human patients

and mouse models, often shifting with disease progression, which needs to be taken into consideration in translational work.

Microglia are notably plastic in their phenotypic expression and have the capacity to shift their functions and behaviour during the course of an inflammatory response (Figure 1A), with different phenotypes often corresponding to distinct *in vivo* states [97]. Following injury or infection, cells become polarized towards inflammatory phenotypes, releasing a battery of pro-inflammatory mediators and reactive oxygen species (ROS), which may contribute to neurodegeneration if uncontrolled [98,99]. Many of the processes and mediators involved in driving this pro-inflammatory phase are also potent pro-resolving signals [100], driving microglia to a more reparative phenotype involving the phagocytosis and removal of apoptotic cells, cellular debris and protein aggregates; all of which accumulate during neurological damage [101] and aging [102,103]. The pro-resolving mediators released at this point are thought to have a number of beneficial effects, concurrently initiating a negative feedback control of pro-inflammatory cytokine production and stimulating the release of pro-resolving factors such as IL-10 and TGFβ [104–106]. Thus, the change in microglial phenotype seen in the progression of an inflammatory reaction is fundamental in both limiting the acute inflammatory response and inducing tissue repair, thereby restoring neural homeostasis [107].

Changes to microglial phenotype have been reported in multiple *post mortem* AD analyses, with increased expression of the activation markers MHC II and CD68 seen repeatedly in different groups of AD patients [108]. In addition, both familial and sporadic AD patients have been shown to bear higher expression of neuroinflammatory pathological markers in the brain areas most affected by the disease, including the entorhinal and temporal cortices and the dentate gyrus of the hippocampus [109]. These findings are further supported by *in vivo* imaging studies of AD patients, where a clear correlation has been found between binding of ligands to the microglial activation marker translocator protein 18 kDa (TSPO) and progression of the disease [110,111]. The advent of detailed transcriptomic [112–114] and proteomic [115] analyses of AD patients have provided further insight into the complexity of microglial phenotypic changes during disease progression, although interestingly these two sources of information do not always concur (Figure 1B).

Microglia, neuroinflammation and neurodegeneration in AD

In healthy individuals, microglial phenotype remains relatively homeostatic, wherein these phagocytes remove dead cells and debris, preventing their accumulation in the brain [88]. However, microglia are long-lived cells, renewing by sometimes imperfect clonal expansion [116], and as they age their degradative capacity becomes less efficient [117], leading to the build-up of unwanted cellular debris and aggregation of both Aβ and tau [118,119]. The relationship between microglial behaviour and AD pathology is complex. Microglia actively phagocytose Aβ plaques and dead/dying cells in what is thought to be an attempt to clear pathology [120], but Aβ, particularly in its oligomeric form, potently activates microglia and can directly contribute to neuronal damage and loss [10,121–123]. Moreover, Several AD risk genes are associated with microglial phagocytosis, including *APOE* [124] and *TREM2* [32], suggesting risk-variants may compound the defective effects of aging on microglial function.

Beyond these deleterious interactions with aging, there are also indications that aberrant microglial phagocytosis may be implicated in early-stage disease. Several AD risk genes are associated with complement [125], a system that interacts with microglia to mediate phagocytic synapse removal in animal models challenged with oAβ [68]. Microglia expressing the complement component C1q are responsible for the proliferation of neurotoxic reactive astrocytes in mice [71]. However, depletion of the complement component C3 can stimulate plaque accumulation and increase neurodegeneration in the APP_{SW} mouse model of AD [126], indicating a complex interaction between microglial function, aging and other immune parameters in disease. This complexity is further underlined by the neuroprotective roles microglia often display in prodromal disease states. Using the 5xFAD model, microglia were shown to phagocytose Aβ via TREM2 without triggering evident neuroinflammation [64]. The role played by TREM2 and microglia appears to change with disease progression however, with TREM2-expressing microglia exhibiting a strong inflammatory phenotype following interaction with tau aggregates, exacerbating neurodegeneration [127].

Microglia can therefore either promote extensive neuroinflammation upon amyloid or tau reaction or assist the clearance of age-associated amyloid accumulation, apparently depending on

the stage of disease progression. Inhibiting the more neuroprotective functions of microglia in AD patients may therefore be detrimental, with blunt microglial inhibition strategies potentially causing more harm than good. Greater understanding of microglial behaviour, and particularly of how to manipulate the phenotypic changes exhibited by these highly plastic cells will be crucial in permitting development of microglial-targeting therapies for AD.

Interactions of microglia with AD hallmarks

Aggregation of large quantities of fAβ is a classical hallmark of AD, most probably linked with degradative enzymatic dysfunction [128,129], and has been shown to correlate with changes in the microglial proteome [130,131], although fAβ is unlikely to be the main toxic form of Aβ [13]. Rather, oAβ species appear to directly contribute to neuroinflammation in AD [132]. Microglial pattern recognition receptors, including several toll-like receptors and the scavenger receptors RAGE and CD36, recognise Aβ and trigger a pro-inflammatory response [133] that impairs learning and memory [134,135]. Murine age-related cognitive impairment is also directly associated with chronic neuroinflammation [136], wherein microglia may damage and remove healthy neurones, further contributing to pathology [137]. Direct interaction of microglia with oAβ also appears to cause the release of a battery of pro-inflammatory cytokines, chemokines and ROS [10,138,139]. Moreover, microglial phagocytic ability appears to be hindered following Aβ-elicited activation [140], suggesting that Aβ may therefore promote its own accumulation, manifesting a self-propagating inflammatory cycle [141].

Evidence from animal models ties microglia to amyloid plaque production, although the exact role these cells play is complex and, to an extent, dependent on disease stage. Depletion studies have revealed both positive and negative effects of microglia with respect to plaque development and consequent behavioural phenotypes. Microglial removal using the CSF1R inhibitor PLX5622 in early stages of the 5xFAD mouse model prevented plaque formation but aggravated behavioural deficits [142], whereas the same group found that removal at later time-points did not affect plaque density but did prevent neuronal loss and improve behavioural measures [143]. In contrast, use of a different CSF1R inhibitor PLX3397 to remove microglia in early stages of the 5xFAD model decreased

plaque burden but improved cognitive behaviour [144]. Similarly, microglial removal using PLX3397 abolished the protective effects of soluble TREM2 administration upon plaque load and cognitive deficits in the 5xFAD model [145]. These discrepancies emphasise both the complexity of microglia-Aβ interactions and our paucity of understanding, although it should be borne in mind that microglial depletion strategies commonly have off-target effects, both within and without the CNS [146], as is highlighted by the finding that the non-depleting CSF1R inhibitor GW2580 prevented synapse loss without modulating Aβ plaque number [147], and the discovery that an alternative viral-mediated microglial removal strategy had no effect on plaque formation or neuritic dystrophy in either APP23 or APP/PS1 animals [148].

While this inter-study variation is important to consider in evaluating murine model data, and may reflect the artificial nature of these systems to an extent, a key observation in human disease is that microglial activation correlates with AD pathology, appearing to occur primarily after plaque development but before tau tangle deposition [101]. This is supported by positron emission tomography studies in patients, which show microglial activation to occur well before clinical AD symptoms are apparent [149,150]. Furthermore, microglial activation correlates well with Aβ deposition in AD patients [151], and brain inflammation has been shown to accompany Aβ deposition in the majority of patients with mild cognitive impairment that progress to having AD [152]. Thus, while the relationship between Aβ pathology and microglial activation is complex, it seems likely that these cells are important in the development of the clinical symptoms associated with Aβ accumulation.

Although the progression of Aβ pathology correlates poorly with clinical symptom development [153], both neuroinflammation and tau pathology correlate well with AD symptom onset and disease severity in humans [23,151,154–156]. In line with this association, microglia may contribute to the pathological seeding of tau, with evidence suggesting that cultured microglia from the tauopathy-associated rTg4510 mouse can release tau seeds that act as foci of aggregation [157]. This argument is supported by the demonstration that transfer of purified microglia from hTau*Cx3cr1*$^{-/-}$ transgenic mice into wild-type animals induced host tau hyperphosphorylation [156] and that depletion of microglia and macrophages by treatment with clodronate liposomes

significantly suppressed tau propagation [158]. Microglia do not appear to be merely passive distributors of tau seeds however, with evidence indicating a direct role for the NLRP3 inflammasome, a major initiator of inflammatory activity through its role in producing IL-1β and IL-18. Specifically, intracerebral injection of brain homogenate from APP/PS1 mice into Tau22 mutant animals effectively induced tau hyperphosphorylation, a response not seen in two different lines of Tau22 mutant and NLRP3 null mice [159].

Thus, microglia appear to be intimately involved in the propagation of AD pathological hallmarks, and to correlate with worsening clinical symptoms and neurodegeneration. As both Aβ and tau pathology appear to be linked to pro-inflammatory microglial behaviour, controlling and reversing microglial activation may be therapeutically beneficial. Exploiting the pathways governing inflammatory resolution which naturally control microglial activity may thus have significant potential in the treatment of AD.

Inflammatory resolution in AD

Over the last 15-20 years we have come to realise that inflammation is naturally a self-limiting response, and that many of the endogenous mediators and receptors activated in the course of an inflammatory response have roles in the termination of that same response, the process termed inflammatory resolution [100]. Resolution of inflammation is a distinct, active process associated with the catabolism of pro-inflammatory mediators, removal of cell debris and tissue repair [160], with its failure often resulting in chronic inflammation, tissue damage and disease [161]. Whereas conventional anti-inflammatory therapies are usually designed as antagonists or inhibitors of specific factors and receptors which drive the inflammatory response, resolution based therapeutics aim to specifically target and upregulate endogenous signalling pathways which reduce the cardinal signs of inflammation, but also actively promote tissue repair and promote a return to homeostasis [162]. This shift in approach could be crucial for neuroinflammatory disease, as events present early in the inflammatory cascade likely engage this co-ordinated endogenous resolution process [100], indicating that blockade of inflammation through the use of traditional anti-inflammatories may also stall the resolution response. Indeed, this effect may have contributed to

the disappointing results of clinical trials investigating NSAID use in treating AD [163] – such suppressive drugs may have halted inflammatory processes, but they will also have impaired resolution and thus initiating stimuli are unlikely to have been fully removed. Moreover, for patients with AD, given that it is above all an age-related disorder, avoiding direct inhibition of the inflammatory pathways may be particularly beneficial as this could avoid compromising immunity and aggravation of the pre-existing enhanced risk the elderly have of infection associated mortality [164].

Many endogenous specialised pro-resolving mediators (SPMs) have been identified [165,166], with a remarkable degree of molecular diversity, ranging from gases such as hydrogen sulphide and carbon monoxide [167], through the lipid mediators lipoxins, maresins, protectins and resolvins [168,169], to proteins such as annexin A1 [170]. The benefit of utilising SPMs for disease was first identified over a decade ago, stemming from reports that both lipoxin A4 and annexin A1 could stimulate production of known anti-inflammatory mediators, such as IL-10 [171,172]. These mediators also appear to stimulate the endogenous production of other SPMs, as was observed for resolvin E1, which upregulated lipoxin A4 expression in mice [173].

Pre-clinical models and patient analysis indicate that endogenous resolution pathways may be dysfunctional in AD. In particular, attention has focused on lipid pro-resolving mediators such as the maresins, protectins and resolvins derived from the omega-3 polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) [174]. Notably, studies of AD patients revealed reduced levels of maresin 1, protectin D1 and resolvin D5 in the entorhinal cortex [175] and reduced levels of lipoxin A4 in the hippocampus and cerebrospinal fluid [176], and expression of the leukotriene B4 receptor BLT1 and the chemerin 1 receptor, both of which bind resolvin E1, associate with higher Braak stages in human AD [177], suggesting a failure in engagement of resolving circuitry. Moreover, exogenous administration of lipid mediators has been shown to improve symptoms in a number murine AD models, suggesting that activation of resolution circuitry may have therapeutic benefit. Namely, DHA modulates glial responses in AD [178], bilateral hippocampal administration of maresin 1 significantly reduced microglial and astrocyte activation and cognitive decline following injection of Aβ aggregates to mice [179], and lipoxin A4 improves cognitive

function and reduces signs of AD including synaptotoxicity, Aβ deposition and tau phosphorylation in both 3xTg-AD [180] and Tg2576 [181] mouse AD models. Lipid mediators themselves are readily oxidised in air, and have poor half-lives and complex storage requirements [182], but synthetic agonists targeting their receptors may be of greater utility.

In particular, the G protein coupled receptor FPR2 (also termed the lipoxin A4 receptor, ALX) has received substantial interest. This receptor plays an important role in governing the behaviour of innate immune cells such as neutrophils, monocytes and macrophages [183], mediating conversion from pro- to anti-inflammatory behaviour and driving inflammatory resolution. Expression of FPR2 has been reported in a number of different CNS cell types, with the strongest evidence being for presence within microglia [176,184], particularly following activation by pro-inflammatory stimuli [185], and in endothelial cells [186,187]. There is some evidence for FPR2 expression within neurons, with reports indicating the receptor is present within hippocampal and cortical projection cells, primarily in the neuropil rather than cell bodies, and in the cerebellum [188], and there is evidence for FPR2 in neural stem cells [189] and in neuroblastoma lines [190]. Whether FPR2 is found in other brain cell types is more controversial, with conflicting reports both indicating [191,192] and refuting [188,193] expression within astrocytes; currently there are no reports of FPR2 expression within oligodendrocytes or other central glial subtypes. Intriguingly, there is compelling evidence to suggest targeting FPR2 may be a viable approach to restraining inflammatory activity in AD.

Formylpeptide receptor 2

FPR2 is a member of the formylpeptide receptors, a family of both class A G protein-coupled receptors (GPCR) and pattern recognition receptors, first identified by homology based cloning to the potently pro-inflammatory formylpeptide receptor 1 (FPR1) [194]. The biological actions of this family of receptors are complex, with three members in humans and eight identified in mice, but members have known roles in chemotaxis, host defence and inflammation [195–197]. FPR2 and its murine homologues Fpr2 and Fpr3 are unusual in having a large number of both pro-inflammatory and anti-inflammatory ligands of remarkable molecular diversity, from lipids to peptides to proteins [56].

The molecular signalling pathways triggered by FPR2 activation are complex and exhibit a significant degree of agonist bias, a feature attributable to a number of factors. Recent determination of the crystal structure of FPR2 bound to the peptide ligand WKYMVm alone [198] or in complex with Gi [199] revealed a remarkably wide and deep ligand binding pocket, capable of differentially accommodating and interacting with the broad variety of molecules known to have potency at this receptor. Notably, functional analysis of FPR2 structure upon binding of different pro- and anti-inflammatory ligands to this pocket revealed distinct, complex and dose-dependent conformational changes between ligands, with evidence for inter-ligand allosteric interactions upon co-administration [200,201]. Classically, FPR2 was thought to couple to inhibitory G proteins and Ca^{2+} mobilisation, but has since been shown to engage a wider repertoire of G proteins [202], with ligand-dependent conformational changes in the receptor translating into recruitment of distinct intracellular signalling pathways [200]. A further layer of complexity to FPR2 signalling is added by its ability to both homodimerize and to heterodimerize with the pro-inflammatory FPR1, particularly upon exposure to higher ligand concentrations, thereby connecting with numerous intracellular signalling pathways [203]. The receptor is thought to constitutively homodimerize in monocytes, with pro-resolving ligands such as lipoxin A4 and annexin A1 inducing a conformational change that leads to activation of p38 MAP kinase, phosphorylation of MAPKAPK and Hsp27 and production of the anti-inflammatory cytokine interleukin-10 [203]. In contrast, the pro-inflammatory ligands of FPR2 such as serum amyloid A, LL-37, and notably in the context of AD, $A\beta_{1-42}$, trigger phosphorylation of JNK and modulation of pro-apoptotic pathways in leukocytes [204], an effect attributed to the ability of FPR2 to form heterodimers with FPR1 [203]. Whilst this pattern of intracellular signalling, and particularly the intricate allosteric interactions between ligands, is without doubt complex, it also offers significant opportunity for the rational design of agents able to selectively target specific downstream functions of FPR2 signalling, potentially minimising off-target actions. In particular, there is now substantial evidence to position FPR2 as a critical actor in inflammatory resolution, helping to terminate an inflammatory response and restore homeostasis [183], raising the possibility of selective development of targeted pro-resolving therapies. The

majority of evidence supports the targeting of interactions between FPR2 and microglia, but this is not necessarily an exclusive mechanism whereby FPR2 agonists could be beneficial.

