ADVANCED BIOLOGY
www.advanced-bio.com

# The Role of Immunity in Alzheimer's Disease

*Róisín M. McManus*

**With the increase in the aging population, age-related conditions such as dementia and Alzheimer's disease will become ever more prevalent in society. As there is no cure for dementia and extremely limited therapeutic options, researchers are examining the mechanisms that contribute to the progression of cognitive decline in hopes of developing better therapies and even an effective, long-lasting treatment for this devastating condition. This review will provide an updated perspective on the role of immunity in triggering the changes that lead to the development of dementia. It will detail the latest findings on A$\beta$- and tau-induced microglial activation, including the role of the inflammasome. The contribution of the adaptive immune system, specifically T cells, will be discussed. Finally, whether the innate and adaptive immune system can be modulated to protect against dementia will be examined, along with an assessment of the prospective candidates for these that are currently in clinical trials.**

## 1. Introduction

A recent United Nations report has predicted that within the next 10 years the number of people over the age of 60 will reach 1.4 billion worldwide, and further grow to 2.1 billion in 2050,[1] more than doubling the number present today. This group is the fastest growing collection of individuals than any other age category, with projections that by 2050 34% of the people in Europe, 28% in Northern America and 25% of those in Asia will be 60 years and over.

However, this increase in life expectancy does not mean a similarly extended increase in years of good health. Instead this change goes hand-in-hand with an increase in age-related diseases as the elderly are spending more of their extended life span in ill-health with multiple co-morbidities including cognitive impairment, chronic illness and disability.[2]

Age is also the most common risk factor for dementia, where the prevalence of Alzheimer's disease (AD)-dementia sky-rockets from 3% of people aged 65–74, 17% in those aged 75–84 and then to 32% in those over 85 based on figures from the US.[3] The cost of providing healthcare to these individuals is also substantial, $277 billion was spent in the US in 2018 alone,[4] this figure already increased to $305 billion in 2020[5] and is expected to jump to $1.1 trillion by 2050.[4] Based on this, it has been suggested that reducing co-morbidities in the elderly and extending the period of healthy aging will have a significant impact on decreasing the number of individuals with such impairments in 2050, with a knock-on effect of reducing the cost of dementia care.

It is widely acknowledged that neuroinflammation is a critical step on the road to dementia. It is produced as a reaction to the ongoing protein deposition and cell loss observed in individuals with cognitive impairment and it has been argued that such inflammatory factors can in turn exacerbate ongoing cellular changes and hasten the progression to severe cognitive decline. This review will detail the role of the innate and adaptive immune system in the progression of AD. Specifically we will cover microglia mediated-neuroinflammation and the contribution of peripheral cells, namely T cells, on the progression to cognitive decline and the potential therapies that are under development to tackle these pathways will be discussed.

## 2. Alzheimer's Disease

The most common cause of cognitive impairment or dementia is AD. This accounts for 60–80% of dementia cases[5] and is characterized by the build-up of two different proteins, amyloid-$\beta$ (A$\beta$) and tau, along with cognitive changes. A$\beta$ is cleaved from amyloid precursor protein (APP) and these monomers aggregate into oligomers and fibrils, ultimately forming A$\beta$-containing plaques that are 200–650 $\mu m^2$ in size.[6] A$\beta$ can also undergo posttranslational modifications such as phosphorylation and nitration, which accelerate this process.[7,8] Tau is a protein found in neurons that is involved in microtubule stabilization, however in AD (and other Frontotemporal dementias – FTDs) tau becomes hyperphosphorylated and accumulates forming neurofibrillary tangles (NFTs). These deposits vary considerably in size from 10 to 500 $\mu m^2$.[9] The severity of pathological changes (particularly the NFTs) correlate with neuronal loss and the increasing cognitive decline in those with AD.[10–12]

The observed cognitive impairment in AD differs significantly across disease stages, and ranges from mild cognitive impairment (MCI), which can progress to moderate and then severe dementia. Indeed 68–80% of those who receive an initial diagnosis of MCI go on to develop AD within 6 years.[13–15] MCI is the first stage of cognitive decline and features initial

R. M. McManus
German Center for Neurodegenerative Diseases (DZNE)
53127 Bonn, Germany
E-mail: roisin.mcmanus@dzne.de

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adbi.202101166.



**DOI: 10.1002/adbi.202101166**

changes in memory or problems with thinking, although these individuals are able to maintain a large degree of independence and carry out routine daily living activities. With moderate dementia, there are clearer signs of cognitive decline such as trouble with routine tasks, verbal repetition, forgetting events and mood changes. In severe dementia, this progresses further to profound memory loss, personality changes including anxiety or aggression and sleep difficulties.

These cognitive changes are used to characterize the stage of dementia, along with memory tests such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA). The presence of AD biomarkers in the cerebral spinal fluid (CSF, the ratio of total-tau or phosphorylated-tau over A$\beta$), positron emission tomography (PET) imaging for A$\beta$ and tau along with a structural magnetic resonance imaging (MRI) or computed tomography (CT) that will highlight regions of atrophy together contribute to the clinical diagnosis of AD. These changes occur along with microglial activation, neuroinflammation and neuronal loss, particularly that of cholinergic neurons, which underlies the observed atrophy in brain regions such as the cortex and hippocampus thus contributing to the associated cognitive changes.

## 3. Current Therapeutic Strategies and Agents in Clinical Trials

To date, there are only four pharmacological compounds that can be prescribed for the treatment of AD, the NMDA receptor antagonist memantine, and three cholinesterase inhibitors: donepezil, galantamine and rivastigmine. These therapies were approved by the FDA and EMA in the period between 1996 and 2003, demonstrating the lack of new compounds on the market. Critically, these treatments can at most delay the progression of symptoms for 6 months or so, they do not affect the underlying AD pathology.

With 126 agents currently in clinical trials,[16] considerable efforts are being made to identify new treatments for AD. Those focused on reducing the pathology directly have ranged from vaccination strategies against A$\beta$[17] to injecting A$\beta$-targeted antibodies, and until recently were largely without success. Recently, the FDA have granted accelerated approval to the monoclonal antibody Aducanumab (Aduhelm™). This is an approval program reserved for serious conditions but an additional study is needed to confirm clinical benefit, known as a phase 4 confirmatory trial. The approval of Aducanumab has sparked many discussions and debates as the phase 3 trial of Aducanumab was terminated in early 2019, before the analysis of a larger data set showed that those on the highest dose of Aducanumab (10 mg/kg) had slowed cognitive decline. Other A$\beta$-targeted therapies currently in clinical trials include Donanemab[18] and Lecanemab[19] which bind a form of aggregated A$\beta$ and soluble A$\beta$ protofibrils respectively. In addition, Gantenerumab and Solanezumab are anti-fibrillar and anti-soluble A$\beta$ antibodies respectively that have been tested in patients and were very successful in reducing A$\beta$ load in a recent study, although they did not slow cognitive decline.[20] Scientists are also focused on tau-targeted therapies such as TRx0237 (LMTX™), which inhibits tau protein aggregation and is in phase 3 clinical trials. Similar to the early studies with A$\beta$, a number of vaccination strategies against tau or administration of tau-specific antibodies are also under investigation[21] with results soon expected for the phase 2 trial with Semorinemab, an anti-tau antibody.

Another approach for therapeutic action to prevent the progression of AD is to target inflammation within the brain directly, thus increased focus on the immune mechanisms that lead to the progression of dementia are being carried out by scientists globally.