Much of our knowledge of the role of FPR2 in inflammatory resolution is derived from studies of its behaviour in the peripheral system. In particular, given the close similarity in ontogeny and behaviour between microglia and monocytes/macrophages, insight into the potential of FPR2 in regulating neuroinflammation can be obtained through analysis of its role in these cells. Studies of both human and rodent systems have identified an important role for FPR2 or its non-human counterparts in the recruitment of monocytes to inflammatory foci, with studies reporting positive chemotactic effects of numerous FPR2 ligands on those cells, including serum amyloid A [205–207], the cathelicidin LL-37 [208], viral and bacterial peptides [209,210], protein cleavage products [211,212] and secreted human proteins such as FAM3D [213] and annexin A1 [195]. These findings have been translated into whole organism settings, with FPR2 having been clearly identified as a key organiser of monocyte recruitment in conditions as diverse as peritonitis [195], bacterial sepsis [214], colitis [215], heart failure [216] and allergic airway inflammation [217]. The signalling pathways engaged in these processes are not fully described, but most work has been undertaken examining the role of the major pro-resolving FPR2 ligand annexin A1, which has been shown to trigger phosphorylation of both ERK1/2 to induce chemokinesis [212] and p38 MAP kinase to induce directed chemotaxis [195]. Whether similar pathways are activated in response to other known chemotactic agents that act through FPR2, such as serum amyloid A or LL-37 is unclear.

As well as recruiting monocytes to inflammatory foci, and following their conversion to macrophages, FPR2 signalling has been shown to play a major role in efferocytosis, the phagocytic removal of dead cells and debris that is essential for efficient termination of an inflammatory reaction and the restoration of tissue homeostasis [218]. FPR2 ligands including lipoxin A4, resolvin D1, annexin A1 and its peptidomimetics have been repeatedly shown to promote clearance of apoptotic cells by macrophages, actions inhibited variously by receptor antagonists or genetic ablation [219–222]. Notably, we and others have shown that FPR2 can play a similar role in microglial efferocytosis and the removal of apoptotic neurons [223–225], thereby preventing their progression to secondary necrosis and initiation of further inflammatory activity. Notably, many of

the genetic risk variants associated with AD are in genes associated with phagocytosis and efferocytosis [226], hence systems involved in promoting efferocytosis, such as FPR2, may be of significant use in disease treatment.

The role of FPR2 in inflammation extends beyond monocyte recruitment and efferocytosis however, as the receptor is central to the phenotypic plasticity that characterises macrophage responses to inflammatory challenge [227]. The FPR2 ligand annexin A1, derived from apoptotic neutrophils in an inflammatory locus, has been shown to engage the receptor on resident and recruited macrophages, triggering expression of an anti-inflammatory surface phenotypic marker profile and production of anti-inflammatory cytokines such as interleukin-10 and TGFβ through activation of AMPK signalling [227]. This effect is particularly intriguing as it links FPR2 signalling with the control of cellular energy homeostasis, a function we are increasingly appreciating as a major regulator of immune cell activity [228,229].

FPR2 & Neuroinflammation in AD

The involvement of FPR2 in neuroinflammation has been relatively understudied by comparison with its effects in the periphery, but evidence does still implicate it as both a mediatory of neuroinflammatory resolution and as a potential target in AD. Initial studies of FPR2 expression were limited by difficulties in distinguishing it from FPR1, but more recent analyses indicate that the receptor is present at a relatively low level within microglia throughout the brain [184,230,231]. While whole brain FPR2 content does not appear to change markedly in AD [190], microglial FPR2 expression is markedly upregulated following exposure to inflammatory stimuli, including TNFα and agonists of toll-like receptors 2, 3, 4 and 7 [232–236], and most notably fibrillar Aβ, such that microglia associated with amyloid plaques express high levels of the receptor [184,237]. This regulation of FPR2 expression by inflammatory stimuli has parallels with the behaviour of the receptor in macrophages where FPR2 expression declines as a pro-resolving phenotype is adopted [214,227]. Given that several studies have now indicated microglia can also be induced to take an anti-inflammatory phenotype by FPR2 activation [193,238,239], this may represent a mechanism to maintain a pro-reparative microglial phenotype.

The increase in FPR2 expression seen in plaque-associated microglia may be associated with the ability of microglia to phagocytose and break down fAβ [132,190,240], as treatment of microglia with pro-resolving FPR2 ligands such as annexin A1 has been shown to stimulate fAβ phagocytosis [190], alongside reducing inflammatory cytokine production [224,241]. Intriguingly, the ability of primary microglia to phagocytose fAβ is inhibited by the actions of oligomeric forms of the peptide [132], providing further support for the idea that oAβ may have greater toxicity. In this vein, micromolar concentrations of oAβ are potent activators of microglia *in vitro* through FPR2, provoking release of inflammatory cytokines and ROS and stimulating chemotaxis [230,235,242], although it should be noted that treatment of microglia with more AD-relevant concentrations of oAβ had a more selective effect, triggering oxidative stress without notable inflammatory change [10]. Significantly, the effects of oAβ on microglia ROS production and metabolic phenotype could be reversed by subsequent treatment with small molecule agonists of FPR2 [10], suggesting a potential avenue for further therapeutic investigation.

Importantly, these interactions between FPR2 and microglial behaviour feeds forward to improvements in cognition in several different animal models of AD. For example, using a rat model of AD in which $A\beta_{1-42}$ was infused intracerebroventricularly, up-regulation of Fpr2 expression was shown to improve working and spatial memory deficits, suppress hippocampal inflammation and Aβ deposition, and induce an anti-inflammatory microglial profile [235]. Similarly suggestive of a beneficial role for FPR2, administration of lipoxin A4 improves recognition memory in the 3xTg-AD mouse [180], and the stable aspirin-triggered 15-epi-lipoxin A4 enhanced performance on the Morris water maze task in the Tg2576 tau transgenic mouse [181]. In contrast, long-term administration of the mixed FPR1/FPR2 antagonist Boc2 improved performance on the Morris water maze task, prevented hippocampal neuron loss and limited microglial activity in APP/PS1 mice [243]. These data further support a role for FPRs in amyloid pathology, although it should be noted that Boc2 has also been shown to possess FPR-independent activity [244]. Thus, while further work is needed to fully define the role of FPR2 in AD and its models, these studies highlight the potential of

the receptor as a target to not only slow neuroinflammation, but to actually improve ultimate cognitive outcomes.

Could FPR2 have therapeutic utility for AD?

Dementia and AD are major and growing healthcare challenges, particularly as despite the significant work and resources that have gone into therapeutic development, there remain no clinically effective treatments. Primarily, efforts have been guided by the amyloid hypothesis, i.e., that neurodegeneration is ultimately driven by the toxic actions of Aβ, and that its suppressed production or enhanced removal would be beneficial [245]. Given that over 300 clinical trials based on this hypothesis have now been performed and have yet to result in a clinically usable therapy, it may be time to expand our horizons beyond the direct role of Aβ and investigate other aspects of AD [246,247]. Neuroinflammation is central to the progression of AD and is thus a key candidate process for investigation, although as directly acting anti-inflammatory agents such as the NSAIDs have also shown little effect in prospective trials, a more considered approach may be needed.

The endogenous processes governing neuroinflammatory resolution have significant potential to control microglial activity in AD, with FPR2 in particular offering an attractive target for pharmacological treatment. Moreover, the evidence describing the intricate allosteric interactions between FPR2 agonists and the complex signalling patterns that result raises the possibility of selective targeting of pro-resolving functions for therapeutic development. Such pro-resolving FPR2 agonists will be able to exert a number of beneficial effects in the brain, including suppression of pro-inflammatory cytokine and ROS production [10,190,235], improving clearance of fAβ [180,190] and apoptotic cells and debris [224] and promoting an anti-inflammatory microglial phenotype [193,238]. More hypothetically, if microglia do behave in a similar manner to their peripheral macrophage cousins [214,227], induction of a pro-resolving phenotype by FPR2 activation may also down-regulate expression of the receptor itself, helping to shield microglia from further pro-inflammatory activation by oAβ. The ability of FPR2 to regulate such a diverse array of microglial processes places the receptor in a key position to govern how microglia behave under neuroinflammatory conditions, and we would argue, positions it as a critical target for

pharmacological exploitation in dementia. Given the lack of therapies available to even slow down AD progression, targeting a system, such as FPR2, that activates the endogenous control pathways that reduce inflammatory activity and promote healing hold significant promise for an intervention that is sorely needed in dementia treatment.

Author contributions

ESW and SM prepared the majority of the text, with contributions from MAI. SJG provided significant comments and suggestions for improvement

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References

1 GBD 2016 Dementia Collaborators E, Szoeke CEI, Vollset SE, Abbasi N, Abd-Allah F, Abdela J, Aichour MTE, Akinyemi RO, Alahdab F, Asgedom SW, Awasthi A, Barker-Collo SL, Baune BT, Béjot Y, Belachew AB, Bennett DA, Biadgo B, Bijani A, Sayeed MS Bin, Brayne C, Carpenter DO, Carvalho F, Catalá-López F, Cerin E, Choi J-YJ, Dang AK, Degefa MG, Djalalinia S, Dubey M, Duken EE, Edvardsson D, Endres M, Eskandarieh S, Faro A, Farzadfar F, Fereshtehnejad S-M, Fernandes E, Filip I, Fischer F, Gebre AK, Geremew D, Ghasemi-Kasman M, Gnedovskaya E V., Gupta R, Hachinski V, Hagos TB, Hamidi S, Hankey GJ, Haro JM, Hay SI, Irvani SSN, Jha RP, Jonas JB, Kalani R, Karch A, Kasaeian A, Khader YS, Khalil IA, Khan EA, Khanna T, Khoja TAM, Khubchandani J, Kisa A, Kissimova-Skarbek K, Kivimäki M, Koyanagi A, Krohn KJ, Logroscino G, Lorkowski S, Majdan M, Malekzadeh R, März W, Massano J, Mengistu G, Meretoja A, Mohammadi M, Mohammadi-Khanaposhtani M, Mokdad AH, Mondello S, Moradi G, Nagel G, Naghavi M, Naik G, Nguyen LH, Nguyen TH, Nirayo YL, Nixon MR, Ofori-Asenso R, Ogbo FA, Olagunju AT, Owolabi MO, Panda-Jonas S, Passos VM de A, Pereira DM, Pinilla-Monsalve GD, Piradov MA, Pond CD, Poustchi H, Qorbani M, Radfar A, Reiner RC, Robinson SR, Roshandel G, Rostami A, Russ TC, Sachdev PS, Safari H, Safiri S, Sahathevan R, Salimi Y, Satpathy M, Sawhney M, Saylan M, Sepanlou SG, Shafieesabet A, Shaikh MA, Sahraian MA, Shigematsu M, Shiri R, Shiue I, Silva JP, Smith M, Sobhani S, Stein DJ, Tabarés-Seisdedos R, Tovani-Palone MR, Tran BX, Tran TT, Tsegay AT, Ullah I, Venketasubramanian N, Vlassov V, Wang Y-P, Weiss J, Westerman R, Wijeratne T, Wyper GMA, Yano Y, Yimer EM, Yonemoto N, Yousefifard M, Zaidi Z, Zare Z, Vos T, Feigin VL & Murray CJL (2019) Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* **18**, 88–106.

2 Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W & Ferri CP (2013) The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* **9**, 63-75 e2.

3 Prince MJ, Wimo A, Guerchet MMM, Gemma-Claire A, Wu Y-T, Prina M, Ali GC, Wu Y-T & Prina M (2015) *World Alzheimer Report 2015: The Global Impact of Dementia - An analysis of*

prevalence, incidence, cost and trends Alzheimer's Disease International.

4 Wittenberg R, Knapp M, Hu B, Comas-Herrera A, King D, Rehill A, Shi C, Banerjee S, Patel A, Jagger C & Kingston A (2019) The costs of dementia in England. *Int J Geriatr Psychiatry* **34**, 1095–1103.

5 Murphy SL, Xu J & Kochanek KD (2013) Deaths: final data for 2010. *Natl Vital Stat Rep* **61**, 1–117.

6 James BD, Leurgans SE, Hebert LE, Scherr PA, Yaffe K & Bennett DA (2014) Contribution of Alzheimer disease to mortality in the United States. *Neurology* **82**, 1045–50.

7 Haass C & De Strooper B (1999) The presenilins in Alzheimer's disease--proteolysis holds the key. *Science* **286**, 916–9.

8 Murphy MP & LeVine H (2010) Alzheimer's Disease and the Amyloid-β Peptide. *J Alzheimer's Dis* **19**, 311–323.

9 Cummings BJ, Pike CJ, Shankle R & Cotman CW (1996) Beta-amyloid deposition and other measures of neuropathology predict cognitive status in Alzheimer's disease. *Neurobiol Aging* **17**, 921–33.

10 Wickstead ES, Karim HA, Manuel RE, Biggs CS, Getting SJ & McArthur S (2020) Reversal of β-Amyloid-Induced Microglial Toxicity In Vitro by Activation of Fpr2/3. *Oxid Med Cell Longev* **2020**, 2139192.

11 Limbocker R, Chia S, Ruggeri FS, Perni M, Cascella R, Heller GT, Meisl G, Mannini B, Habchi J, Michaels TCT, Challa PK, Ahn M, Casford ST, Fernando N, Xu CK, Kloss ND, Cohen SIA, Kumita JR, Cecchi C, Zasloff M, Linse S, Knowles TPJ, Chiti F, Vendruscolo M & Dobson CM (2019) Trodusquemine enhances Aβ42 aggregation but suppresses its toxicity by displacing oligomers from cell membranes. *Nat Commun* **10**, 225.

12 Beckman D, Ott S, Donis-Cox K, Janssen WG, Bliss-Moreau E, Rudebeck PH, Baxter MG & Morrison JH (2019) Oligomeric Aβ in the monkey brain impacts synaptic integrity and induces accelerated cortical aging. *Proc Natl Acad Sci U S A* **116**, 26239–26246.

13 Cline EN, Bicca MA, Viola KL & Klein WL (2018) The Amyloid-β Oligomer Hypothesis: Beginning of

the Third Decade. *J Alzheimer's Dis* **64**, S567–S610.

14 Mietelska-Porowska A, Wasik U, Goras M, Filipek A & Niewiadomska G (2014) Tau Protein Modifications and Interactions: Their Role in Function and Dysfunction. *Int J Mol Sci* **15**, 4671–4713.

15 Guo T, Noble W & Hanger DP (2017) Roles of tau protein in health and disease. *Acta Neuropathol* **133**, 665–704.

16 Busche MA, Wegmann S, Dujardin S, Commins C, Schiantarelli J, Klickstein N, Kamath T V, Carlson GA, Nelken I & Hyman BT (2019) Tau impairs neural circuits, dominating amyloid-β effects, in Alzheimer models in vivo. *Nat Neurosci* **22**, 57–64.

17 Lewcock JW, Schlepckow K, Di Paolo G, Tahirovic S, Monroe KM & Haass C (2020) Emerging Microglia Biology Defines Novel Therapeutic Approaches for Alzheimer's Disease. *Neuron* **S0896-6273**, 30753–4.

18 Sadick JS & Liddelow SA (2019) Don't forget astrocytes when targeting Alzheimer's disease. *Br J Pharmacol* **176**, 3585–3598.

19 Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, Boland A, Vronskaya M, van der Lee SJ, Amlie-Wolf A, Bellenguez C, Frizatti A, Chouraki V, Martin ER, Sleegers K, Badarinarayan N, Jakobsdottir J, Hamilton-Nelson KL, Moreno-Grau S, Olaso R, Raybould R, Chen Y, Kuzma AB, Hiltunen M, Morgan T, Ahmad S, Vardarajan BN, Epelbaum J, Hoffmann P, Boada M, Beecham GW, Garnier JG, Harold D, Fitzpatrick AL, Valladares O, Moutet ML, Gerrish A, Smith A V., Qu L, Bacq D, Denning N, Jian X, Zhao Y, Del Zompo M, Fox NC, Choi SH, Mateo I, Hughes JT, Adams HH, Malamon J, Sanchez-Garcia F, Patel Y, Brody JA, Dombroski BA, Naranjo MCD, Daniilidou M, Eiriksdottir G, Mukherjee S, Wallon D, Uphill J, Aspelund T, Cantwell LB, Garzia F, Galimberti D, Hofer E, Butkiewicz M, Fin B, Scarpini E, Sarnowski C, Bush WS, Meslage S, Kornhuber J, White CC, Song Y, Barber RC, Engelborghs S, Sordon S, Voijnovic D, Adams PM, Vandenberghe R, Mayhaus M, Cupples LA, Albert MS, De Deyn PP, Gu W, Himali JJ, Beekly D, Squassina A, Hartmann AM, Orellana A, Blacker D, Rodriguez-Rodriguez E, Lovestone S, Garcia ME, Doody RS,

Munoz-Fernadez C, Sussams R, Lin H, Fairchild TJ, Benito YA, Holmes C, Karamujić-Čomić H, Frosch MP, Thonberg H, Maier W, Roschupkin G, Ghetti B, Giedraitis V, Kawalia A, Li S, Huebinger RM, Kilander L, Moebus S, Hernández I, Kamboh MI, Brundin RM, Turton J, Yang Q, Katz MJ, Concari L, Lord J, Beiser AS, Keene CD, Helisalmi S, Kloszewska I, Kukull WA, Koivisto AM, Lynch A, Tarraga L, Larson EB, Haapasalo A, Lawlor B, Mosley TH, Lipton RB, Solfrizzi V, Gill M, Longstreth WT, Montine TJ, Frisardi V, Diez-Fairen M, Rivadeneira F, Petersen RC, Deramecourt V, Alvarez I, Salani F, Ciaramella A, Boerwinkle E, Reiman EM, Fievet N, Rotter JI, Reisch JS, Hanon O, Cupidi C, Andre Uitterlinden AG, Royall DR, Dufouil C, Maletta RG, de Rojas I, Sano M, Brice A, Cecchetti R, George-Hyslop PS, Ritchie K, Tsolaki M, Tsuang DW, Dubois B, Craig D, Wu CK, Soininen H, Avramidou D, Albin RL, Fratiglioni L, Germanou A, Apostolova LG, Keller L, Koutroumani M, Arnold SE, Panza F, Gkatzima O, Asthana S, Hannequin D, Whitehead P, Atwood CS, Caffarra P, Hampel H, Quintela I, Carracedo Á, Lannfelt L, Rubinsztein DC, Barnes LL, Pasquier F, Frölich L, Barral S, McGuinness B, Beach TG, Johnston JA, Becker JT, Passmore P, Bigio EH, Schott JM, Bird TD, Warren JD, Boeve BF, Lupton MK, Bowen JD, Proitsi P, Boxer A, Powell JF, Burke JR, Kauwe JSK, Burns JM, Mancuso M, Buxbaum JD, Bonuccelli U, Cairns NJ, McQuillin A, Cao C, Livingston G, Carlson CS, Bass NJ, Carlsson CM, Hardy J, Carney RM, Bras J, Carrasquillo MM, Guerreiro R, Allen M, Chui HC, Fisher E, Masullo C, Crocco EA, DeCarli C, Bisceglio G, Dick M, Ma L, Duara R, Graff-Radford NR, Evans DA, Hodges A, Faber KM, Scherer M, Fallon KB, Riemenschneider M, Fardo DW, Heun R, Farlow MR, Kölsch H, Ferris S, Leber M, Foroud TM, Heuser I, Galasko DR, Giegling I, Gearing M, Hüll M, Geschwind DH, Gilbert JR, Morris J, Green RC, Mayo K, Growdon JH, Feulner T, Hamilton RL, Harrell LE, Drichel D, Honig LS, Cushion TD, Huentelman MJ, Hollingworth P, Hulette CM, Hyman BT, Marshall R, Jarvik GP, Meggy A, Abner E, Menzies GE, Jin LW, Leonenko G, Real LM, Jun GR, Baldwin CT, Grozeva D, Karydas A, Russo G, Kaye JA, Kim R, Jessen F, Kowall NW, Vellas B, Kramer JH, Vardy E, LaFerla FM, Jöckel KH, Lah JJ, Dichgans M, Leverenz JB, Mann D, Levey AI, Pickering-Brown S, Lieberman AP, Klopp N, Lunetta KL, Wichmann HE, Lyketsos CG, Morgan K, Marson DC, Brown K, Martiniuk F, Medway C, Mash DC, Nöthen MM, Masliah E, Hooper NM, McCormick WC, Daniele A, McCurry SM, Bayer A, McDavid AN, Gallacher J, McKee AC, van den Bussche H, Mesulam M,

Brayne C, Miller BL, Riedel-Heller S, Miller CA, Miller JW, Al-Chalabi A, Morris JC, Shaw CE, Myers AJ, Wiltfang J, O'Bryant S, Olichney JM, Alvarez V, Parisi JE, Singleton AB, Paulson HL, Collinge J, Perry WR, Mead S, Peskind E, Cribbs DH, Rossor M, Pierce A, Ryan NS, Poon WW, Nacmias B, Potter H, Sorbi S, Quinn JF, Sacchinelli E, Raj A, Spalletta G, Raskind M, Caltagirone C, Bossù P, Orfei MD, Reisberg B, Clarke R, Reitz C, Smith AD, Ringman JM, Warden D, Roberson ED, Wilcock G, Rogaeva E, Bruni AC, Rosen HJ, Gallo M, Rosenberg RN, Ben-Shlomo Y, Sager MA, Mecocci P, Saykin AJ, Pastor P, Cuccaro ML, Vance JM, Schneider JA, Schneider LS, Slifer S, Seeley WW, Smith AG, Sonnen JA, Spina S, Stern RA, Swerdlow RH, Tang M, Tanzi RE, Trojanowski JQ, Troncoso JC, Van Deerlin VM, Van Eldik LJ, Vinters H V., Vonsattel JP, Weintraub S, Welsh-Bohmer KA, Wilhelmsen KC, Williamson J, Wingo TS, Woltjer RL, Wright CB, Yu CE, Yu L, Saba Y, Pilotto A, Bullido MJ, Peters O, Crane PK, Bennett D, Bosco P, Coto E, Boccardi V, De Jager PL, Lleo A, Warner N, Lopez OL, Ingelsson M, Deloukas P, Cruchaga C, Graff C, Gwilliam R, Fornage M, Goate AM, Sanchez-Juan P, Kehoe PG, Amin N, Ertekin-Taner N, Berr C, Debette S, Love S, Launer LJ, Younkin SG, Dartigues JF, Corcoran C, Ikram MA, Dickson DW, Nicolas G, Campion D, Tschanz JA, Schmidt H, Hakonarson H, Clarimon J, Munger R, Schmidt R, Farrer LA, Van Broeckhoven C, C. O'Donovan M, DeStefano AL, Jones L, Haines JL, Deleuze JF, Owen MJ, Gudnason V, Mayeux R, Escott-Price V, Psaty BM, Ramirez A, Wang LS, Ruiz A, van Duijn CM, Holmans PA, Seshadri S, Williams J, Amouyel P, Schellenberg GD, Lambert JC & Pericak-Vance MA (2019) Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat Genet* **51**, 414–430.

20 Lambert J-C, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, Jun G, DeStefano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thornton-Wells TA, Jones N, Smith A V, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin C-F, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau M-T, Choi S-H, Reitz C, Pasquier F, Hollingworth P, Ramirez A, Hanon O, Fitzpatrick AL, Buxbaum JD, Campion D, Crane PK, Baldwin C, Becker T, Gudnason V, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Morón FJ, Rubinsztein DC, Eiriksdottir G,

Sleegers K, Goate AM, Fiévet N, Huentelman MJ, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuinness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossù P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Naranjo MCD, Bosco P, Clarke R, Brayne C, Galimberti D, Mancuso M, Matthews F, Moebus S, Mecocci P, Del Zompo M, Maier W, Hampel H, Pilotto A, Bullido M, Panza F, Caffarra P, Nacmias B, Gilbert JR, Mayhaus M, Lannfelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson P V, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley TH, Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RFAG, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JSK, Boerwinkle E, Riemenschneider M, Boada M, Hiltunen M, Martin ER, Schmidt R, Rujescu D, Wang L-S, Dartigues J-F, Mayeux R, Tzourio C, Hofman A, Nöthen MM, Graff C, Psaty BM, Jones L, Haines JL, Holmans PA, Lathrop M, Pericak-Vance MA, Launer LJ, Farrer LA, van Duijn CM, Van Broeckhoven C, Moskvina V, Seshadri S, Williams J, Schellenberg GD & Amouyel P (2013) Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet* **45**, 1452–1458.

21 Tang R & Liu H (2019) Identification of Temporal Characteristic Networks of Peripheral Blood Changes in Alzheimer's Disease Based on Weighted Gene Co-expression Network Analysis. *Front Aging Neurosci* **11**, 83.

22 Zhang B, Gaiteri C, Bodea L-G, Wang Z, McElwee J, Podtelezhnikov AA, Zhang C, Xie T, Tran L, Dobrin R, Fluder E, Clurman B, Melquist S, Narayanan M, Suver C, Shah H, Mahajan M, Gillis T, Mysore J, MacDonald ME, Lamb JR, Bennett DA, Molony C, Stone DJ, Gudnason V, Myers AJ, Schadt EE, Neumann H, Zhu J & Emilsson V (2013) Integrated Systems Approach Identifies Genetic Nodes and Networks in Late-Onset Alzheimer's Disease. *Cell* **153**, 707–720.

23 Kreisl WC, Lyoo CH, McGwier M, Snow J, Jenko KJ, Kimura N, Corona W, Morse CL, Zoghbi SS, Pike

VW, McMahon FJ, Turner RS, Innis RB & Biomarkers Consortium PET Radioligand Project Team (2013) In vivo radioligand binding to translocator protein correlates with severity of Alzheimer's disease. *Brain* **136**, 2228–2238.

24 Kreisl WC, Lyoo CH, Liow J-S, Wei M, Snow J, Page E, Jenko KJ, Morse CL, Zoghbi SS, Pike VW, Turner RS & Innis RB (2016) 11 C-PBR28 binding to translocator protein increases with progression of Alzheimer's disease. *Neurobiol Aging* **44**, 53–61.

25 He X-F, Xu J-H, Li G, Li M-Y, Li L-L, Pei Z, Zhang L-Y & Hu X-Q (2020) NLRP3-dependent microglial training impaired the clearance of amyloid-beta and aggravated the cognitive decline in Alzheimer's disease. *Cell Death Dis* **11**, 849.

26 Birch AM, Katsouri L & Sastre M (2014) Modulation of inflammation in transgenic models of Alzheimer's disease. *J Neuroinflammation* **11**, 25.

27 Liu C-C, Liu C-C, Kanekiyo T, Xu H & Bu G (2013) Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol* **9**, 106–18.

28 Deming Y, Filipello F, Cignarella F, Cantoni C, Hsu S, Mikesell R, Li Z, Del-Aguila JL, Dube U, Farias FG, Bradley J, Budde J, Ibanez L, Fernandez MV, Blennow K, Zetterberg H, Heslegrave A, Johansson PM, Svensson J, Nellgård B, Lleo A, Alcolea D, Clarimon J, Rami L, Molinuevo JL, Suárez-Calvet M, Morenas-Rodríguez E, Kleinberger G, Ewers M, Harari O, Haass C, Brett TJ, Benitez BA, Karch CM, Piccio L & Cruchaga C (2019) The MS4A gene cluster is a key modulator of soluble TREM2 and Alzheimer's disease risk. *Sci Transl Med* **11**, eaau2291.

29 Hollingworth P, Harold D, Sims R, Gerrish A, Lambert J-C, Carrasquillo MM, Abraham R, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Jones N, Stretton A, Thomas C, Richards A, Ivanov D, Widdowson C, Chapman J, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Beaumont H, Warden D, Wilcock G, Love S, Kehoe PG, Hooper NM, Vardy ERLC, Hardy J, Mead S, Fox NC, Rossor M, Collinge J, Maier W, Jessen F, Rüther E, Schürmann B, Heun R, Kölsch H, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frölich L,

Hampel H, Gallacher J, Hüll M, Rujescu D, Giegling I, Goate AM, Kauwe JSK, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Mühleisen TW, Nöthen MM, Moebus S, Jöckel K-H, Klopp N, Wichmann H-E, Pankratz VS, Sando SB, Aasly JO, Barcikowska M, Wszolek ZK, Dickson DW, Graff-Radford NR, Petersen RC, van Duijn CM, Breteler MMB, Ikram MA, DeStefano AL, Fitzpatrick AL, Lopez O, Launer LJ, Seshadri S, Berr C, Campion D, Epelbaum J, Dartigues J-F, Tzourio C, Alpérovitch A, Lathrop M, Feulner TM, Friedrich P, Riehle C, Krawczak M, Schreiber S, Mayhaus M, Nicolhaus S, Wagenpfeil S, Steinberg S, Stefansson H, Stefansson K, Snædal J, Björnsson S, Jonsson P V, Chouraki V, Genier-Boley B, Hiltunen M, Soininen H, Combarros O, Zelenika D, Delepine M, Bullido MJ, Pasquier F, Mateo I, Frank-Garcia A, Porcellini E, Hanon O, Coto E, Alvarez V, Bosco P, Siciliano G, Mancuso M, Panza F, Solfrizzi V, Nacmias B, Sorbi S, Bossù P, Piccardi P, Arosio B, Annoni G, Seripa D, Pilotto A, Scarpini E, Galimberti D, Brice A, Hannequin D, Licastro F, Jones L, Holmans PA, Jonsson T, Riemenschneider M, Morgan K, Younkin SG, Owen MJ, O'Donovan M, Amouyel P, Williams J, O'Donovan M, Amouyel P & Williams J (2011) Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nat Genet* **43**, 429–435.

30 Mecca C, Giambanco I, Donato R & Arcuri C (2018) Microglia and aging: The role of the TREM2–DAP12 and CX3CL1-CX3CR1 Axes. *Int J Mol Sci* **19**, 318.

31 Ulrich JD, Ulland TK, Colonna M & Holtzman DM (2017) Elucidating the Role of TREM2 in Alzheimer's Disease. *Neuron* **94**, 237–248.

32 Ulland TK, Song WM, Huang SCC, Ulrich JD, Sergushichev A, Beatty WL, Loboda AA, Zhou Y, Cairns NJ, Kambal A, Loginicheva E, Gilfillan S, Cella M, Virgin HW, Unanue ER, Wang Y, Artyomov MN, Holtzman DM & Colonna M (2017) TREM2 Maintains Microglial Metabolic Fitness in Alzheimer's Disease. *Cell* **170**, 649-663.e13.

33 Turnbull IR, Gilfillan S, Cella M, Aoshi T, Miller M, Piccio L, Hernandez M & Colonna M (2006) Cutting edge: TREM-2 attenuates macrophage activation. *J Immunol* **177**, 3520–4.

34 Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, Cruchaga C, Sassi C, Kauwe JSK, Younkin S, Hazrati L, Collinge J, Pocock J, Lashley T, Williams J, Lambert J-C, Amouyel P, Goate A, Rademakers R, Morgan K, Powell J, St. George-Hyslop P, Singleton A, Hardy J & Alzheimer Genetic Analysis Group (2013) *TREM2* Variants in Alzheimer's Disease. *N Engl J Med* **368**, 117–127.

35 Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson P V., Snaedal J, Bjornsson S, Huttenlocher J, Levey AI, Lah JJ, Rujescu D, Hampel H, Giegling I, Andreassen OA, Engedal K, Ulstein I, Djurovic S, Ibrahim-Verbaas C, Hofman A, Ikram MA, van Duijn CM, Thorsteinsdottir U, Kong A & Stefansson K (2013) Variant of *TREM2* Associated with the Risk of Alzheimer's Disease. *N Engl J Med* **368**, 107–116.