## 4. Innate Immune System and AD

Much of what we understand about the innate immune system, has come initially from studies on macrophages. These are myeloid cells (like microglia) and form part of the first line of defence against infection by microorganisms such as bacteria, viruses and fungi. Cells of the innate immune system have a repertoire of germ-line encoded pattern-recognition receptors (PRRs) that recognise the conserved molecular patterns on invading organisms known as pattern-associated molecular patterns (PAMPs). In addition, the PRRs sense danger-associated molecular patterns (DAMPs), that are released during incidences of sterile inflammation such as mechanical trauma or ischemia. PRRs are broadly divided into four categories, Toll-like receptors (TLR), Nucleotide-binding oligomerization domain-like receptors (NLR), C-type lectin receptors (CLR) and RIG-1 like receptors (RLR). They are strategically localized throughout the cell, ready to act should they encounter their specific PAMP or DAMP. A typical example is TLR4, which is expressed on the cell surface and recognizes lipopolysaccharide, that forms part of the bacterial cell wall. TLR3 on the other hand, is expressed intracellularly and recognizes double stranded RNA, common to viruses. Activation of these PRRs triggers a rapid signal transduction pathway, altering transcription to produce cytokines and chemokines and impacting cell function, such as by triggering migration and inflammatory, antimicrobial activity. Part of the innate immune response includes a "switching off" period where after an immune challenge, the cells release anti-inflammatory cytokines and are involved in tissue repair.

Microglia form the innate immune system in the brain, they express PRRs and are central to protecting the brain during infections that trigger encephalitis for example or head injury. Additionally, scientists have demonstrated a clear role for microglial mediated neuroinflammation in the progression of AD. Alois Alzheimer himself noted the first signs of microglial activation when he described AD in 1911 and many risk genes identified in genome studies are highly expressed in microglia such as TREM2 or CD33.[22] Importantly, the peptides found in the AD brain also trigger activation of the microglial innate immune system, but as the amount of these peptides continues to build instead of being removed from the environment of the microglia, this results in chronic microglial activation. A$\beta$ is recognised by a range of receptors on microglia including TLR2, TLR4, Receptors for Advanced Glycation Endpoints (RAGE), Fc Receptors (FcRs), Scavenger receptors (scavenger receptor type-A, scavenger receptor type-B1, CD36 and CD40) and TREM2.[23,24] These receptors facilitate the phagocytosis of

A$\beta$, where the phagosome containing the taken-up A$\beta$ material fuses intracellularly with the lysosome for subsequent degradation. Indeed absence of TLR4[25] or TLR2[26] increased AD-pathology with greater memory impairments in murine models of disease.[26] Similarly, TREM2 regulates A$\beta$-induced microglial activation[27] and absence of TREM2 enhances A$\beta$ deposition in murine models.[24] Additionally, TREM2 affects how microglia interact with the amyloid plaques as TREM2$^{-/-}$ mice have reduced numbers of microglia surrounding A$\beta$ deposits and the plaque morphology is significantly more diffuse and less compact.[28] Both human and murine microglia are also capable of taking up tau,[29] absence of TREM2 also enhances tau hyperphosphorylation and increases tau spreading in multiple murine models of disease.[30–32] However, the other receptors mediating tau phagocytosis are not well characterised.

## 5. Neuroinflammation in AD

On binding, PRR receptors can mediate phagocytosis but they also trigger downstream signalling and activation of transcription factors to produce inflammatory cytokines and chemokines that, initially at least, can help with the detection and removal of pathogens. A$\beta$ itself can trigger the microglial production and release of TNF$\alpha$, IL-1$\beta$ and IL-6 both in vitro and in vivo.[33,34] However, such pro-inflammatory cytokines enhance the activity of the $\beta$- and $\gamma$-secretases that cleave APP into A$\beta$ of different lengths (although typically 40 and 42 amino acids long), increasing the presence of A$\beta$ within the brain.[35,36] TNF$\alpha$ and IL-1$\beta$ also inhibit the ability of microglia to phagocytose A$\beta$,[37,38] which together means an increased production along with a reduction in the removal of A$\beta$, collectively facilitating the aggregation and deposition of A$\beta$ in AD. In a similar fashion, tau can induce microglial activation[39] and cytokine release such as IL-1$\beta$.[40,41] In turn, activated microglia enhance the spreading of tau, which is in part mediated via IL-1$\beta$,[41] thus continuing the propagation of tau-related pathology throughout the brain.

The vicious cycle continues whereby increasing levels of A$\beta$ and tau can cause not only physical disruption to neuronal processes but also impaired neuronal activity. A$\beta$[7,33] and tau[42] are capable of reducing neuronal long-term potentiation (LTP), a process that strengthens the synapses between neurons and is essential for memory formation. Tau is neurotoxic to neurons[43] and also contributes to A$\beta$-induced neuronal changes as Tau$^{-/-}$ neurons are protected from both the A$\beta$-triggered cell death[44] and reduction in LTP.[45] Additionally the neuroinflammatory environment within the AD brain adds to the neuronal decline where microglial-mediated release of pro-inflammatory cytokines including TNF$\alpha$ or IL-1$\beta$ also cause neuronal apoptosis.[46,47]

Based on these findings, targeting microglial-mediated inflammatory signalling could provide an attractive strategy to interrupt the cytokine-triggered changes in AD-pathology and resulting neuronal dysfunction. First looking to TNF$\alpha$, this is a classical cytokine where transcription can be initiated within minutes of TLR activation. Translation of TNF$\alpha$ occurs within some hours, and via the endoplasmic-reticulum (ER)-Golgi network it is trafficked and released at the cell surface, in the so-called "conventional" secretion pathway.[48,49] TNF$\alpha$-targeted therapies are already approved for patients with rheumatoid arthritis and psoriasis, and interestingly a recent retrospective case-study found that TNF$\alpha$-blocking agents significantly reduced the risk of AD development in these individuals.[50] A phase 2 clinical trial examined whether 24 weeks of Etanercept (which blocks TNF$\alpha$ signalling) was protective in patients with mild to moderate AD, although no significant changes to cognitive decline were observed.[51]

In comparison with TNF$\alpha$, the production of IL-1$\beta$ is an entirely different process that eluded scientists for years. This potent inflammatory cytokine requires two cellular events to trigger its transcription, translation and release, and importantly requires the assembly of a large multiprotein complex called an inflammasome to do so.

## 6. The NLRP3 Inflammasome

The inflammasome was first discovered by Jürg Tschopp and his lab in 2002,[52] and since this time, it has been implicated as a central player in many diseases ranging from gout,[53] atherosclerosis[54] and AD.[55] An inflammasome is formed by 3 main components, a sensor protein (often an NLR, such as NOD-, LRR- and pyrin domain-containing 3, NLRP3), an adaptor molecule known as apoptosis-associated speck-like protein containing a CARD (ASC) and pro-caspase-1. This is a tightly regulated process with multiple intricate steps before the assembly and activation of the full inflammasome protein complex.