36 Kunkle BW, Schmidt M, Klein H-U, Naj AC, Hamilton-Nelson KL, Larson EB, Evans DA, De Jager PL, Crane PK, Buxbaum JD, Ertekin-Taner N, Barnes LL, Fallin MD, Manly JJ, Go RCP, Obisesan TO, Kamboh MI, Bennett DA, Hall KS, Goate AM, Foroud TM, Martin ER, Wang L-S, Byrd GS, Farrer LA, Haines JL, Schellenberg GD, Mayeux R, Pericak-Vance MA, Reitz C, Alzheimer's Disease Genetics Consortium (ADGC) G-R, Graff-Radford NR, Martinez I, Ayodele T, Logue MW, Cantwell LB, Jean-Francois M, Kuzma AB, Adams LD, Vance JM, Cuccaro ML, Chung J, Mez J, Lunetta KL, Jun GR, Lopez OL, Hendrie HC, Reiman EM, Kowall NW, Leverenz JB, Small SA, Levey AI, Golde TE, Saykin AJ, Starks TD, Albert MS, Hyman BT, Petersen RC, Sano M, Wisniewski T, Vassar R, Kaye JA, Henderson VW, DeCarli C, LaFerla FM, Brewer JB, Miller BL, Swerdlow RH, Van Eldik LJ, Paulson HL, Trojanowski JQ, Chui HC, Rosenberg RN, Craft S, Grabowski TJ, Asthana S, Morris JC, Strittmatter SM & Kukull WA (2020) Novel Alzheimer Disease Risk Loci and Pathways in African American Individuals Using the African Genome Resources Panel: A Meta-analysis. *JAMA Neurol*, e203536.

37 Tosto G, Vardarajan B, Sariya S, Brickman AM, Andrews H, Manly JJ, Schupf N, Reyes-Dumeyer D, Lantigua R, Bennett DA, De Jager PL & Mayeux R (2019) Association of Variants in PINX1 and TREM2 With Late-Onset Alzheimer Disease. *JAMA Neurol* **76**, 942–948.

38 Crocker PR, Paulson JC & Varki A (2007) Siglecs and their roles in the immune system. *Nat Rev*

Immunol **7**, 255–66.

39 Ishida A, Akita K, Mori Y, Tanida S, Toda M, Inoue M & Nakada H (2014) Negative regulation of Toll-like receptor-4 signaling through the binding of glycosylphosphatidylinositol-anchored glycoprotein, CD14, with the sialic acid-binding lectin, CD33. *J Biol Chem* **289**, 25341–50.

40 Bradshaw EM, Chibnik LB, Keenan BT, Ottoboni L, Raj T, Tang A, Rosenkrantz LL, Imboywa S, Lee M, Von Korff A, Morris MC, Evans DA, Johnson K, Sperling RA, Schneider JA, Bennett DA, De Jager PL & De Jager PL (2013) CD33 Alzheimer's disease locus: altered monocyte function and amyloid biology. *Nat Neurosci* **16**, 848–850.

41 Karch CM, Jeng AT, Nowotny P, Cady J, Cruchaga C & Goate AM (2012) Expression of Novel Alzheimer's Disease Risk Genes in Control and Alzheimer's Disease Brains. *PLoS One* **7**, e50976.

42 Yokoyama JS, Wang Y, Schork AJ, Thompson WK, Karch CM, Cruchaga C, McEvoy LK, Witoelar A, Chen C-HH, Holland D, Brewer JB, Franke A, Dillon WP, Wilson DM, Mukherjee P, Hess CP, Miller Z, Bonham LW, Shen J, Rabinovici GD, Rosen HJ, Miller BL, Hyman BT, Schellenberg GD, Karlsen TH, Andreassen OA, Dale AM, Desikan RS & Alzheimer's Disease Neuroimaging Initiative (2016) Association Between Genetic Traits for Immune-Mediated Diseases and Alzheimer Disease. *JAMA Neurol* **73**, 691–7.

43 Hansen D V., Hanson JE & Sheng M (2018) Microglia in Alzheimer's disease. *J Cell Biol* **217**, 459–472.

44 Novikova G, Kapoor M, TCW J, Abud EM, Efthymiou AG, Cheng H, Fullard JF, Bendl J, Roussos P, Poon WW, Hao K, Marcora E & Goate AM (2019) Integration of Alzheimer's disease genetics and myeloid genomics reveals novel disease risk mechanisms. *bioRxiv*, 694281.

45 Jassam YN, Izzy S, Whalen M, McGavern DB & El Khoury J (2017) Neuroimmunology of Traumatic Brain Injury: Time for a Paradigm Shift. *Neuron* **95**, 1246–1265.

46 Simon DW, McGeachy MJ, Bayır H, Clark RSB, Loane DJ & Kochanek PM (2017) The far-reaching scope of neuroinflammation after traumatic brain injury. *Nat Rev Neurol* **13**, 171–191.

47 Dams-O'Connor K, Guetta G, Hahn-Ketter AE & Fedor A (2016) Traumatic brain injury as a risk

factor for Alzheimer's disease: current knowledge and future directions. *Neurodegener Dis Manag* **6**, 417–29.

48 DeKosky ST, Abrahamson EE, Ciallella JR, Paljug WR, Wisniewski SR, Clark RSB & Ikonomovic MD (2007) Association of increased cortical soluble abeta42 levels with diffuse plaques after severe brain injury in humans. *Arch Neurol* **64**, 541–4.

49 Johnson VE, Stewart W & Smith DH (2012) Widespread τ and amyloid-β pathology many years after a single traumatic brain injury in humans. *Brain Pathol* **22**, 142–9.

50 Dioguardi M, Crincoli V, Laino L, Alovisi M, Sovereto D, Mastrangelo F, Lo Russo L & Lo Muzio L (2020) The Role of Periodontitis and Periodontal Bacteria in the Onset and Progression of Alzheimer's Disease: A Systematic Review. *J Clin Med* **9**, 495.

51 Santos CY, Snyder PJ, Wu W, Zhang M, Echeverria A & Alber J (2017) Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. *Alzheimer's Dement Diagnosis, Assess Dis Monit* **7**, 69–87.

52 Arvanitakis Z, Wilson RS, Bienias JL, Evans DA & Bennett DA (2004) Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function. *Arch Neurol* **61**, 661–666.

53 Whitmer RA (2007) Type 2 diabetes and risk of cognitive impairment and dementia. *Curr Neurol Neurosci Rep* **7**, 373–380.

54 André P, Samieri C, Buisson C, Dartigues J-F, Helmer C, Laugerette F & Féart C (2019) Lipopolysaccharide-Binding Protein, Soluble CD14, and the Long-Term Risk of Alzheimer's Disease: A Nested Case-Control Pilot Study of Older Community Dwellers from the Three-City Cohort. *J Alzheimers Dis* **71**, 751–761.

55 Tao Q, Ang TFA, DeCarli C, Auerbach SH, Devine S, Stein TD, Zhang X, Massaro J, Au R & Qiu WQ (2018) Association of Chronic Low-grade Inflammation With Risk of Alzheimer Disease in ApoE4 Carriers. *JAMA Netw open* **1**, e183597.

56 He H-Q & Ye R (2017) The Formyl Peptide Receptors: Diversity of Ligands and Mechanism for Recognition. *Molecules* **22**, 455.

57 Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, Burton MA, Goldstein LE, Duong S, Tanzi RE & Moir RD (2010) The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. *PLoS One* **5**, e9505.

58 Spitzer P, Condic M, Herrmann M, Oberstein TJ, Scharin-Mehlmann M, Gilbert DF, Friedrich O, Gromer T, Kornhuber J, Lang R & Maler JM (2016) Amyloidogenic amyloid-beta-peptide variants induce microbial agglutination and exert antimicrobial activity. *Sci Rep* **6**, 32228.

59 Kumar DKV, Choi SH, Washicosky KJ, Eimer WA, Tucker S, Ghofrani J, Lefkowitz A, McColl G, Goldstein LE, Tanzi RE & Moir RD (2016) Amyloid-beta peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. *Sci Transl Med* **8**, 340ra72.

60 Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B & Jamieson GA (1997) Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. *Lancet (London, England)* **349**, 241–244.

61 Kountouras J, Tsolaki M, Gavalas E, Boziki M, Zavos C, Karatzoglou P, Chatzopoulos D & Venizelos I (2006) Relationship between Helicobacter pylori infection and Alzheimer disease. *Neurology* **66**, 938–940.

62 Miklossy J, Kis A, Radenovic A, Miller L, Forro L, Martins R, Reiss K, Darbinian N, Darekar P, Mihaly L & Khalili K (2006) Beta-amyloid deposition and Alzheimer's type changes induced by Borrelia spirochetes. *Neurobiol Aging* **27**, 228–236.

63 Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A, Nguyen M, Haditsch U, Raha D, Griffin C, Holsinger LJ, Arastu-Kapur S, Kaba S, Lee A, Ryder MI, Potempa B, Mydel P, Hellvard A, Adamowicz K, Hasturk H, Walker GD, Reynolds EC, Faull RLM, Curtis MA, Dragunow M & Potempa J (2019) Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Sci Adv* **5**, eaau3333.

64 Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, Ulland TK, David E, Baruch K, Lara-Astaiso D, Toth B, Itzkovitz S, Colonna M, Schwartz M & Amit I (2017) A Unique Microglia Type Associated with Restricting Development of Alzheimer's Disease. *Cell* **169**, 1276-1290.e17.

65 Olah M, Menon V, Habib N, Taga MF, Ma Y, Yung CJ, Cimpean M, Khairallah A, Coronas-Samano G, Sankowski R, Grün D, Kroshilina AA, Dionne D, Sarkis RA, Cosgrove GR, Helgager J, Golden JA, Pennell PB, Prinz M, Vonsattel JPG, Teich AF, Schneider JA, Bennett DA, Regev A, Elyaman W, Bradshaw EM & De Jager PL (2020) Single cell RNA sequencing of human microglia uncovers a subset associated with Alzheimer's disease. *Nat Commun* **11**, 6129.

66 Mathys H, Adaikkan C, Gao F, Young JZ, Manet E, Hemberg M, De Jager PL, Ransohoff RM, Regev A & Tsai L-H (2017) Temporal Tracking of Microglia Activation in Neurodegeneration at Single-Cell Resolution. *Cell Rep* **21**, 366–380.

67 Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, Yamasaki R, Ransohoff RM, Greenberg ME, Barres BA & Stevens B (2012) Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron* **74**, 691–705.

68 Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, Merry KM, Shi Q, Rosenthal A, Barres BA, Lemere CA, Selkoe DJ & Stevens B (2016) Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science (80-)* **352**, 712–716.

69 Shi Q, Chowdhury S, Ma R, Le KX, Hong S, Caldarone BJ, Stevens B & Lemere CA (2017) Complement C3 deficiency protects against neurodegeneration in aged plaque-rich APP/PS1 mice. *Sci Transl Med* **9**, eaaf6295.

70 Wu T, Dejanovic B, Gandham VD, Gogineni A, Edmonds R, Schauer S, Srinivasan K, Huntley MA, Wang Y, Wang T-M, Hedehus M, Barck KH, Stark M, Ngu H, Foreman O, Meilandt WJ, Elstrott J, Chang MC, Hansen D V, Carano RAD, Sheng M & Hanson JE (2019) Complement C3 Is Activated in Human AD Brain and Is Required for Neurodegeneration in Mouse Models of Amyloidosis and Tauopathy. *Cell Rep* **28**, 2111-2123.e6.

71 Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML, Münch AE, Chung W-S, Peterson TC, Wilton DK, Frouin A, Napier BA, Panicker N, Kumar M, Buckwalter MS, Rowitch DH, Dawson VL, Dawson TM, Stevens B & Barres BA (2017) Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* **541**, 481–487.

72 Reichenbach N, Delekate A, Plescher M, Schmitt F, Krauss S, Blank N, Halle A & Petzold GC (2019) Inhibition of Stat3-mediated astrogliosis ameliorates pathology in an Alzheimer's disease model. *EMBO Mol Med* **11**, e9665.

73 Kraft AW, Hu X, Yoon H, Yan P, Xiao Q, Wang Y, Gil SC, Brown J, Wilhelmsson U, Restivo JL, Cirrito JR, Holtzman DM, Kim J, Pekny M & Lee J-M (2013) Attenuating astrocyte activation accelerates plaque pathogenesis in APP/PS1 mice. *FASEB J* **27**, 187–98.

74 Katsouri L, Birch AM, Renziehausen AWJ, Zach C, Aman Y, Steeds H, Bonsu A, Palmer EOC, Mirzaei N, Ries M & Sastre M (2020) Ablation of reactive astrocytes exacerbates disease pathology in a model of Alzheimer's disease. *Glia* **68**, 1017–1030.

75 Fuller JP, Stavenhagen JB, Christensen S, Kartberg F, Glennie MJ & Teeling JL (2015) Comparing the efficacy and neuroinflammatory potential of three anti-abeta antibodies. *Acta Neuropathol* **130**, 699–711.

76 Gong Z, Huang J, Xu B, Ou Z, Zhang L, Lin X, Ye X, Kong X, Long D, Sun X, He X, Xu L, Li Q & Xuan A (2019) Urolithin A attenuates memory impairment and neuroinflammation in APP/PS1 mice. *J Neuroinflammation* **16**, 62.

77 Robison LS, Popescu DL, Anderson ME, Francis N, Hatfield J, Sullivan JK, Beigelman SI, Xu F, Anderson BJ, Van Nostrand WE & Robinson JK (2019) Long-term voluntary wheel running does not alter vascular amyloid burden but reduces neuroinflammation in the Tg-SwDI mouse model of cerebral amyloid angiopathy. *J Neuroinflammation* **16**, 144.

78 Balasubramaniam M, Parcon PA, Bose C, Liu L, Jones RA, Farlow MR, Mrak RE, Barger SW & Griffin WST (2019) Interleukin-1β drives NEDD8 nuclear-to-cytoplasmic translocation, fostering parkin activation via NEDD8 binding to the P-ubiquitin activating site. *J Neuroinflammation* **16**, 275.

79 Sturchler-Pierrat C, Abramowski D, Duke M, Wiederhold KH, Mistl C, Rothacher S, Ledermann B, Bürki K, Frey P, Paganetti PA, Waridel C, Calhoun ME, Jucker M, Probst A, Staufenbiel M & Sommer B (1997) Two amyloid precursor protein transgenic mouse models with Alzheimer

disease-like pathology. *Proc Natl Acad Sci U S A* **94**, 13287–92.

80 Yoshiyama Y, Higuchi M, Zhang B, Huang S-M, Iwata N, Saido TC, Maeda J, Suhara T, Trojanowski JQ & Lee VM-Y (2007) Synapse Loss and Microglial Activation Precede Tangles in a P301S Tauopathy Mouse Model. *Neuron* **53**, 337–351.

81 Balducci C, Santamaria G, La Vitola P, Brandi E, Grandi F, Viscomi AR, Beeg M, Gobbi M, Salmona M, Ottonello S & Forloni G (2018) Doxycycline counteracts neuroinflammation restoring memory in Alzheimer's disease mouse models. *Neurobiol Aging* **70**, 128–139.

82 Yun SP, Kam T-I, Panicker N, Kim S, Oh Y, Park J-S, Kwon S-H, Park YJ, Karuppagounder SS, Park H, Kim S, Oh N, Kim NA, Lee S, Brahmachari S, Mao X, Lee JH, Kumar M, An D, Kang S-U, Lee Y, Lee KC, Na DH, Kim D, Lee SH, Roschke V V., Liddelow SA, Mari Z, Barres BA, Dawson VL, Lee S, Dawson TM & Ko HS (2018) Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. *Nat Med* **24**, 931–938.

83 Lapenna A, De Palma M & Lewis CE (2018) Perivascular macrophages in health and disease. *Nat Rev Immunol* **18**, 689–702.

84 Colonna M & Butovsky O (2017) Microglia Function in the Central Nervous System During Health and Neurodegeneration. *Annu Rev Immunol* **35**, 441–468.

85 Cable J, Holtzman DM, Hyman BT, Tansey MG, Colonna M, Kellis M, Brinton RD, Albert M, Wellington CL, Sisodia SS & Tanzi RE (2020) Alternatives to amyloid for Alzheimer's disease therapies-a symposium report. *Ann N Y Acad Sci* **1475**, 3–14.

86 Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, Mehler MF, Conway SJ, Ng LG, Stanley ER, Samokhvalov IM & Merad M (2010) Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science* **330**, 841–5.

87 Michell-Robinson MA, Touil H, Healy LM, Owen DR, Durafourt BA, Bar-Or A, Antel JP & Moore CS (2015) Roles of microglia in brain development, tissue maintenance and repair. *Brain* **138**, 1138–59.

88 Ransohoff RM & El Khoury J (2015) Microglia in Health and Disease. *Cold Spring Harb Perspect* **8**,

a020560.

89 Neumann H, Kotter MR & Franklin RJM (2009) Debris clearance by microglia: an essential link between degeneration and regeneration. *Brain* **132**, 288–295.

90 Parkhurst CN, Yang G, Ninan I, Savas JN, Yates JR, Lafaille JJ, Hempstead BL, Littman DR & Gan W-B (2013) Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. *Cell* **155**, 1596–609.

91 Wake H, Moorhouse AJ, Jinno S, Kohsaka S & Nabekura J (2009) Resting Microglia Directly Monitor the Functional State of Synapses In Vivo and Determine the Fate of Ischemic Terminals. *J Neurosci* **29**, 3974–3980.

92 Koellhoffer E, McCullough L & Ritzel R (2017) Old Maids: Aging and Its Impact on Microglia Function. *Int J Mol Sci* **18**, 769.

93 Perry VH (1998) A revised view of the central nervous system microenvironment and major histocompatibility complex class II antigen presentation. *J Neuroimmunol* **90**, 113–21.

94 Lawson LJ, Perry VH, Dri P & Gordon S (1990) Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. *Neuroscience* **39**, 151–170.

95 Hammond TR, Dufort C, Dissing-Olesen L, Giera S, Young A, Wysoker A, Walker AJ, Gergits F, Segel M, Nemesh J, Marsh SE, Saunders A, Macosko E, Ginhoux F, Chen J, Franklin RJMM, Piao X, McCarroll SA & Stevens B (2019) Single-Cell RNA Sequencing of Microglia throughout the Mouse Lifespan and in the Injured Brain Reveals Complex Cell-State Changes. *Immunity* **50**, 253-271.e6.

96 Mathys H, Davila-Velderrain J, Peng Z, Gao F, Mohammadi S, Young JZ, Menon M, He L, Abdurrob F, Jiang X, Martorell AJ, Ransohoff RM, Hafler BP, Bennett DA, Kellis M & Tsai L-H (2019) Single-cell transcriptomic analysis of Alzheimer's disease. *Nature* **570**, 332.

97 Holtman IR, Skola D & Glass CK (2017) Transcriptional control of microglia phenotypes in health and disease. *J Clin Invest* **127**, 3220–3229.

98 Hickman S, Izzy S, Sen P, Morsett L & El Khoury J (2018) Microglia in Neurodegeneration. *Nat Neurosci* **21**, 1359–1369.

99 Ransohoff RM (2016) How neuroinflammation contributes to neurodegeneration. *Science* **353**, 777–83.

100 Serhan CN & Savill J (2005) Resolution of inflammation: the beginning programs the end. *Nat Immunol* **6**, 1191–7.

101 Felsky D, Roostaei T, Nho K, Risacher SL, Bradshaw EM, Petyuk V, Schneider JA, Saykin A, Bennett DA & De Jager PL (2019) Neuropathological correlates and genetic architecture of microglial activation in elderly human brain. *Nat Commun* **10**, 409.

102 Pluvinage J V., Haney MS, Smith BAH, Sun J, Iram T, Bonanno L, Li L, Lee DP, Morgens DW, Yang AC, Shuken SR, Gate D, Scott M, Khatri P, Luo J, Bertozzi CR, Bassik MC & Wyss-Coray T (2019) CD22 blockade restores homeostatic microglial phagocytosis in ageing brains. *Nature* **568**, 187–192.

103 Zhou Y, Cai J, Zhang W, Gong X, Yan S, Zhang K, Luo Z, Sun J, Jiang Q & Lou M (2020) Impairment of the Glymphatic Pathway and Putative Meningeal Lymphatic Vessels in the Aging Human. *Ann Neurol* **87**, 357–369.

104 Sugimoto MA, Sousa LP, Pinho V, Perretti M & Teixeira MM (2016) Resolution of Inflammation: What Controls Its Onset? *Front Immunol* **7**, 160.

105 Lobo-Silva D, Carriche GM, Castro AG, Roque S & Saraiva M (2016) Balancing the immune response in the brain: IL-10 and its regulation. *J Neuroinflammation* **13**, 297.

106 Heneka MT, Kummer MP & Latz E (2014) Innate immune activation in neurodegenerative disease. *Nat Rev Immunol* **14**, 463–77.

107 Chen Z & Trapp BD (2016) Microglia and neuroprotection. *J Neurochem* **136 Suppl**, 10–7.

108 Hopperton KE, Mohammad D, Trépanier MO, Giuliano V & Bazinet RP (2018) Markers of microglia in post-mortem brain samples from patients with Alzheimer's disease: a systematic

review. *Mol Psychiatry* **23**, 177–198.

109 Taipa R, Ferreira V, Brochado P, Robinson A, Reis I, Marques F, Mann DM, Melo-Pires M & Sousa N (2018) Inflammatory pathology markers (activated microglia and reactive astrocytes) in early and late onset Alzheimer disease: a *post mortem* study. *Neuropathol Appl Neurobiol* **44**, 298–313.

110 Chandra A, Valkimadi PE, Pagano G, Cousins O, Dervenoulas G & Politis M (2019) Applications of amyloid, tau, and neuroinflammation PET imaging to Alzheimer's disease and mild cognitive impairment. *Hum Brain Mapp* **40**, 5424–5442.

111 Hommet C, Mondon K, Camus V, Ribeiro MJ, Beaufils E, Arlicot N, Corcia P, Paccalin M, Minier F, Gosselin T, Page G, Guilloteau D & Chalon S (2014) Neuroinflammation and β amyloid deposition in alzheimer's disease: In vivo quantification with molecular imaging. *Dement Geriatr Cogn Disord* **37**, 1–18.

112 Deczkowska A, Matcovitch-Natan O, Tsitsou-Kampeli A, Ben-Hamo S, Dvir-Szternfeld R, Spinrad A, Singer O, David E, Winter DR, Smith LK, Kertser A, Baruch K, Rosenzweig N, Terem A, Prinz M, Villeda S, Citri A, Amit I & Schwartz M (2017) Mef2C restrains microglial inflammatory response and is lost in brain ageing in an IFN-I-dependent manner. *Nat Commun* **8**, 717.

113 Ubelmann F, Burrinha T, Salavessa L, Gomes R, Ferreira C, Moreno N & Guimas Almeida C (2017) Bin1 and CD 2 AP polarise the endocytic generation of beta-amyloid. *EMBO Rep* **18**, 102–122.

114 Sims R, van der Lee SJ, Naj AC, Bellenguez C, Badarinarayan N, Jakobsdottir J, Kunkle BW, Boland A, Raybould R, Bis JC, Martin ER, Grenier-Boley B, Heilmann-Heimbach S, Chouraki V, Kuzma AB, Sleegers K, Vronskaya M, Ruiz A, Graham RR, Olaso R, Hoffmann P, Grove ML, Vardarajan BN, Hiltunen M, Nöthen MM, White CC, Hamilton-Nelson KL, Epelbaum J, Maier W, Choi S-H, Beecham GW, Dulary C, Herms S, Smith A V, Funk CC, Derbois C, Forstner AJ, Ahmad S, Li H, Bacq D, Harold D, Satizabal CL, Valladares O, Squassina A, Thomas R, Brody JA, Qu L, Sánchez-Juan P, Morgan T, Wolters FJ, Zhao Y, Garcia FS, Denning N, Fornage M, Malamon J, Naranjo MCD, Majounie E, Mosley TH, Dombroski B, Wallon D, Lupton MK, Dupuis J, Whitehead P,

Fratiglioni L, Medway C, Jian X, Mukherjee S, Keller L, Brown K, Lin H, Cantwell LB, Panza F, McGuinness B, Moreno-Grau S, Burgess JD, Solfrizzi V, Proitsi P, Adams HH, Allen M, Seripa D, Pastor P, Cupples LA, Price ND, Hannequin D, Frank-García A, Levy D, Chakrabarty P, Caffarra P, Giegling I, Beiser AS, Giedraitis V, Hampel H, Garcia ME, Wang X, Lannfelt L, Mecocci P, Eiriksdottir G, Crane PK, Pasquier F, Boccardi V, Henández I, Barber RC, Scherer M, Tarraga L, Adams PM, Leber M, Chen Y, Albert MS, Riedel-Heller S, Emilsson V, Beekly D, Braae A, Schmidt R, Blacker D, Masullo C, Schmidt H, Doody RS, Spalletta G, Jr WTL, Fairchild TJ, Bossù P, Lopez OL, Frosch MP, Sacchinelli E, Ghetti B, Yang Q, Huebinger RM, Jessen F, Li S, Kamboh MI, Morris J, Sotolongo-Grau O, Katz MJ, Corcoran C, Dunstan M, Braddel A, Thomas C, Meggy A, Marshall R, Gerrish A, Chapman J, Aguilar M, Taylor S, Hill M, Fairén MD, Hodges A, Vellas B, Soininen H, Kloszewska I, Daniilidou M, Uphill J, Patel Y, Hughes JT, Lord J, Turton J, Hartmann AM, Cecchetti R, Fenoglio C, Serpente M, Arcaro M, Caltagirone C, Orfei MD, Ciaramella A, Pichler S, Mayhaus M, Gu W, Lleó A, Fortea J, Blesa R, Barber IS, Brookes K, Cupidi C, Maletta RG, Carrell D, Sorbi S, Moebus S, Urbano M, Pilotto A, Kornhuber J, Bosco P, Todd S, Craig D, Johnston J, Gill M, Lawlor B, Lynch A, Fox NC, Hardy J, Albin RL, Apostolova LG, Arnold SE, Asthana S, Atwood CS, Baldwin CT, Barnes LL, Barral S, Beach TG, Becker JT, Bigio EH, Bird TD, Boeve BF, Bowen JD, Boxer A, Burke JR, Burns JM, Buxbaum JD, Cairns NJ, Cao C, Carlson CS, Carlsson CM, Carney RM, Carrasquillo MM, Carroll SL, Diaz CC, Chui HC, Clark DG, Cribbs DH, Crocco EA, DeCarli C, Dick M, Duara R, Evans DA, Faber KM, Fallon KB, Fardo DW, Farlow MR, Ferris S, Foroud TM, Galasko DR, Gearing M, Geschwind DH, Gilbert JR, Graff-Radford NR, Green RC, Growdon JH, Hamilton RL, Harrell LE, Honig LS, Huentelman MJ, Hulette CM, Hyman BT, Jarvik GP, Abner E, Jin L-W, Jun G, Karydas A, Kaye JA, Kim R, Kowall NW, Kramer JH, LaFerla FM, Lah JJ, Leverenz JB, Levey AI, Li G, Lieberman AP, Lunetta KL, Lyketsos CG, Marson DC, Martiniuk F, Mash DC, Masliah E, McCormick WC, McCurry SM, McDavid AN, McKee AC, Mesulam M, Miller BL, Miller CA, Miller JW, Morris JC, Murrell JR, Myers AJ, O'Bryant S, Olichney JM, Pankratz VS, Parisi JE, Paulson HL, Perry W, Peskind E, Pierce A, Poon WW, Potter H, Quinn JF, Raj A, Raskind M, Reisberg B, Reitz C, Ringman JM, Roberson ED, Rogaeva E, Rosen HJ, Rosenberg RN, Sager MA, Saykin AJ, Schneider JA, Schneider LS, Seeley WW, Smith AG, Sonnen JA, Spina S, Stern RA,

Swerdlow RH, Tanzi RE, Thornton-Wells TA, Trojanowski JQ, Troncoso JC, Van Deerlin VM, Van Eldik LJ, Vinters H V, Vonsattel JP, Weintraub S, Welsh-Bohmer KA, Wilhelmsen KC, Williamson J, Wingo TS, Woltjer RL, Wright CB, Yu C-E, Yu L, Garzia F, Golamaully F, Septier G, Engelborghs S, Vandenberghe R, De Deyn PP, Fernadez CM, Benito YA, Thonberg H, Forsell C, Lilius L, Kinhult-Stählbom A, Kilander L, Brundin R, Concari L, Helisalmi S, Koivisto AM, Haapasalo A, Dermecourt V, Fievet N, Hanon O, Dufouil C, Brice A, Ritchie K, Dubois B, Himali JJ, Keene CD, Tschanz J, Fitzpatrick AL, Kukull WA, Norton M, Aspelund T, Larson EB, Munger R, Rotter JI, Lipton RB, Bullido MJ, Hofman A, Montine TJ, Coto E, Boerwinkle E, Petersen RC, Alvarez V, Rivadeneira F, Reiman EM, Gallo M, O'Donnell CJ, Reisch JS, Bruni AC, Royall DR, Dichgans M, Sano M, Galimberti D, St George-Hyslop P, Scarpini E, Tsuang DW, Mancuso M, Bonuccelli U, Winslow AR, Daniele A, Wu C-K, Peters O, Nacmias B, Riemenschneider M, Heun R, Brayne C, Rubinsztein DC, Bras J, Guerreiro R, Al-Chalabi A, Shaw CE, Collinge J, Mann D, Tsolaki M, Clarimón J, Sussams R, Lovestone S, O'Donovan MC, Owen MJ, Behrens TW, Mead S, Goate AM, Uitterlinden AG, Holmes C, Cruchaga C, Ingelsson M, Bennett DA, Powell J, Golde TE, Graff C, De Jager PL, Morgan K, Ertekin-Taner N, Combarros O, Psaty BM, Passmore P, Younkin SG, Berr C, Gudnason V, Rujescu D, Dickson DW, Dartigues J-F, DeStefano AL, Ortega-Cubero S, Hakonarson H, Campion D, Boada M, Kauwe JK, Farrer LA, Van Broeckhoven C, Ikram MA, Jones L, Haines JL, Tzourio C, Launer LJ, Escott-Price V, Mayeux R, Deleuze J-F, Amin N, Holmans PA, Pericak-Vance MA, Amouyel P, van Duijn CM, Ramirez A, Wang L-S, Lambert J-C, Seshadri S, Williams J, Schellenberg GD, Williams J & Schellenberg GD (2017) Rare coding variants in PLCG2, ABI3, and TREM2 implicate microglial-mediated innate immunity in Alzheimer's disease. *Nat Genet* **49**, 1373–1384.

115 Johnson ECB, Dammer EB, Duong DM, Ping L, Zhou M, Yin L, Higginbotham LA, Guajardo A, White B, Troncoso JC, Thambisetty M, Montine TJ, Lee EB, Trojanowski JQ, Beach TG, Reiman EM, Haroutunian V, Wang M, Schadt E, Zhang B, Dickson DW, Ertekin-Taner N, Golde TE, Petyuk VA, De Jager PL, Bennett DA, Wingo TS, Rangaraju S, Hajjar I, Shulman JM, Lah JJ, Levey AI & Seyfried NT (2020) Large-scale proteomic analysis of Alzheimer's disease brain and

cerebrospinal fluid reveals early changes in energy metabolism associated with microglia and astrocyte activation. *Nat Med* **26**, 769–780.

116 Réu P, Khosravi A, Bernard S, Mold JE, Salehpour M, Alkass K, Perl S, Tisdale J, Possnert G, Druid H & Frisén J (2017) The Lifespan and Turnover of Microglia in the Human Brain. *Cell Rep* **20**, 779–784.

117 Ritzel RM, Patel AR, Pan S, Crapser J, Hammond M, Jellison E & McCullough LD (2015) Age- and location-related changes in microglial function. *Neurobiol Aging* **36**, 2153–63.

118 Floden AM & Combs CK (2011) Microglia demonstrate age-dependent interaction with amyloid-β fibrils. *J Alzheimers Dis* **25**, 279–93.

119 Bolós M, Llorens-Martín M, Jurado-Arjona J, Hernández F, Rábano A & Avila J (2016) Direct Evidence of Internalization of Tau by Microglia In Vitro and In Vivo. *J Alzheimers Dis* **50**, 77–87.