There are a number of proteins that form the sensor of inflammasomes (including NLRP1, NLRC4 and AIM2),[56] and of these NLRP3 is the best studied and will be the focus of this review. Signalling through a TLR or cytokine receptor via the NF-$\kappa$B pathway induces an increase in *Nlrp3* transcription and subsequent translation although NLRP3 is initially maintained in an auto-inhibited state (**Figure 1**). A second signal is needed to release this autoinhibition and allow for oligomerization of NLRP3. Typical signals include lysosomal or mitochondrial disruption and agents that cause efflux of $K^+$, these trigger post-translational modifications on NLRP3 such as phosphorylation and deubiquitination[57] allowing for NLRP3 oligomerization. This in turn nucleates the formation of ASC into ASC-specks, that act as a platform to recruit pro-caspase-1 and facilitate the auto-catalysis of this protein to its cleaved and active form. Caspase-1 is a powerful enzyme with a number of substrates. Active caspase-1 in turn cleaves pro-IL-1$\beta$, pro-IL-18 and Gasdermin D (GSDMD), directly licensing their activation. The unleashed N-terminal domain of GSDMD has pore-forming activity, and assembles these pores at the cell membrane allowing the release of active IL-1$\beta$ and active IL-18 where they carry out inflammatory activity.[58,59] ASC specks can also leave the cell during this process where they can be taken up by neighbouring cells.[60] This propagates the inflammatory signalling, as the new cells now have an ASC speck molecular platform to activate caspase-1 and IL-1$\beta$ thereafter, without the need for the initial inflammasome activation and assembly.[60] However, GSDMD isn't a requirement for the release of IL-1$\beta$. The process of cleaving the negatively charged pro-piece from pro-IL-1$\beta$, facilitates relocation of the mature IL-1$\beta$ to the plasma membrane where it can be released even in the absence of

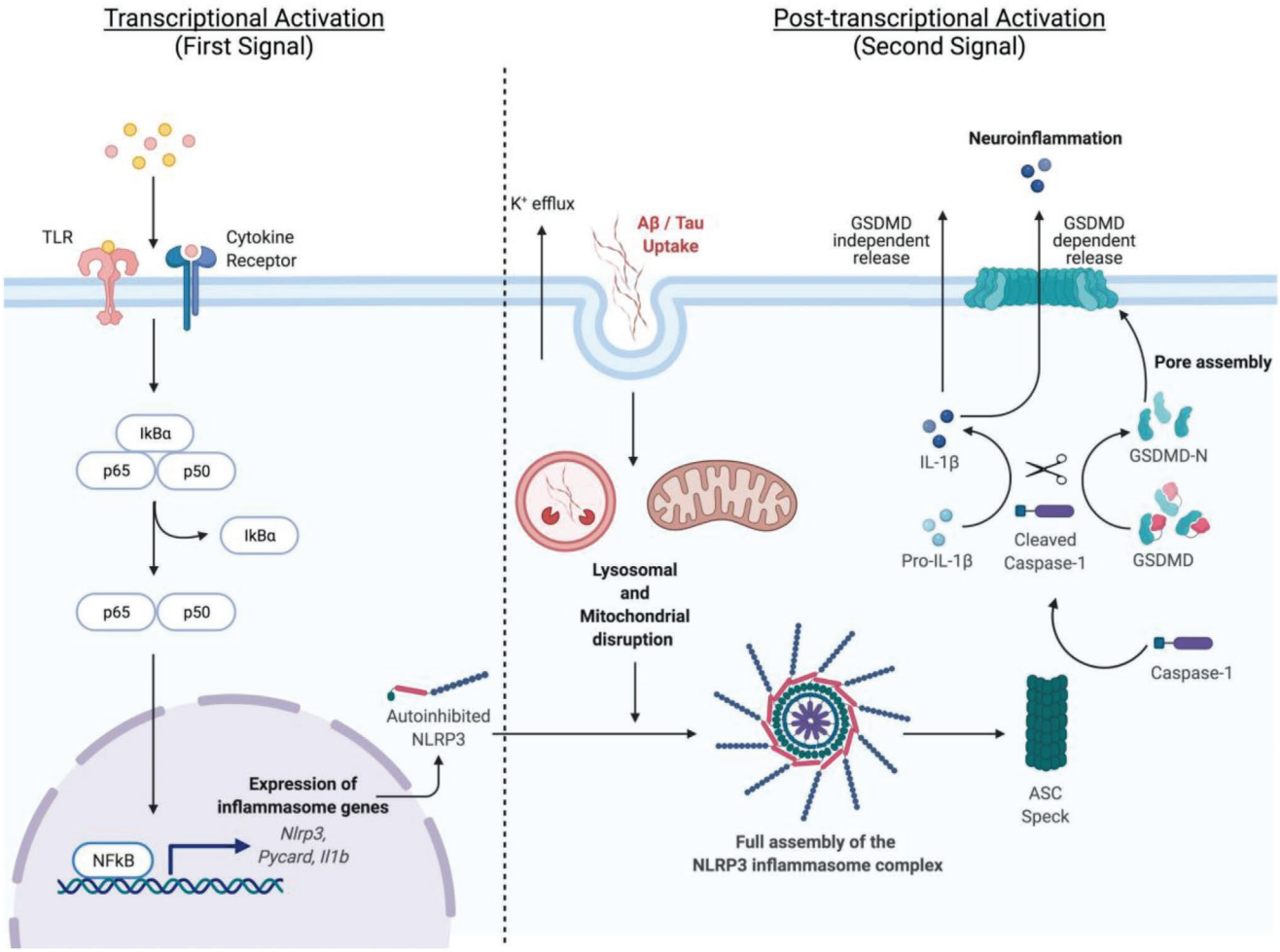


**Figure 1.** Activation of the NLRP3 inflammasome in Alzheimer's disease. A priming step is required for upregulation of NLRP3, although it is initially kept in an auto-inhibited state. A second signal (such as A$\beta$ or tau) is needed to release this autoinhibition and allow for oligomerization of NLRP3 via lysosomal or mitochondrial disruption. NLRP3 oligomerizes, nucleates the helical formation of ASC into ASC-specks, that provide a platform to recruit pro-caspase-1 and its subsequent activation. Caspase-1 cleaves pro-IL-1$\beta$, pro-IL-18 and GSDMD, allowing GSDMD to form pores at the cell membrane. IL-1$\beta$ and IL-18 are released by the cell where they can perpetuate inflammatory signalling. TLR, Toll like receptor; ASC, apoptosis-associated speck-like protein containing a CARD; GSDMD, Gasdermin D

GSDMD.[61] This unconventional secretion occurs over a longer period of time than via GSDMD pores, and may be a mechanism for IL-1$\beta$ release in non-pyroptotic cells and in chronic inflammatory diseases. Gasdermin E (GSDME) can also be activated downstream of the inflammasome, where it forms pores facilitating the movement of IL-1$\beta$ out of the cell.[62] Once the number of GSDMD or GSDME pores reach a certain threshold, they also mediate an inflammatory form of cell death known as pyroptosis, releasing the contents of the cell to the extracellular space. It should also be noted that NLRP3 can function as a transcription factor in T cells,[63] although whether such activity occurs in macrophages or microglia is unknown.

## 7. NLRP3 Activation and Progression to Dementia

The NLRP3 inflammasome has been found to have a critical role in the microglial innate immune response in AD. The NLRP3 inflammasome is activated in the brains of AD patients[55] and oligomeric and fibrillar A$\beta$ can trigger assembly of the NLRP3 inflammasome complex in vitro,[64–66] which is thought to occur via A$\beta$-induced cathepsin B release from lysosomes.[65] Importantly, absence of NLRP3 in the APP/PS1 transgenic model of AD protected mice from A$\beta$ deposition, reduced the levels of cleaved-caspase-1 and IL-1$\beta$ in the brain and critically, rescued memory impairments.[55] NLRP3 activation in microglia also releases the protein ASC in speck formation, which in turn rapidly enhanced the aggregation of A$\beta$, and hastened cognitive decline in these animal models of disease.[67] A$\beta$-ASC composites are highly inflammatory, and triggered cleaved-caspase-1, mature IL-1$\beta$ and pyroptosis in microglia, greater than that induced by A$\beta$ or ASC alone.[68] Together this demonstrates that an initial increase in A$\beta$ triggers a vicious circle, resulting in a never-ending cycle of inflammation and A$\beta$ deposition in the AD brain. In line with this, inflammasome activation has also

been detected in the brains of those with FTD, where cleaved-caspase-1 and mature IL-1$\beta$ were increased in the FTD post-mortem brain.[40] Tau also induces assembly of the NLRP3 inflammasome in vitro and in vivo, and strikingly, absence of NLRP3 or ASC protected Tau22 transgenic mice from developing tau pathology.[40] Similarly, overexpression of IL-1$\beta$ worsened tau pathology in the 3xTG-model of AD.[69]

## 8. Inhibition of NLRP3 as a Strategy for Protection in AD

Efforts to target NLRP3 and IL-1$\beta$ signalling have been examined in both A$\beta$ and tau models of dementia. CRID3 is a NLRP3-specific inhibitor and it was successful at preventing A$\beta$ or A$\beta$-ASC induced IL-1$\beta$ release in vitro, and 3 months treatment in APP/PS1 mice rescued cognitive changes and A$\beta$ deposition in vivo.[37,68] In line with this, caspase-1 inhibition using VX-765 significantly reversed memory impairment in the J20 murine model of AD.[70] CRID3 was also successful at reducing the tau-triggered secretion of IL-1$\beta$ by microglia in vitro[40] and intracerebral administration of CRID3 attenuated the tau-induced microglial activation and resulting tau spreading in vivo.[71] Administration of an IL-1R blocking antibody also produced similar results in 3xTg-AD mice, where treatment enhanced microglial phagocytosis and rescued both the A$\beta$ and tau pathology in the murine brains.[72]

A number of pharmaceutical companies are looking to the NLRP3 inflammasome as a therapeutic strategy for many diseases, including those of the brain. Novartis recently acquired IFM Tre, who have three NLRP3-targeting candidates, including one that is brain-penetrant. Novartis are currently recruiting patients for a phase 2 trial with one of these compounds, DFV890, in participants with Familial Cold Auto-inflammatory Syndrome (FCAS), which is one of the Cryopyrin-associated periodic syndromes (CAPS) and caused by mutations in NLRP3. Interestingly, they have recently completed a phase 2 trial with DFV890 in COVID-19 patients and the results are pending.

Roche's Genentech bought Jecure Therapeutics in 2018, with its range of NLRP3 inhibitors, and followed this in 2020 when Roche purchased Inflazome, which has two NLRP3 inhibitors that are in the clinic. Of these, Inzomelid is a brain-penetrant compound, and therefore has potential to treat neuroinflammatory and neurodegenerative conditions such as AD, whereas Somalix is peripherally restrictive. Inzomelid has completed phase 1 clinical trials for patients with CAPS, although the results have not been published yet.

Olatec Therapeutics also have a NLRP3 compound known as Dapansutrile (OLT1177) that is undergoing clinical trials for COVID-19 (ongoing), osteoarthritis of the knee (phase 2 completed) and melanoma (planned). In addition, NodThera have NT-0167, which they are advancing to clinical trials. Together the results of these studies are being eagerly awaited by the scientific and patient communities. As the NLRP3 inflammasome is central to many conditions, including AD where there are so few therapeutic options, these findings will be of great interest to patients and caregivers alike.

## 9. Immunometabolism in AD

In addition to the role of A$\beta$ in triggering inflammasome activation and cytokine release, it has also been linked with altering microglial metabolic activity. To date, few papers have even examined microglial metabolism[73] however, of these it has been shown that microglia can use glucose, amino acids such as glutamine, and fatty acid oxidation to fuel their cellular activities.[74] In imaging studies involving AD patients, it was found that the microglia are significantly activated, which correlated with regional reductions in metabolic activity, specifically the utilisation of glucose as determined by PET.[75] In vitro studies by Baik and colleagues have found that A$\beta$ reduces oxidative phosphorylation (oxphos) in primary microglia with a corresponding switch to glycolysis.[76] Similarly, inflammasome activation with LPS priming and A$\beta$ triggers a switch to glycolysis with a simultaneous decrease in oxphos in murine macrophages in vitro.[77] In AD models, microglia from aged APP/PS1 mice also have enhanced glycolysis, in comparison with their wildtype counterparts, with an increase in glycolytic enzymes.[78,79] Indeed, it was recently found that the female APP/PS1 murine microglia had greater glycolytic activity than the male APP/PS1 cells, which corresponded with enhanced plaque deposition in the female APP/PS1 mice.[80] The microglial switch to glycolysis and away from oxphos can further perpetuate inflammatory signaling as glycolysis can directly activate the mTOR pathway, which enhances the microglial production of IL-1$\beta$ and TNF$\alpha$. Indeed, blocking glycolysis or mTOR significantly attenuated the A$\beta$-induced release of both IL-1$\beta$ and TNF$\alpha$.[76]

## 10. Disruption to the Neurovascular Unit in AD

The increase in inflammatory cytokines and A$\beta$ deposition also induces changes to the neurovascular unit (NVU) and the blood-brain barrier (BBB).[81,82] The NVU is made up of neurons, astrocytes, pericytes and endothelial cells of the brain vasculature. To protect the brain, the endothelial cells have specialised tight junction forming proteins; occludin, claudin-3, claudin-5 and junctional adhesion molecules that form a zipper-like structure between the cells. Together with pericytes and astrocytic end feet of the glia limitans, they make up the BBB and tightly regulate the movement of molecules and cells into the brain.[82] However, the A$\beta$-associated blood vessels of patients have a significant reduction in claudin-5 and occludin,[83] and higher amounts of tau correlate with lower levels claudin-5 and occludin in AD brains.[84] Additionally, those with AD have endothelial cells that are smaller and thinner than age-matched, healthy controls.[85] A$\beta$-deposition along the vasculature is also associated with a reduction in both the number and coverage of pericytes,[86] with a retraction of astrocytic end feet that normally support the endothelial cells and the BBB.[87,88] Animal models have shown that loss of pericytes in turn increases A$\beta$ and tau pathology leading to early neuronal loss and cognitive decline.[89] Together this deterioration in the NVU and BBB integrity facilitates movement of peripheral proteins and cells into the brain. The plasma proteins fibrinogen and thrombin, and IgG have been found in the AD post-mortem brain tissue,

and interestingly in close apposition with activated microglia and A$\beta$ deposits.[90–93] Production of inflammatory cytokines including IL-1$\beta$ and TNF$\alpha$ can reduce the levels of BBB tight junction proteins,[94,95] while affecting the integrity of the endothelial barrier.[96] IL-1$\beta$ and TNF$\alpha$ also induce the release of chemokines such as CXCL10, CCL2, CCL5 from pericytes at the BBB,[96,97] which together with the structural alterations to the BBB and NVU, can both attract peripheral immune cells and ease their entry to the CNS.