120 Fetler L & Amigorena S (2005) NEUROSCIENCE: Brain Under Surveillance: The Microglia Patrol. *Science (80-)* **309**, 392–393.

121 Maezawa I, Zimin PI, Wulff H & Jin L-W (2011) Amyloid-β Protein Oligomer at Low Nanomolar Concentrations Activates Microglia and Induces Microglial Neurotoxicity. *J Biol Chem* **286**, 3693–3706.

122 Fekete C, Vastagh C, Dénes Á, Hrabovszky E, Nyiri G, Kalló I, Liposits Z & Sárvári M (2018) Chronic Amyloid β Oligomer Infusion Evokes Sustained Inflammation and Microglial Changes in the Rat Hippocampus via NLRP3. *Neuroscience* **405**, 35–46.

123 Ahmad MH, Fatima M & Mondal AC (2019) Influence of microglia and astrocyte activation in the neuroinflammatory pathogenesis of Alzheimer's disease: Rational insights for the therapeutic approaches. *J Clin Neurosci* **59**, 6–11.

124 Terwel D, Steffensen KR, Verghese PB, Kummer MP, Gustafsson J-Å, Holtzman DM & Heneka MT (2011) Critical role of astroglial apolipoprotein E and liver X receptor-α expression for microglial Aβ phagocytosis. *J Neurosci* **31**, 7049–59.

125 Lambert J-C, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fiévet N, Barberger-Gateau P, Engelborghs S, De Deyn P, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O, de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossù P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Ritchie K, Blanché H, Dartigues J-F, Tzourio C, Gut I, Van Broeckhoven C, Alpérovitch A, Lathrop M & Amouyel P (2009) Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* **41**, 1094–9.

126 Maier M, Peng Y, Jiang L, Seabrook TJ, Carroll MC & Lemere CA (2008) Complement C3 deficiency leads to accelerated amyloid beta plaque deposition and neurodegeneration and modulation of the microglia/macrophage phenotype in amyloid precursor protein transgenic mice. *J Neurosci* **28**, 6333–41.

127 Leyns CEG, Ulrich JD, Finn MB, Stewart FR, Koscal LJ, Remolina Serrano J, Robinson GO, Anderson E, Colonna M & Holtzman DM (2017) TREM2 deficiency attenuates neuroinflammation and protects against neurodegeneration in a mouse model of tauopathy. *Proc Natl Acad Sci U S A* **114**, 11524–11529.

128 Miners JS, Baig S, Tayler H, Kehoe PG & Love S (2009) Neprilysin and insulin-degrading enzyme levels are increased in Alzheimer disease in relation to disease severity. *J Neuropathol Exp Neurol* **68**, 902–14.

129 Orr ME & Oddo S (2013) Autophagic/lysosomal dysfunction in Alzheimer's disease. *Alzheimer's Res Ther* **5**, 53.

130 Monasor LS, Müller SA, Colombo AV, Tanrioever G, König J, Roth S, Liesz A, Berghofer A, Piechotta A, Prestel M, Saito T, Saido TC, Herms J, Willem M, Haass C, Lichtenthaler SF & Tahirovic S (2020) Fibrillar aβ triggers microglial proteome alterations and dysfunction in alzheimer mouse models. *Elife* **9**, 1–33.

131 López-Picón FR, Snellman A, Eskola O, Helin S, Solin O, Haaparanta-Solin M & Rinne JO (2018)

Neuroinflammation Appears Early on PET Imaging and Then Plateaus in a Mouse Model of Alzheimer Disease. *J Nucl Med* **59**, 509–515.

132 Pan XD, Zhu YG, Lin N, Zhang J, Ye QY, Huang HP & Chen XC (2011) Microglial phagocytosis induced by fibrillar β-amyloid is attenuated by oligomeric β-amyloid: implications for Alzheimer's disease. *Mol Neurodegener* **6**, 45.

133 Yu Y & Ye RD (2014) Microglial Aβ Receptors in Alzheimer's Disease. *Cell Mol Neurobiol* **35**, 71–83.

134 Balducci C, Frasca A, Zotti M, La Vitola P, Mhillaj E, Grigoli E, Iacobellis M, Grandi F, Messa M, Colombo L, Molteni M, Trabace L, Rossetti C, Salmona M & Forloni G (2017) Toll-like receptor 4-dependent glial cell activation mediates the impairment in memory establishment induced by β-amyloid oligomers in an acute mouse model of Alzheimer's disease. *Brain Behav Immun* **60**, 188–197.

135 Fang F, Lue L-F, Yan S, Xu H, Luddy JS, Chen D, Walker DG, Stern DM, Yan S, Schmidt AM, Chen JX & Yan SS (2010) RAGE-dependent signaling in microglia contributes to neuroinflammation, Abeta accumulation, and impaired learning/memory in a mouse model of Alzheimer's disease. *FASEB J* **24**, 1043–55.

136 d'Avila JC, Siqueira LD, Mazeraud A, Azevedo EP, Foguel D, Castro-Faria-Neto HC, Sharshar T, Chrétien F & Bozza FA (2018) Age-related cognitive impairment is associated with long-term neuroinflammation and oxidative stress in a mouse model of episodic systemic inflammation. *J Neuroinflammation* **15**, 28.

137 Bouvier DS & Murai KK (2015) Synergistic actions of microglia and astrocytes in the progression of Alzheimer's disease. *J Alzheimers Dis* **45**, 1001–14.

138 Heneka MT, Carson MJ, Khoury J El, Landreth GE, Brosseron F, Feinstein DL, Jacobs AH, Wyss-Coray T, Vitorica J, Ransohoff RM, Herrup K, Frautschy SA, Finsen B, Brown GC, Verkhratsky A, Yamanaka K, Koistinaho J, Latz E, Halle A, Petzold GC, Town T, Morgan D, Shinohara ML, Perry VH, Holmes C, Bazan NG, Brooks DJ, Hunot S, Joseph B, Deigendesch N, Garaschuk O, Boddeke

E, Dinarello CA, Breitner JC, Cole GM, Golenbock DT & Kummer MP (2015) Neuroinflammation in Alzheimer's disease. *Lancet Neurol* **14**, 388–405.

139 Wilkinson BL, Cramer PE, Varvel NH, Reed-Geaghan E, Jiang Q, Szabo A, Herrup K, Lamb BT & Landreth GE (2012) Ibuprofen attenuates oxidative damage through NOX2 inhibition in Alzheimer's disease. *Neurobiol Aging* **33**, 197.e21-197.e32.

140 Hickman SE, Allison EK & El Khoury J (2008) Microglial Dysfunction and Defective Beta-Amyloid Clearance Pathways in Aging Alzheimer's Disease Mice. *J Neurosci* **28**, 8354–8360.

141 Herbst-Robinson KJ, Liu L, James M, Yao Y, Xie SX & Brunden KR (2016) Inflammatory Eicosanoids Increase Amyloid Precursor Protein Expression via Activation of Multiple Neuronal Receptors. *Sci Rep* **5**, 18286.

142 Spangenberg E, Severson PL, Hohsfield LA, Crapser J, Zhang J, Burton EA, Zhang Y, Spevak W, Lin J, Phan NY, Habets G, Rymar A, Tsang G, Walters J, Nespi M, Singh P, Broome S, Ibrahim P, Zhang C, Bollag G, West BL & Green KN (2019) Sustained microglial depletion with CSF1R inhibitor impairs parenchymal plaque development in an Alzheimer's disease model. *Nat Commun* **10**, 3758.

143 Spangenberg E, Lee RJ, Najafi AR, Rice RA, Elmore MRP, Blurton-Jones M, West BL & Green KN (2016) Eliminating microglia in Alzheimer's mice prevents neuronal loss without modulating amyloid-β pathology. *Brain* **139**, 1265–1281.

144 Sosna J, Philipp S, Albay R, Reyes-Ruiz JM, Baglietto-Vargas D, LaFerla FM & Glabe CG (2018) Early long-term administration of the CSF1R inhibitor PLX3397 ablates microglia and reduces accumulation of intraneuronal amyloid, neuritic plaque deposition and pre-fibrillar oligomers in 5XFAD mouse model of Alzheimer's disease. *Mol Neurodegener* **13**, 11.

145 Zhong L, Xu Y, Zhuo R, Wang T, Wang K, Huang R, Wang D, Gao Y, Zhu Y, Sheng X, Chen K, Wang N, Zhu L, Can D, Marten Y, Shinohara M, Liu C-C, Du D, Sun H, Wen L, Xu H, Bu G & Chen X-F (2019) Soluble TREM2 ameliorates pathological phenotypes by modulating microglial functions in an Alzheimer's disease model. *Nat Commun* **10**, 1365.

146 Lei F, Cui N, Zhou C, Chodosh J, Vavvas DG & Paschalis EI (2020) CSF1R inhibition by a small-molecule inhibitor is not microglia specific; Affecting hematopoiesis and the function of macrophages. *Proc Natl Acad Sci U S A* **117**, 23336–23338.

147 Olmos-Alonso A, Schetters STT, Sri S, Askew K, Mancuso R, Vargas-Caballero M, Holscher C, Perry VH & Gomez-Nicola D (2016) Pharmacological targeting of CSF1R inhibits microglial proliferation and prevents the progression of Alzheimer's-like pathology. *Brain*, 1–17.

148 Grathwohl SA, Kälin RE, Bolmont T, Prokop S, Winkelmann G, Kaeser SA, Odenthal J, Radde R, Eldh T, Gandy S, Aguzzi A, Staufenbiel M, Mathews PM, Wolburg H, Heppner FL & Jucker M (2009) Formation and maintenance of Alzheimer's disease beta-amyloid plaques in the absence of microglia. *Nat Neurosci* **12**, 1361–3.

149 Hamelin L, Lagarde J, Dorothée G, Leroy C, Labit M, Comley RA, de Souza LC, Corne H, Dauphinot L, Bertoux M, Dubois B, Gervais P, Colliot O, Potier MC, Bottlaender M, Sarazin M & Clinical IMABio3 team (2016) Early and protective microglial activation in Alzheimer's disease: a prospective study using 18F-DPA-714 PET imaging. *Brain* **139**, 1252–64.

150 Yasuno F, Kosaka J, Ota M, Higuchi M, Ito H, Fujimura Y, Nozaki S, Takahashi S, Mizukami K, Asada T & Suhara T (2012) Increased binding of peripheral benzodiazepine receptor in mild cognitive impairment-dementia converters measured by positron emission tomography with [^{11}C]DAA1106. *Psychiatry Res* **203**, 67–74.

151 Dani M, Wood M, Mizoguchi R, Fan Z, Walker Z, Morgan R, Hinz R, Biju M, Kuruvilla T, Brooks DJ & Edison P (2018) Microglial activation correlates in vivo with both tau and amyloid in Alzheimer's disease. *Brain* **141**, 2740–2754.

152 Parbo P, Ismail R, Hansen K V., Amidi A, Mårup FH, Gottrup H, Brændgaard H, Eriksson BO, Eskildsen SF, Lund TE, Tietze A, Edison P, Pavese N, Stokholm MG, Borghammer P, Hinz R, Aanerud J & Brooks DJ (2017) Brain inflammation accompanies amyloid in the majority of mild cognitive impairment cases due to Alzheimer's disease. *Brain* **140**, 2002–2011.

153 Serrano-Pozo A, Frosch MP, Masliah E & Hyman BT (2011) Neuropathological Alterations in

Alzheimer Disease. *Cold Spring Harb Perspect Med* **1**, a006189.

154 Bejanin A, Schonhaut DR, La Joie R, Kramer JH, Baker SL, Sosa N, Ayakta N, Cantwell A, Janabi M, Lauriola M, O'Neil JP, Gorno-Tempini ML, Miller ZA, Rosen HJ, Miller BL, Jagust WJ & Rabinovici GD (2017) Tau pathology and neurodegeneration contribute to cognitive impairment in Alzheimer's disease. *Brain* **140**, 3286–3300.

155 Ossenkoppele R, Schonhaut DR, Schöll M, Lockhart SN, Ayakta N, Baker SL, O'Neil JP, Janabi M, Lazaris A, Cantwell A, Vogel J, Santos M, Miller ZA, Bettcher BM, Vossel KA, Kramer JH, Gorno-Tempini ML, Miller BL, Jagust WJ & Rabinovici GD (2016) Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain* **139**, 1551–1567.

156 Maphis N, Xu G, Kokiko-Cochran ON, Jiang S, Cardona A, Ransohoff RM, Lamb BT & Bhaskar K (2015) Reactive microglia drive tau pathology and contribute to the spreading of pathological tau in the brain. *Brain* **138**, 1738–1755.

157 Hopp SC, Lin Y, Oakley D, Roe AD, Devos SL, Hanlon D & Hyman BT (2018) The role of microglia in processing and spreading of bioactive tau seeds in Alzheimer's disease. *J Neuroinflammation* **15**, 269.

158 Asai H, Ikezu S, Tsunoda S, Medalla M, Luebke J, Haydar T, Wolozin B, Butovsky O, Kügler S & Ikezu T (2015) Depletion of microglia and inhibition of exosome synthesis halt tau propagation. *Nat Neurosci* **18**, 1584–93.

159 Ising C, Venegas C, Zhang S, Scheiblich H, Schmidt S V, Vieira-Saecker A, Schwartz S, Albasset S, McManus RM, Tejera D, Griep A, Santarelli F, Brosseron F, Opitz S, Stunden J, Merten M, Kayed R, Golenbock DT, Blum D, Latz E, Buée L & Heneka MT (2019) NLRP3 inflammasome activation drives tau pathology. *Nature* **575**, 669–673.

160 Yang W, Tao Y, Wu Y, Zhao X, Ye W, Zhao D, Fu L, Tian C, Yang J, He F & Tang L (2019) Neutrophils promote the development of reparative macrophages mediated by ROS to orchestrate liver repair. *Nat Commun* **10**, 1076.

161 Nathan C & Ding A (2010) Nonresolving inflammation. *Cell* **140**, 871–82.

162 Serhan CN, Chiang N & Van Dyke TE (2008) Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* **8**, 349–61.

163 Villarejo-Galende A, González-Sánchez M, Blanco-Palmero VA, Velasco SL & Benito-León J (2020) Non-steroidal anti-inflammatory drugs as candidates for the prevention or treatment of Alzheimer's disease: Do they still have a role? *Curr Alzheimer Res* **17**, Online ahead of print.

164 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H & Cao B (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet (London, England)* **395**, 1054.

165 Fullerton JN & Gilroy DW (2016) Resolution of inflammation: a new therapeutic frontier. *Nat Rev Drug Discov* **15**, 551–567.

166 Sugimoto MA, Vago JP, Perretti M & Teixeira MM (2019) Mediators of the Resolution of the Inflammatory Response. *Trends Immunol* **40**, 212–227.

167 Wallace JL, Ianaro A, Flannigan KL & Cirino G (2015) Gaseous mediators in resolution of inflammation. *Semin Immunol* **27**, 227–233.

168 Serhan CN, Chiang N, Dalli J & Levy BD (2014) Lipid Mediators in the Resolution of Inflammation. *Cold Spring Harb Perspect Biol*, 1–21.

169 Guo Z, Hu Q, Xu L, Guo Z-N, Ou Y, He Y, Yin C, Sun X, Tang J & Zhang JH (2016) Lipoxin A4 Reduces Inflammation Through Formyl Peptide Receptor 2/p38 MAPK Signaling Pathway in Subarachnoid Hemorrhage Rats. *Stroke* **47**, 490–7.

170 Perretti M & D'Acquisto F (2009) Annexin A1 and glucocorticoids as effectors of the resolution of inflammation. *Nat Rev Immunol* **9**, 62–70.

171 Souza DG, Fagundes CT, Amaral FA, Cisalpino D, Sousa LP, Vieira AT, Pinho V, Nicoli JR, Vieira LQ, Fierro IM & Teixeira MM (2007) The Required Role of Endogenously Produced Lipoxin A4 and Annexin-1 for the Production of IL-10 and Inflammatory Hyporesponsiveness in Mice. *J Immunol* **179**, 8533–8543.

172 Serhan CN (2005) Lipoxins and aspirin-triggered 15-epi-lipoxins are the first lipid mediators of endogenous anti-inflammation and resolution. *Prostaglandins Leukot Essent Fat Acids* **73**, 141–162.

173 Haworth O, Cernadas M, Yang R, Serhan CN & Levy BD (2008) Resolvin E1 regulates interleukin 23, interferon-gamma and lipoxin A4 to promote the resolution of allergic airway inflammation. *Nat Immunol* **9**, 873–9.

174 Duvall MG & Levy BD (2016) DHA- and EPA-derived resolvins, protectins, and maresins in airway inflammation. *Eur J Pharmacol* **785**, 144–155.

175 Zhu M, Wang X, Hjorth E, Colas RA, Schroeder L, Granholm A-C, Serhan CN & Schultzberg M (2016) Pro-Resolving Lipid Mediators Improve Neuronal Survival and Increase Aβ42 Phagocytosis. *Mol Neurobiol* **53**, 2733–49.

176 Wang X, Zhu M, Hjorth E, Cortés-Toro V, Eyjolfsdottir H, Graff C, Nennesmo I, Palmblad J, Eriksdotter M, Sambamurti K, Fitzgerald JM, Serhan CN, Granholm A-CC & Schultzberg M (2015) Resolution of inflammation is altered in Alzheimer's disease. *Alzheimer's Dement* **11**, 40-50.e2.

177 Emre C, Hjorth E, Bharani K, Carroll S, Granholm A-C & Schultzberg M (2020) Receptors for pro-resolving mediators are increased in Alzheimer's disease brain. *Brain Pathol* **30**, 614–640.

178 Heras-Sandoval D, Pedraza-Chaverri J & Pérez-Rojas JM (2016) Role of docosahexaenoic acid in the modulation of glial cells in Alzheimer's disease. *J Neuroinflammation* **13**, 61.

179 Yin P, Wang X, Wang S, Wei Y, Feng J & Zhu M (2019) Maresin 1 Improves Cognitive Decline and Ameliorates Inflammation in a Mouse Model of Alzheimer's Disease. *Front Cell Neurosci* **13**, 466.

180 Dunn HC, Ager RR, Baglietto-Vargas D, Cheng D, Kitazawa M, Cribbs DH & Medeiros R (2015) Restoration of lipoxin A4 signaling reduces Alzheimer's disease-like pathology in the 3xTg-AD mouse model. *J Alzheimers Dis* **43**, 893–903.

181 Medeiros R, Kitazawa M, Passos GF, Baglietto-Vargas D, Cheng D, Cribbs DH & LaFerla FM (2013) Aspirin-triggered lipoxin A4 stimulates alternative activation of microglia and reduces Alzheimer

disease-like pathology in mice. *Am J Pathol* **182**, 1780–9.

182 Fukuda H, Muromoto R, Takakura Y, Ishimura K, Kanada R, Fushihara D, Tanabe M, Matsubara K, Hirao T, Hirashima K, Abe H, Arisawa M, Matsuda T & Shuto S (2016) Design and Synthesis of Cyclopropane Congeners of Resolvin E2, an Endogenous Proresolving Lipid Mediator, as Its Stable Equivalents. *Org Lett* **18**, 6224–6227.

183 Perretti M & Godson C (2020) Formyl peptide receptor type 2 agonists to kick-start resolution pharmacology. *Br J Pharmacol* **177**, 4595–4600.

184 Le Y, Gong W, Tiffany HL, Tumanov A, Nedospasov S, Shen W, Dunlop NM, Gao JL, Murphy PM, Oppenheim JJ & Wang JM (2001) Amyloid (beta)42 activates a G-protein-coupled chemoattractant receptor, FPR-like-1. *J Neurosci* **21**, RC123.

185 Cui YH, Le Y, Zhang X, Gong W, Abe K, Sun R, Van Damme J, Proost P & Wang JM (2002) Up-regulation of FPR2, a chemotactic receptor for amyloid β 1-42 (Aβ42), in murine microglial cells by TNFα1. *Neurobiol Dis* **10**, 366–77.

186 Cristante E, McArthur S, Mauro C, Maggioli E, Romero IAIAA, Wylezinska-Arridge M, Couraud POPOO, Lopez-Tremoleda J, Christian HCHCC, Weksler BB, Malaspina A & Solito E (2013) Identification of an essential endogenous regulator of blood-brain barrier integrity, and its pathological and therapeutic implications. *Proc Natl Acad Sci U S A* **110**, 832–841.

187 Park JC, Baik SH, Han SH, Cho HJ, Choi H, Kim HJ, Choi H, Lee W, Kim DK & Mook-Jung I (2017) Annexin A1 restores Aβ1-42-induced blood–brain barrier disruption through the inhibition of RhoA-ROCK signaling pathway. *Aging Cell* **16**, 149–161.

188 Ho CF-Y, Ismail NB, Koh JK-Z, Gunaseelan S, Low Y-H, Ng Y-K, Chua JJ-E & Ong W-Y (2018) Localisation of Formyl-Peptide Receptor 2 in the Rat Central Nervous System and Its Role in Axonal and Dendritic Outgrowth. *Neurochem Res* **43**, 1587–1598.

189 Wang G, Zhang L, Chen X, Xue X, Guo Q, Liu M & Zhao J (2016) Formylpeptide Receptors Promote the Migration and Differentiation of Rat Neural Stem Cells. *Sci Rep* **6**, 25946.

190 Ries M, Loiola R, Shah UNN, Gentleman SMM, Solito E & Sastre M (2016) The anti-inflammatory

Annexin A1 induces the clearance and degradation of the amyloid-β peptide. *J Neuroinflammation* **13**, 234.

191 Bisicchia E, Sasso V, Catanzaro G, Leuti A, Besharat ZM, Chiacchiarini M, Molinari M, Ferretti E, Viscomi MT & Chiurchiù V (2018) Resolvin D1 Halts Remote Neuroinflammation and Improves Functional Recovery after Focal Brain Damage Via ALX/FPR2 Receptor-Regulated MicroRNAs. *Mol Neurobiol* **55**, 6894–6905.

192 Ren Y-ZZ, Zhang B-ZZ, Zhao X-JJ & Zhang Z-YY (2020) Resolvin D1 ameliorates cognitive impairment following traumatic brain injury via protecting astrocytic mitochondria. *J Neurochem* **154**, 530–546.

193 Liu GJ, Tao T, Wang H, Zhou Y, Gao X, Gao YY, Hang CH & Li W (2020) Functions of resolvin D1-ALX/FPR2 receptor interaction in the hemoglobin-induced microglial inflammatory response and neuronal injury. *J Neuroinflammation* **17**, 239.

194 Bao L, Gerard NP, Eddy RL, Shows TB & Gerard C (1992) Mapping of genes for the human C5a receptor (C5AR), human FMLP receptor (FPR), and two FMLP receptor homologue orphan receptors (FPRH1, FPRH2) to chromosome 19. *Genomics* **13**, 437–440.

195 McArthur S, Gobbetti T, Kusters DHM, Reutelingsperger CP, Flower RJ & Perretti M (2015) Definition of a Novel Pathway Centered on Lysophosphatidic Acid To Recruit Monocytes during the Resolution Phase of Tissue Inflammation. *J Immunol* **195**, 1500733.

196 Migeotte I, Communi D & Parmentier M (2006) Formyl peptide receptors: A promiscuous subfamily of G protein-coupled receptors controlling immune responses. *Cytokine Growth Factor Rev* **17**, 501–519.

197 Ye RD, Boulay F, Wang JM, Dahlgren C, Gerard C, Parmentier M, Serhan CN & Murphy PM (2009) International Union of Basic and Clinical Pharmacology. LXXIII. Nomenclature for the Formyl Peptide Receptor (FPR) Family. *Pharmacol Rev* **61**, 119–161.

198 Chen T, Xiong M, Zong X, Ge Y, Zhang H, Wang M, Won Han G, Yi C, Ma L, Ye RD, Xu Y, Zhao Q & Wu B (2020) Structural basis of ligand binding modes at the human formyl peptide receptor 2.

Nat Commun **11**, 1208.

199 Zhuang Y, Liu H, Edward Zhou X, Kumar Verma R, de Waal PW, Jang W, Xu T-HH, Wang L, Meng X, Zhao G, Kang Y, Melcher K, Fan H, Lambert NA, Eric Xu H & Zhang C (2020) Structure of formylpeptide receptor 2-Gi complex reveals insights into ligand recognition and signaling. *Nat Commun* **11**, 885.

200 Ge Y, Zhang S, Wang J, Xia F, Wan JB, Lu J & Ye RD (2020) Dual modulation of formyl peptide receptor 2 by aspirin-triggered lipoxin contributes to its anti-inflammatory activity. *FASEB J* **34**, 6920–6933.

201 Zhang S, Gong H, Ge Y & Ye RD (2020) Biased allosteric modulation of formyl peptide receptor 2 leads to distinct receptor conformational states for pro- and anti-inflammatory signaling. *Pharmacol Res* **161**, 105117.

202 Inoue A, Raimondi F, Kadji FMN, Singh G, Kishi T, Uwamizu A, Ono Y, Shinjo Y, Ishida S, Arang N, Kawakami K, Gutkind JS, Aoki J & Russell RB (2019) Illuminating G-Protein-Coupling Selectivity of GPCRs. *Cell* **177**, 1933-1947.e25.

203 Cooray SN, Gobbetti T, Montero-Melendez T, McArthur S, Thompson D, Clark AJL, Flower RJ & Perretti M (2013) Ligand-specific conformational change of the G-protein-coupled receptor ALX/FPR2 determines proresolving functional responses. *Proc Natl Acad Sci U S A* **110**, 18232–18237.

204 El Kebir D, József L & Filep JG (2008) Opposing regulation of neutrophil apoptosis through the formyl peptide receptor-like 1/lipoxin A 4 receptor: implications for resolution of inflammation . *J Leukoc Biol* **84**, 600–606.

205 Su SB, Gong W, Gao JL, Shen W, Murphy PM, Oppenheim JJ & Wang JM (1999) A seven-transmembrane, G protein-coupled receptor, FPRL1, mediates the chemotactic activity of serum amyloid A for human phagocytic cells. *J Exp Med* **189**, 395–402.

206 De Buck M, Berghmans N, Pörtner N, Vanbrabant L, Cockx M, Struyf S, Opdenakker G, Proost P, Van Damme J & Gouwy M (2015) Serum amyloid A1α induces paracrine IL-8/CXCL8 via TLR2

and directly synergizes with this chemokine via CXCR2 and formyl peptide receptor 2 to recruit neutrophils. *J Leukoc Biol* **98**, 1049–1060.

207 Abouelasrar Salama S, De Bondt M, De Buck M, Berghmans N, Proost P, Oliveira VLS, Amaral FA, Gouwy M, Van Damme J & Struyf S (2020) Serum Amyloid A1 (SAA1) Revisited: Restricted Leukocyte-Activating Properties of Homogeneous SAA1. *Front Immunol* **11**, 843.

208 De Yang B, Chen Q, Schmidt AP, Anderson GM, Wang JM, Wooters J, Oppenheim JJ, Chertov O, Yang D, Chen Q, Schmidt AP, Anderson GM, Wang JM, Wooters J, Oppenheim JJ, Chertov O, De Yang, Chen Q, Schmidt AP, Anderson GM, Wang JM, Wooters J, Oppenheim JJ & Chertov O (2000) LL-37, the neutrophil granule- and epithelial cell-derived cathelicidin, utilizes formyl peptide receptor-like 1 (FPRL1) as a receptor to chemoattract human peripheral blood neutrophils, monocytes, and T cells. *J Exp Med* **192**, 1069–1074.

209 Betten Å, Bylund J, Cristophe T, Boulay F, Romero A, Hellstrand K & Dahlgren C (2001) A proinflammatory peptide from Helicobacter pylori activates monocytes to induce lymphocyte dysfunction and apoptosis. *J Clin Invest* **108**, 1221–1228.

210 Wood MP, Cole AMALAM, Eade CR, Chen LM, Chai KX & Cole AMALAM (2014) The HIV-1 gp41 ectodomain is cleaved by matriptase to produce a chemotactic peptide that acts through FPR2. *Immunology* **142**, 474–483.

211 Migeotte I, Riboldi E, Franssen JD, Grégoire F, Loison C, Wittamer V, Detheux M, Robberecht P, Costagliola S, Vassart G, Sozzani S, Parmentier M & Communi D (2005) Identification and characterization of an endogenous chemotactic ligand specific for FPRL2. *J Exp Med* **201**, 83–93.

212 Dalli J, Montero-Melendez T, McArthur S & Perretti M (2012) Annexin A1 N-terminal derived peptide Ac2-26 exerts chemokinetic effects on human neutrophils. *Front Pharmacol* **3**, 28.

213 Peng X, Xu E, Liang W, Pei X, Chen D, Zheng D, Zhang YYY, Zheng C, Wang P, She S, Zhang YYY, Ma J, Mo X, Zhang YYY, Ma D & Wang Y (2016) Identification of FAM3D as a newendogenous chemotaxis agonist for the formyl peptide receptors. *J Cell Sci* **129**, 1831–1842.

214 Gobbetti T, Coldewey SMMSM, Chen J, McArthur S, le Faouder P, Cenac N, Flower RJRJJ,

Thiemermann C & Perretti M (2014) Nonredundant protective properties of FPR2/ALX in polymicrobial murine sepsis. *Proc Natl Acad Sci U S A* **111**, 18685–18690.

215 Birkl D, O'Leary MN, Quiros M, Azcutia V, Schaller M, Reed M, Nishio H, Keeney J, Neish AS, Lukacs NW, Parkos CA & Nusrat A (2019) Formyl peptide receptor 2 regulates monocyte recruitment to promote intestinal mucosal wound repair. *FASEB J* **33**, 13632–13643.

216 Kain V, Jadapalli JK, Tourki B & Halade G V. (2019) Inhibition of FPR2 impaired leukocytes recruitment and elicited non-resolving inflammation in acute heart failure. *Pharmacol Res* **146**, 104295.

217 Chen K, Le Y, Liu Y, Gong W, Ying G, Huang J, Yoshimura T, Tessarollo L & Wang JM (2010) Cutting Edge: A Critical Role for the G Protein-Coupled Receptor mFPR2 in Airway Inflammation and Immune Responses. *J Immunol* **184**, 3331–3335.

218 Henson PM (2017) Cell removal: Efferocytosis. *Annu Rev Cell Dev Biol* **33**, 127–144.

219 Scannell M, Flanagan MB, deStefani A, Wynne KJ, Cagney G, Godson C & Maderna P (2007) Annexin-1 and peptide derivatives are released by apoptotic cells and stimulate phagocytosis of apoptotic neutrophils by macrophages. *J Immunol* **178**, 4595–605.

220 Maderna P, Yona S, Perretti M & Godson C (2005) Modulation of phagocytosis of apoptotic neutrophils by supernatant from dexamethasone-treated macrophages and annexin-derived peptide Ac(2-26). *J Immunol* **174**, 3727–33.

221 Kang JW & Lee SM (2016) Resolvin D1 protects the liver from ischemia/reperfusion injury by enhancing: M2 macrophage polarization and efferocytosis. *Biochim Biophys Acta - Mol Cell Biol Lipids* **1861**, 1025–1035.

222 Maderna P, Cottell DC, Toivonen T, Dufton N, Dalli J, Perretti M & Godson C (2010) FPR2/ALX receptor expression and internalization are critical for lipoxin A4 and annexin-derived peptide-stimulated phagocytosis. *FASEB J* **24**, 4240–9.

223 da Rocha GHO, Loiola RA, Pantaleão L do N, Reutelingsperger C, Solito E & Farsky SHP (2019) Control of expression and activity of peroxisome proliferated-activated receptor γ by Annexin

A1 on microglia during efferocytosis. *Cell Biochem Funct* **37**, 560–568.

224 McArthur S, Cristante E, Paterno M, Christian H, Roncaroli F, Gillies GEE & Solito E (2010) Annexin A1: a central player in the anti-inflammatory and neuroprotective role of microglia. *J Immunol* **185**, 6317–6328.

225 Loiola RARA, Wickstead ESES, Solito E & McArthur S (2019) Estrogen promotes pro-resolving microglial behaviour and phagocytic cell clearance through the actions of annexin A1. *Front Endocrinol (Lausanne)* **10**, 420.