## 11. The Adaptive Immune System: T Cells in Health and Healthy Aging

When one considers the brain, it is easy to regard this area as separate from the rest of the body with minimal interaction between the two, however a number of other highly specialized mechanisms are in place to monitor the brain for infection and insult. This occurs in addition to the contribution of the innate immune system (i.e., microglia) as described above. These mechanisms involve activation of the adaptive immune system, which provides antigen-specific responses that are connected to the particular pathogen. This is a finely tuned immune response, developed to handle challenges that are not resolved by the broadly activated innate immune system. The adaptive immune system is largely made up of T and B cells, and this review will focus on the contribution of T cells. During an infectious challenge, T cells specific for the particular antigen expand in numbers and provide much needed support to rid the body of the bacteria or virus in terms of cytokine production or even directly killing infected host cells. This is followed by a period of cellular contraction although a subset of memory T cells remain, which will rapidly respond should they encounter their specific antigen again.

To generate antigen-experienced T cells, naïve T cells in a lymphoid organ must first be primed by an antigen-presenting cell (typically a dendritic cell -DC) that presents the specific antigen via a major histocompatibility (MHC) complex to a T cell that recognizes the peptide sequence on its T cell receptor (TCR) (**Figure 2**). The T cell becomes activated, leaves the lymph node and will be guided to the site of infection or immune challenge based on chemokine signalling, where it subsequently can carry out its effector activity.

There are a number of mechanisms of antigen drainage from the brain to highlight the presence of any foreign antigen to the adaptive immune system and thus facilitate the priming of T cells in the draining lymph nodes for this organ, which include the cervical lymph nodes. In humans, solutes and antigen

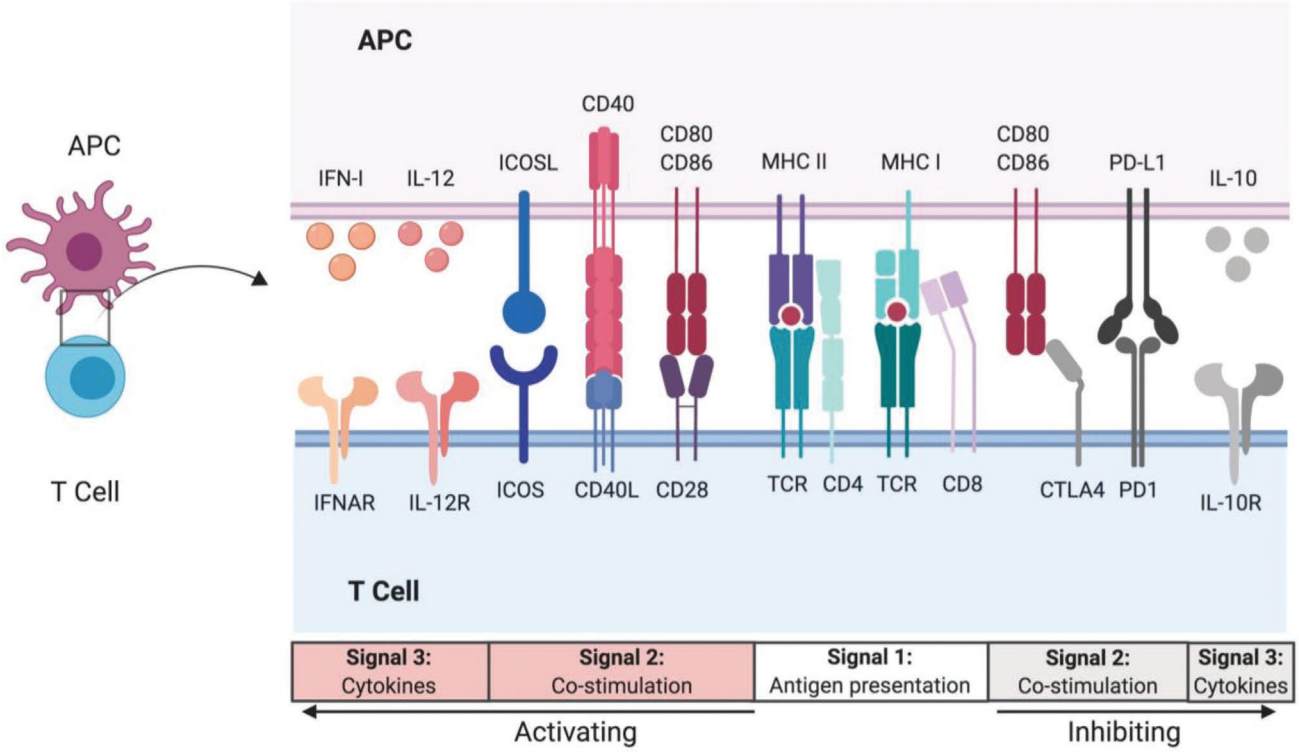


**Figure 2.** T cell - antigen presenting cell interaction. Activation of a naïve T cell requires three signals. 1) The TCR: MHC interaction; professional APCs phagocytose pathogens and load a peptide from this into the groove of an MHC complex. If the TCR recognizes the peptide and MHC complex it becomes activated, and the binding of the co-receptor CD4/8 to the MHC class II/I respectively supports this process. 2) Activation of the TCR and the co-stimulatory receptor CD28 together induce production of IL-2 which functions in an autocrine manner on the T cell triggering differentiation. Additional signalling occurs; CD40 binding CD40L can signal bi-directionally promoting activation. 3) The APC also produces cytokines (such as IL-12) in response to the pathogen, which influences the T cell polarisation. T cell activation is also modulated by co-inhibitory receptors, e.g., programmed cell death (PD)-1, which binds programmed death-ligand 1 (PD-L1), or cytokine signalling (such as IL-10). PRR, pattern recognition receptor; PAMP, pathogen-associated molecular pattern; DAMP, danger-associated molecular pattern.

present in the interstitial fluid (ISF) can drain out of the brain along the basement membrane of capillaries, to arteries that continue to the carotid artery at the base of the skull and then to the cervical lymph nodes.[98] Unlike in peripheral organs, it is believed that cells are unable to drain from the brain using this pathway.[99] In humans much of the CSF drains to the venous blood, through regions such as the arachnoid villi.[98,100] These structures are larger in humans than in rodents, where instead up to 50% of rodent CSF drains to the cervical lymph node via the subarachnoid space to the cribiform plate, on to the nasal submucosa and thereafter to the lymph node.[98] For a long time, this was believed to be the principal method of antigen drainage from the brain, however recent findings have uncovered a new mechanism of lymphatic drainage where lymphatic vessels were found to line the dural sinus, and are directly connected to the deep cervical lymph nodes.[101]

Tissue resident memory T cells ($CD4^+$ and $CD8^+$) have been found in the post mortem brain of adults, whose presence is believed to provide protection against neurotropic viruses as they had high levels of checkpoint inhibitors and thus were under tight control from mediating inflammation.[102] Approximately 150–170000 cells are found in the CSF of healthy individuals without neurological disease.[103,104] The majority of these are T cells with approximately 70% $CD4^+$ and 30% $CD8^+$.[105] Many of the T cells have a central memory phenotype ($CD46RA^-CD27^+$ meaning that they are antigen experienced), while some granulocytes and macrophages are also present.[104] This is an active process where the cells in the CSF are replaced about two times per day and re-enter the bloodstream from the CSF.[103]

## 12. T Cells in AD

T cells were first identified in the AD brain over 30 years ago,[106] and this finding has been replicated many times since.[107–112] It has been demonstrated that the number of these cells was increased in the hippocampal parenchyma,[113–116] and correlated with tau pathology.[112,117] Animal models of AD have produced similar results, where T cell infiltration was significantly increased in APP/PS1 mice[118–120] and in Tau22 transgenic mice.[121] These cells were found clustered in areas associated with AD including the hippocampus and around A$\beta$-deposits.[122] T cells have been directly implicated in mediating AD-related changes as Laurent and colleagues showed that T cell depletion rescued memory impairments in the Tau22 mice, which was associated with a reduction in neuroinflammation but not with a change to tau load.[121] Similar results were found in the APP/PS1 mouse model, absence of T cells (by crossing with $RAG2^{-/-}$ mice) reduced plaque load,[123] conversely transfer of T cells enhanced plaque load and worsened memory impairment in APP/PS1 mice.[124]

A number of research groups have demonstrated that T cells from AD patients have increased reactivity to A$\beta$,[125–127] which may partly explain this increased T cell homing to the AD brain. In addition, the T cells from AD patients have increased expression of CCL3, and the chemokine receptors CXCR2, CCR2, CCR4, CCR5 and CCR6,[128–132] many of which bind chemokines that are, coincidentally, also increased in the AD brain such as CCL2, CCL3, CCL4 and CCL5.[133] Altogether this facilitates adhesion to the BBB and with the increase in BBB permeability in AD these modifications can promote the entry of T cells across the endothelial layer of the BBB to the perivascular space, where antigen recognition by the T cell is necessary to breach the glial limitans and enter the brain parenchyma.[82] Importantly the proteases released by the T cell after antigen recognition can facilitate the movement of other activated immune cells into the brain. Once inside the brain, the T cells interact with microglia or astrocytes acting as antigen presenting cells (APC), and thus can carry out their effector functions,[82] although the proliferation of T cells in the AD brain is believed to be minimal.[113]

In AD patients, the microglia surrounding A$\beta$ plaques express MHC class II and CD40,[108,134–136] which are key for T cell interaction. In animal models of AD, microglia also have increased expression of MHC class II, CD40 and CD80.[118,124] In vitro, microglia can act as APCs for A$\beta$-specific Th1, Th2 and Th17 cells, where the Th1 and Th17 cells increased MHC class II, CD86 and CD40 expression on microglia and triggered production of TNF$\alpha$, IL-6 and IL-1$\beta$ from the A$\beta$-activated microglia.[137] Furthermore, when A$\beta$-specific Th1 cells (which are IFN-$\gamma^+$) were transferred intravenously (i.v.) to recipient APP/PS1 mice, this resulted in significantly increased A$\beta$-deposition, with microglial activation and enhanced cognitive impairment.[124]

The circulating T cells in AD patients have a similar shift in their inflammatory phenotype, with an increase in $CD4^+$IFN-$\gamma^+$ and $CD8^+$IFN-$\gamma^+$ T cells in AD patients in comparison with aged controls.[138,139] In addition, patients with amnestic MCI, a preclinical stage of AD, had proportions of $CD45^+$IFN-$\gamma^+$ and $CD45^+$IL-$17^+$ lymphocytes in the CSF that were comparable with untreated MS patients.[140] Leug and colleagues also reported an increase in activated $CD8^+$ T cells in the CSF of AD patients in comparison with age matched controls,[105] whereas others have found a shift in the circulating T cells to a IL-$17^+$ phenotype.[141,142] Indeed, a recent report identified an increase in $CD8^+$ T effector memory cells ($T_{EMRA}$) in AD patients in the CSF. Not only were these T cells clonally expanded, but increased numbers of these cells was associated with worse cognitive scores in those with AD.[115] In contrast, resting regulatory T cells (Tregs), which suppress immune function, are decreased in AD with levels similar to patients with MS.[143] Indeed, a recent study found that the Tregs in AD patients had lost their suppressive activity and were unable to control the expansion of $CD4^+$ T cells.[144] In vivo, depletion of Treg cells in APP/PS1 mice exacerbated cognitive decline whereas increasing the Treg population rescued cognitive function and increased the number of plaque-associated microglia.[145,146]

The memory status of T cells in the blood of patients has been examined by a number of groups who all found similar, corroborating results, namely decreased levels of circulating naïve T cells and a corresponding increase in effector memory and terminally differentiated $CD4^+$ and $CD8^+$ T cells in comparison with aged matched controls.[142,147–150] Furthermore, the T cells from AD patients had shorter telomeres than healthy controls, suggesting an exhaustion of the adaptive immune system.[151] This is of particular concern in AD, as if the cells that have infiltrated the brain have the same activated profile as

the IFN-$\gamma^+$ or IL-17$^+$, effector memory or terminally differentiated T cells that were identified in the blood, they may easily be contributing to the exacerbated inflammation occurring in this condition.

## 13. Infection Driven Changes in T Cells

As infection triggers activation of the innate and specifically the adaptive immune system, many researchers have been examining the role of infectious challenge on the progression of AD. A number of specific bacterial and viral infections have been linked with AD, including *Chlamydia pneumonia*, spirochete infection, Herpes simplex virus (HSV)-1 and cytomegalovirus (CMV).[152]

*Chlamydia pneumonia* is an intercellular gram-negative bacteria, that has been found in the AD brain,[153,154] where cells infected with *C. pneumonia* are located in close proximity to plaques in AD postmortem brain tissue.[153] *C. pneumonia* can enhance the activity of $\beta$-secretase,[155] and in line with this in vivo studies found that infection of wildtype mice with *C. pneumonia* triggered AD pathology that was even detectable 3 months post infection.[156]

Spirochete infection is another example of a bacterial infection that has been associated with AD. Spirochetes are gram-negative bacteria that are neurotropic, and many have been detected in the postmortem brain tissue of those with AD, including *Treponema*,[157] *P. gingivalis*[158] and *B. burgdorferi*.[159] Spirochetes are a common cause of periodontitis, which has also been associated with increased A$\beta$ load in the elderly.[160] Murine studies have confirmed these findings, where oral infection of APP transgenic mice with *P. gingivalis* increased the concentration of IL-1$\beta$ and TNF$\alpha$ in the brain and also enhanced A$\beta$ deposition.[161] Similar results have been found by other groups, who found that *P. gingivalis* infection of wildtype mice also increased IL-1$\beta$ and TNF$\alpha$ in the cortex and induced memory changes.[162,163] A phase 2/3 clinical trial is currently underway to examine whether targeting this pathway could be protective in patients. This trial is using Atuzaginstat (also known as COR388) to inhibit gingipains, which are proteases belonging to *P. gingivalis*. The estimated study completion date is 2022.