226 Podleśny-Drabiniok A, Marcora E & Goate AM (2020) Microglial Phagocytosis: A Disease-Associated Process Emerging from Alzheimer's Disease Genetics. *Trends Neurosci* **43**, 965–979.

227 McArthur S, Juban G, Gobbetti T, Desgeorges T, Theret M, Gondin J, Toller-Kawahisa JE, Reutelingsperger CP, Chazaud B, Perretti M & Mounier R (2020) Annexin A1 drives macrophage skewing to accelerate muscle regeneration through AMPK activation. *J Clin Invest* **130**, 1156–1167.

228 O'Neill LAJ, Kishton RJ & Rathmell J (2016) A guide to immunometabolism for immunologists. *Nat Rev Immunol* **16**, 553–565.

229 Van den Bossche J, O'Neill LA & Menon D (2017) Macrophage Immunometabolism: Where Are We (Going)? *Trends Immunol* **38**, 395–406.

230 Lorton D, Schaller J, Lala A & De Nardin E (2000) Chemotactic-like receptors and Aβ peptide induced responses in Alzheimer's disease. *Neurobiol Aging* **21**, 463–473.

231 Cui Y-HH, Le Y, Gong W, Proost P, Van Damme J, Murphy WJ & Wang JM (2002) Bacterial lipopolysaccharide selectively up-regulates the function of the chemotactic peptide receptor formyl peptide receptor 2 in murine microglial cells. *J Immunol* **168**, 434–42.

232 Cui YH, Le Y, Zhang X, Gong W, Abe K, Sun R, Van Damme J, Proost P & Wang JM (2002) Up-regulation of FPR2, a chemotactic receptor for amyloid beta 1-42 (A beta 42), in murine microglial cells by TNF alpha. *Neurobiol Dis* **10**, 366–77.

233 Chen K, Iribarren P, Hu J, Chen J, Gong W, Cho EH, Lockett S, Dunlop NM & Ji MW (2006) Activation of toll-like receptor 2 on microglia promotes cell uptake of alzheimer disease-associated amyloid β peptide. *J Biol Chem* **281**, 3651–3659.

234 Chen K, Huang J, Liu Y, Gong W, Cui Y & Wang JM (2009) Synergy of TRIF-dependent TLR3 and MyD88-dependent TLR7 in up-regulating expression of mouse FPR2, a promiscuous G-protein-coupled receptor, in microglial cells. *J Neuroimmunol* **213**, 69–77.

235 Pourbadie HG, Sayyah M, Khoshkholgh-Sima B, Choopani S, Nategh M, Motamedi F & Shokrgozar MA (2018) Early minor stimulation of microglial TLR2 and TLR4 receptors attenuates Alzheimer's disease–related cognitive deficit in rats: behavioral, molecular, and electrophysiological evidence. *Neurobiol Aging* **70**, 203–216.

236 Zhu M, Wang X, Schultzberg M & Hjorth E (2014) Differential regulation of resolution in inflammation induced by amyloid-β42 and lipopolysaccharides in human microglia. *J Alzheimer's Dis* **43**, 1237–1250.

237 Slowik A, Merres J, Elfgen A, Jansen S, Mohr F, Wruck CJ, Pufe T & Brandenburg LO (2012) Involvement of formyl peptide receptors in receptor for advanced glycation end products (RAGE) - And amyloid beta 1-42-induced signal transduction in glial cells. *Mol Neurodegener* **7**, 1.

238 Li L, Wu Y, Wang Y, Wu J, Song L, Xian W, Yuan S, Pei L & Shang Y (2014) Resolvin D1 promotes the interleukin-4-induced alternative activation in BV-2 microglial cells. *J Neuroinflammation* **11**, 72.

239 Wickstead ES, Elliott BT, Biggs C, Getting SJ & McArthur S (2020) Activation of the pro-resolving receptors Fpr2/3 attenuate lipopolysaccharide-induced inflammatory microglial activation. *bioRxiv*, 2020.07.09.195198.

240 Kong Y, Ruan L, Qian L, Liu X & Le Y (2010) Norepinephrine promotes microglia to uptake and degrade amyloid beta peptide through upregulation of mouse formyl peptide receptor 2 and induction of insulin-degrading enzyme. *J Neurosci* **30**, 11848–57.

241 Pantaleão L, Rocha GHO, Reutelingsperger C, Tiago M, Maria-Engler SS, Solito E & Farsky SP (2018) Connections of annexin A1 and translocator protein-18 kDa on toll like receptor stimulated BV-2 cells. *Exp Cell Res* **367**, 282–290.

242 Tiffany HL, Lavigne MC, Cui YH, Wang JM, Leto TL, Gao JL & Murphy PM (2001) Amyloid-beta induces chemotaxis and oxidant stress by acting at formylpeptide receptor 2, a G protein-coupled receptor expressed in phagocytes and brain. *J Biol Chem* **276**, 23645–52.

243 Schröder N, Schaffrath A, Welter JA, Putzka T, Griep A, Ziegler P, Brandt E, Samer S, Heneka MT, Kaddatz H, Zhan J, Kipp E, Pufe T, Tauber SC, Kipp M & Brandenburg LO (2020) Inhibition of formyl peptide receptors improves the outcome in a mouse model of Alzheimer disease. *J Neuroinflammation* **17**.

244 Nawaz IM, Chiodelli P, Rezzola S, Paganini G, Corsini M, Lodola A, Di Ianni A, Mor M & Presta M (2018) N-tert-butyloxycarbonyl-Phe-Leu-Phe-Leu-Phe (BOC2) inhibits the angiogenic activity of heparin-binding growth factors. *Angiogenesis* **21**, 47–59.

245 Selkoe DJ & Hardy J (2016) The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med* **8**, 595–608.

246 Makin S (2018) The amyloid hypothesis on trial. *Nature* **559**, S4–S7.

247 Panza F, Lozupone M, Logroscino G & Imbimbo BP (2019) A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease. *Nat Rev Neurol* **15**, 73–88.

248 Jiang Y-T, Li H-Y, Cao X-P & Tan L (2018) Meta-analysis of the association between CD33 and Alzheimer's disease. *Ann Transl Med* **6**, 169.

249 Griciuc A, Serrano-Pozo A, Parrado AR, Lesinski AN, Asselin CN, Mullin K, Hooli B, Choi SH, Hyman BT & Tanzi RE (2013) Alzheimer's Disease Risk Gene CD33 Inhibits Microglial Uptake of Amyloid Beta. *Neuron* **78**, 631–643.

250 Jun G, Naj AC, Beecham GW, Wang L-S, Buros J, Gallins PJ, Buxbaum JD, Ertekin-Taner N, Fallin MD, Friedland R, Inzelberg R, Kramer P, Rogaeva E, George-Hyslop P St., Arnold SE, Baldwin CT, Barber R, Beach T, Bigio EH, Bird TD, Boxer A, Burke JR, Cairns N, Carroll SL, Chui HC, Clark DG,

Cotman CW, Cummings JL, DeCarli C, Diaz-Arrastia R, Dick M, Dickson DW, Ellis WG, Fallon KB, Farlow MR, Ferris S, Frosch MP, Galasko DR, Gearing M, Geschwind DH, Ghetti B, Gilman S, Giordani B, Glass J, Graff-Radford NR, Green RC, Growdon JH, Hamilton RL, Harrell LE, Head E, Honig LS, Hulette CM, Hyman BT, Jicha GA, Jin L-W, Johnson N, Karlawish J, Karydas A, Kaye JA, Kim R, Koo EH, Kowall NW, Lah JJ, Levey AI, Lieberman A, Lopez OL, Mack WJ, Markesbery W, Marson DC, Martiniuk F, Masliah E, McKee AC, Mesulam M, Miller JW, Miller BL, Miller CA, Parisi JE, Perl DP, Peskind E, Petersen RC, Poon W, Quinn JF, Raskind M, Reisberg B, Ringman JM, Roberson ED, Rosenberg RN, Sano M, Schneider JA, Schneider LS, Seeley W, Shelanski ML, Smith CD, Spina S, Stern RA, Tanzi RE, Trojanowski JQ, Troncoso JC, Deerlin VM Van, Vinters H V., Vonsattel JP, Weintraub S, Welsh-Bohmer KA, Woltjer RL, Younkin SG, Cantwell LB, Dombroski BA, Saykin AJ, Reiman EM, Bennett DA, Morris JC, Lunetta KL, Martin ER, Montine TJ, Goate AM, Blacker D, Tsuang DW, Beekly D, Cupples LA, Hakonarson H, Kukull W, Foroud TM, Haines J, Mayeux R, Farrer LA, Pericak-Vance MA & Schellenberg GD (2010) Meta-analysis Confirms CR1, CLU, and PICALM as Alzheimer Disease Risk Loci and Reveals Interactions With APOE Genotypes. *Arch Neurol* **67**, 1473.

251 Fairfax BP, Humburg P, Makino S, Naranbhai V, Wong D, Lau E, Jostins L, Plant K, Andrews R, McGee C & Knight JC (2014) Innate Immune Activity Conditions the Effect of Regulatory Variants upon Monocyte Gene Expression. *Science (80-)* **343**, 1246949.

252 Pinet V, Vergelli M, Martini R, Bakke O & Long EO (1995) Antigen presentation mediated by recycling of surface HLA-DR molecules. *Nature* **375**, 603–606.

253 Pedicone C, Fernandes S, Dungan OM, Dormann SM, Viernes DR, Adhikari AA, Choi LB, Jong EP De, Chisholm JD & Kerr WG (2020) Pan-SHIP1/2 inhibitors promote microglia effector functions essential for CNS homeostasis. *J Cell Sci* **133**, jcs238030.

254 Ando K, Brion J-P, Stygelbout V, Suain V, Authelet M, Dedecker R, Chanut A, Lacor P, Lavaur J, Sazdovitch V, Rogaeva E, Potier M-C & Duyckaerts C (2013) Clathrin adaptor CALM/PICALM is associated with neurofibrillary tangles and is cleaved in Alzheimer's brains. *Acta Neuropathol* **125**, 861–878.

255 Zhao Z, Sagare AP, Ma Q, Halliday MR, Kong P, Kisler K, Winkler EA, Ramanathan A, Kanekiyo T, Bu G, Owens NC, Rege S V, Si G, Ahuja A, Zhu D, Miller CA, Schneider JA, Maeda M, Maeda T, Sugawara T, Ichida JK & Zlokovic B V (2015) Central role for PICALM in amyloid-β blood-brain barrier transcytosis and clearance. *Nat Neurosci* **18**, 978–987.

256 Kim WS, Li H, Ruberu K, Chan S, Elliott DA, Low JK, Cheng D, Karl T & Garner B (2013) Deletion of Abca7 Increases Cerebral Amyloid-β Accumulation in the J20 Mouse Model of Alzheimer's Disease. *J Neurosci* **33**, 4387–4394.

257 Sakae N, Liu C-C, Shinohara M, Frisch-Daiello J, Ma L, Yamazaki Y, Tachibana M, Younkin L, Kurti A, Carrasquillo MM, Zou F, Sevlever D, Bisceglio G, Gan M, Fol R, Knight P, Wang M, Han X, Fryer JD, Fitzgerald ML, Ohyagi Y, Younkin SG, Bu G & Kanekiyo T (2016) ABCA7 Deficiency Accelerates Amyloid-β Generation and Alzheimer's Neuronal Pathology. *J Neurosci* **36**, 3848–3859.

258 Huang K, Marcora E, Pimenova AA, Narzo AF Di, Kapoor M, Jin SC, Harari O, Bertelsen S, Fairfax BP, Czajkowski J, Chouraki V, Grenier-Boley B, Bellenguez C, Deming Y, McKenzie A, Raj T, Renton AE, Budde J, Smith A, Fitzpatrick A, Bis JC, DeStefano A, Adams HH, Ikram MA, Lee S van der, Del-Aguila JL, Fernandez MV, Ibañez L, Project TIG of A, Initiative TADN, Sims R, Escott-Price V, Mayeux R, Haines JL, Farrer LA, Pericak-Vance MA, Lambert JC, Duijn C van, Launer L, Seshadri S, Williams J, Amouyel P, Schellenberg GD, Zhang B, Borecki I, Kauwe JSK, Cruchaga C, Hao K & Goate AM (2017) A common haplotype lowers PU.1 expression in myeloid cells and delaysonset of Alzheimer's disease. *Nat Neurosci* **20**, 1052.

259 Bell RD, Sagare AP, Friedman AE, Bedi GS, Holtzman DM, Deane R & Zlokovic B V (2006) Transport pathways for clearance of human Alzheimer's amyloid β-peptide and apolipoproteins E and J in the mouse central nervous system. *J Cereb Blood Flow Metab* **27**, 909–18.

260 Dourlen P, Fernandez-Gomez FJ, Dupont C, Grenier-Boley B, Bellenguez C, Obriot H, Caillierez R, Sottejeau Y, Chapuis J, Bretteville A, Abdelfettah F, Delay C, Malmanche N, Soininen H, Hiltunen M, Galas M-C, Amouyel P, Sergeant N, Buée L, Lambert J-C & Dermaut B (2017) Functional screening of Alzheimer risk loci identifies PTK2B as an in vivo modulator and early marker of

Tau pathology. *Mol Psychiatry* **22**, 874–883.

261 Nott A, Holtman IR, Coufal NG, Schlachetzki JCM, Yu M, Hu R, Han CZ, Pena M, Xiao J, Wu Y, Keulen Z, Pasillas MP, O'Connor C, Nickl CK, Schafer ST, Shen Z, Rissman RA, Brewer JB, Gosselin D, Gonda DD, Levy ML, Rosenfeld MG, McVicker G, Gage FH, Ren B & Glass CK (2019) Brain cell type-specific enhancer-promoter interactome maps and disease-risk association. *Science* **366**, 1134–1139.

262 Calafate S, Flavin W, Verstreken P & Moechars D (2016) Loss of Bin1 Promotes the Propagation of Tau Pathology. *Cell Rep* **17**, 931–940.

Table 1. Microglial genes with risk variants for sporadic AD. Functions listed correlate to potential roles in AD progression, and do not encompass all biological functions that these genes are associated with.

Gene	Function	Source
CD33	Immune regulator, can reduce phagocytosis and clearance of Aβ	[29,248,249]
CR1	Complement cascade regulator. Receptor for complement components C3b and C4b.	[20,250]
TREM2	Phagocytosis, cell differentiation and proliferation	[35,114]
ABI3	Innate immunity through interferon-associated signalling	[114,251]
MS4A gene cluster	Modulates cerebrospinal fluid levels of soluble TREM2	[19,28]
HLA-DRB1	Antigen presentation	[19,252]
INPP5D	Regulator of microglial proliferation and phagocytosis of both cellular debris and Aβ	[20,253]
PICALM	Accessory protein in endocytosis. Involved in APP processing, Aβ clearance and tau pathology	[250,254,255]
ABCA7	Phagocytosis and lipid metabolism; associated with APP processing and Aβ clearance	[19,256,257]
SPI1	Transcription factor and phagocytosis regulator	[258]
CLU	Extracellular chaperone linked to Aβ clearance	[250,259]
EPHA1	Endocytosis. Tau toxicity modulator	[29,260]
BIN1	Clathrin-mediated endocytosis and recycling. APP processing and tau pathology propagation.	[113,261,262]
MEF2C	Modulates microglial inflammatory responses	[96,112]
SORL1	Endocytosis receptor. Limits amyloidogenic processing of APP.	[19]

Figure Legend

Figure 1: Microglial phenotypes are diverse, wide ranging and modifiable. A) With nine transcriptionally unique microglial subsets identified in mice, it is important to emphasize the complexity of microglia, whereby aging, pathogen exposure and disease progression are all thought to modify microglial phenotype. Moreover, despite often being classified as 'pro-inflammatory' or 'anti-inflammatory', a more mixed phenotype is often the case, with cells displaying characteristic features of each immune state, or a combination of both. B) Transcriptomic and proteomic studies have identified key changes in microglial phenotype in AD, highlighting the diversity of microglial actions in the brain, and their potential for involvement in key disease-related processes. Intriguingly, pathways identified by transcriptomic and proteomic analyses do not always overlap, highlighting the scope for further investigation that still lies in this field.

Figure 1