HSV-1 is a risk factor for AD in those carrying an APOE4 allele,[164,165] and using a 3D model of human-induced neural stem cells, Cairns and colleagues demonstrated that HSV-1 caused glial activation, and enhanced the production of TNF$\alpha$ and A$\beta$.[166] Similar results have been obtained in mice, where HSV-1 increased A$\beta$ and tau pathology.[167] Another member of the herpes virus family is Epstein-Barr virus (EBV), which had been detected in the AD brain, where AD patients also had increased serological positivity to EBV.[168] Additionally, AD patients have clonally expanded T cells in the CSF that recognise EBV antigens.[115]

The elderly are more vulnerable to respiratory infections in general than younger individuals[169,170] however, those with AD have an even greater incidence of infections including of the respiratory and urinary tract than their age-matched counterparts.[171] Indeed peripheral challenge (including by infection) enhanced cognitive decline when assessed just 6 months afterwards.[172,173] In contrast, vaccination against infections including influenza is protective against the development of dementia.[174,175] Using the gram-negative bacteria *Bordetella pertussis* to model a typical lung infection, it was found that aged APP/PS1 mice were more vulnerable to this pathogen than the aged wildtype or younger APP/PS1 counterparts. Specifically, *B. pertussis* triggered enhanced infiltration of IFN-$\gamma^+$ and IL-17$^+$ T cells to the brains of APP/PS1 mice, which was associated with increased microglial activation and A$\beta$ deposition.[118] Importantly, treating mice with FTY720 prevented the infection-induced T cell increase in the brain and attenuated these inflammatory changes.[119] FTY720 has also been shown to be protective in the 5xFAD model, where it reduced plaque load and rescued microglial activation.[176,177] FTY720 (brand name Gilenya) is a currently approved therapy for MS, although its efficacy in AD patients is unexamined.

In light of the recent global COVID-19 (SARS-Cov-2) pandemic, there is also growing concern about the impact of this coronavirus infection on the brain. A number of studies have reported that neurological symptoms are apparent in those with an active infection of COVID-19, which range from stroke to loss of taste and smell, to cognitive changes.[178–182] Many patients continue to experience symptoms long after they have cleared the virus, a condition that has become commonly known as "Long-COVID" and is characterised by conditions including chronic fatigue, brain fog or ongoing respiratory problems.[183–185] These symptoms suggest a continued involvement of the brain or neuroinflammation and in line with this, COVID-19 viral particles were recently reported in the brain of a patient who died from the infection.[186] In vitro studies have demonstrated that COVID-19 can infect neural cells derived from induced pluripotent stem cells[187] and a recent preprint (which has not yet undergone peer review) found that COVID-19 can infect astrocytes,[188] although it is important to note that other groups have not been able to find molecular traces of COVID-19 in the post-mortem brain tissue.[189,190] Transcriptomic analysis on those who died from COVID-19 found significant microglial activation[189,190] with enhanced infiltration of activated CD8$^+$ T cells into the brain parenchyma.[190] These findings have been observed by others, along with damage to the brain microvasculature including microhaemorrhages and leakage of fibrinogen into the parenchyma.[191] One issue from these post-mortem studies is that they provide a snapshot of the events at the end of life for these patients, many of whom were undergoing an extremely active, aggressive infection with COVID-19. Hemming and colleagues recently performed single cell sequencing on the CSF cells of patients with an ongoing COVID-19 infection and interestingly, there was an increase in exhausted T cells here that were also clonally expanded.[181] A recent study involving hundreds of participants who had recovered from COVID-19 found that those who had the greatest severity of infection (i.e., hospitalisation and ventilation) were cognitively worse than individuals who had mild symptoms.[182] Indeed a smaller study with 18 participants (who were 20–105 days post COVID-19 infection) also had persistent cognitive changes.[192] Together this work highlights the strong, continuing effect that COVID-19 infectious challenge is having on the brain. Within the last two years we have learned a lot about its pathogenesis, however this field is still in its infancy and we are

continuously learning more about the long-term effects of the COVID-19 virus which has touched so many around the world.

## 14. Conclusion and Future Perspectives

Within the last 15 years, the developing field of neuroimmunology has provided many new and important insights into the sequence of inflammatory events that contribute to the development of AD. Sophisticated experiments, using the state-of-the-art techniques in immunology and neuroscience research have unveiled the intricate, combined roles of the innate and adaptive immune system in driving these changes (**Figure 3**). This review highlights the impact of microglial- and T cell-signalling that drive pathology in AD, and discusses how outside forces such as peripheral infection also have a significant role to play.

It is clear that microglia are a central player in the progression of AD and dementia. The initial deposition of A$\beta$ and tau cause well-characterised microglial activation, assembly of the NLRP3 inflammasome and release of cytokines and proteins.[40,55,67] However, as the initial stimuli (i.e., A$\beta$ and tau) are not resolved the persistent microglial activation further enhances AD pathology, triggering a feed-forward cycle of increased protein deposition and more neuroinflammation. As discussed, these changes occur in a multifactorial way. The microglial-released ASC-specks act as a scaffold for A$\beta$ deposition,[67] and the glial-derived pro-inflammatory cytokines such as IL-1$\beta$ and TNF$\alpha$ enhance APP-cleaving enzyme activity thereby increasing A$\beta$ deposition[35,36] while also simultaneously reducing microglial phagocytic capacity.[37,38] The ongoing pathology and microglial activation can also cause changes to the BBB and the NVU.[82,83] Without an intact BBB, peripheral immune cells such as T cells have easier access to the CNS and together induce increased neuroinflammation on entry to the parenchyma.[112,115] This complex process worsens under conditions of infection. In cases of existing AD-pathology, peripheral infection triggers further BBB disruption, increased leakage of normally peripherally-restricted proteins like fibrinogen and enhanced infiltration of inflammatory T cells to the CNS.[118,119] These T cells contribute to the ongoing neuroinflammation by interacting with local glial cells and releasing their potent pro-inflammatory cytokines and enzymes.[115,124,137] Bacteria and viruses have also been found within the AD brain, located near plaques or microglial cells.[152,153,160,165,168] Together this inflammatory cascade has a detrimental impact on cognitive abilities, where patients with AD become more impaired with subsequent infectious challenges.[172,173,193]

However, numerous therapies are under development to target neuroinflammation to protect against cognitive decline in those who have, and will be diagnosed with dementia and

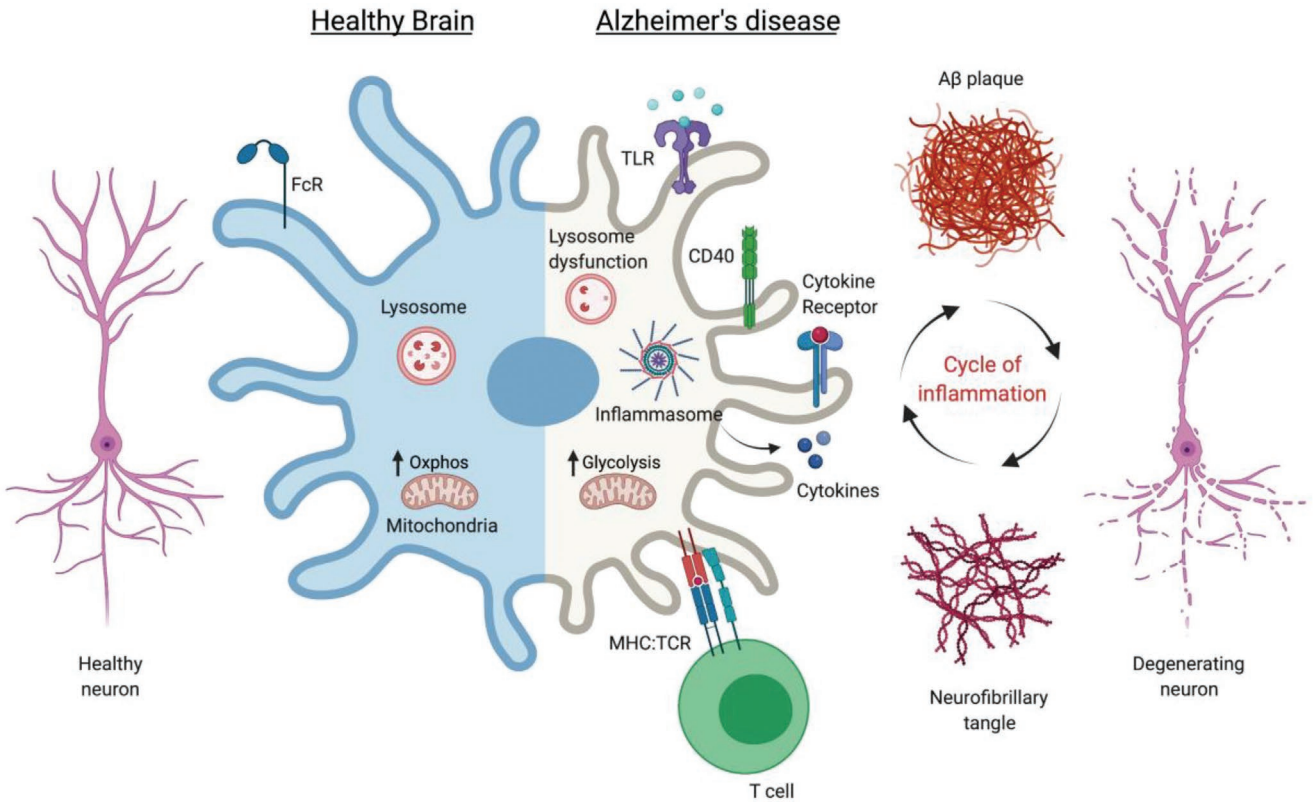


**Figure 3.** The brain in Alzheimer's disease. During healthy aging, the microglia provide homeostatic support to neurons, they are anti-inflammatory and efficient at phagocytosis. In AD, the microglia become chronically activated due to the growing presence of A$\beta$ or tau. In addition, there is increased infiltration of T cells in the AD brain, which contribute to the inflammatory environment. Together this creates an endless cycle of inflammation; A$\beta$ or tau trigger metabolic changes and cytokine production, this impairs phagocytosis, primes neighbouring cells and increases secretase activity together enhancing the AD-related pathology. Ultimately the growing levels of A$\beta$ or tau induce neuronal degeneration and loss (which further activate the microglia), underpinning the cognitive decline observed in patients with dementia.

AD. There are many NLRP3-targeted compounds in clinical trials that hold great promise as the future of AD treatments. In the meantime, to prevent a rapid increase in AD-symptoms, protection against infection is vital. Vaccination programs (such as for influenza and COVID-19 for example) in the elderly and those with AD have a very important role in shielding the brain from extra inflammatory stimulation. This is especially relevant while there are no effective AD-related therapies that are widely available. Indeed, as we learn more about the connections between the brain and the periphery, vaccination and rapid treatment of infections will likely remain a cornerstone of effective care for the elderly.

With many immune-targeted therapies in development, the future of AD treatment looks promising. Time will tell whether modulating the immune response in AD could present a solution for this devastating condition, which has long eluded doctors and researchers alike.

## Acknowledgements

R.M.M. was supported by a grant from the Alzheimer's Forschung Initiative (#20 043) and by the German Center for Neurodegenerative Diseases (DZNE). All figures were created in BioRender.com. In Figure 1, the Gasdermin D pore subimage was adapted from 'Suppression of Inflammasome by IRF4 and IRF8 is Critical for T cell Priming' by BioRender.com with permission (2022) and retrieved from https://app.biorender.com/biorender-templates.

Open Access funding enabled and organized by Projekt DEAL.

## Conflict of Interest

The authors declare no conflict of interest.

## Keywords

Alzheimer's disease, amyloid beta, infections, inflammasomes, microglia, T cells, tau

Received: September 1, 2021
Revised: February 3, 2022
Published online: March 7, 2022

[1] United Nations Department of Economic and Social Affairs Population Division, World Population Ageing 2015, Report ST/ESA/SER.A/390, **2015**, http://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf (accessed: July 2021).
[2] C Brayne, *Nat. Rev. Neurosci.* **2007**, *8*, 233.
[3] L. E. Hebert, J. Weuve, P. A. Scherr, D. A Evans, *Neurology* **2013**, *80*, 1778.
[4] Alzheimer's Association Report, *Alzheimer's Dementia* **2018**, *14*, 367.
[5] Alzheimer's Association Report, *Alzheimer's Dementia* **2020**, *16*, 391.
[6] A. Serrano-Pozo, M. L. Mielke, A. Muzitansky, T. Gómez-Isla, J. H. Growdon, B. J. Bacskai, R. A. Betensky, M. P. Frosch, B. T. Hyman, *J. Neuropathol. Exp. Neurol.* **2012**, *71*, 694.
[7] M. P. Kummer, M. Hermes, A. Delekarte, T. Hammerschmidt, S. Kumar, D. Terwel, J. Walter, H. C. Pape, S. König, S. Roeber, F. Jessen, T. Klockgether, M. Korte, M. T. Heneka, *Neuron* **2011**, *71*, 833.
[8] S. Kumar, O. Wirths, K. Stüber, P. Wunderlich, P. Koch, S. Theil, N. Rezaei-Ghaleh, M. Zweckstetter, T. A. Bayer, O. Brüstle, D. R. Thal, J. Walter, *Acta Neuropathol.* **2016**, *131*, 525.
[9] B. F. Maziuk, D. J. Apicco, A. Lourdes Cruz, L. Jiang, P. E. A. Ash, E. L. da Rocha, C. Zhang, W. Haung Yu, J. Leszyk, J. F. Abisambra, H. Li, B. Wolozin, *Acta Neuropathol. Commun.* **2018**, *6*, 71.
[10] H. Braak, E Braak, *Acta Neuropathol.* **1991**, *82*, 239.
[11] H. Braak, I. Alafuzoff, T. Arzberger, H. Kretzschmar, K Del Tredici, *Acta Neuropathol.* **2006**, *112*, 389.
[12] G. Nelson, J. Wordsworth, C. Wang, D. Jurk, C. Lawless, C. Martin-Ruiz, T. von Zglinicki, *Aging Cell* **2012**, *11*, 345.
[13] M. Mauri, E. Sinforiani, C. Zucchella, M. G. Cuzzoni, G Bono, *Funct. Neurol.* **2012**, *27*, 49.
[14] R. S. Wilson, S. E. Leurgans, P. A. Boyle, D. A Bennett, *Arch. Neurol.* **2011**, *68*, 351.
[15] O. L Lopez, *Continuum* **2013**, *19*, 411.
[16] J. Cummings, G. Lee, K. Zhong, J. Fonseca, K Taghva, *Alzheimer's Dementia Transl. Res. Clin Interventions* **2021**, *7*, 12179.
[17] J. A. R. Nicoll, G. R. Buckland, C. H. Harrison, A. Page, S. Harris, S. Love, J. W. Neal, C. Holmes, D. Boche, *Brain* **2019**, *142*, 2113.
[18] M. A. Mintun, A. C. Lo, C. Duggan Evans, A. M. Wessels, P. A. Ardayfio, S. W. Andersen, S. Shcherbinin, J. D. Sparks, J. R. Sims, M. Brys, L. G. Apostolova, S. P. Salloway, D. M. Skovronsky, *N. Engl. J. Med.* **2021**, *384*, 1691.
[19] C. J. Swanson, Y. Zhang, S. Dhadda, J. Wang, J. Kaplow, R. Y. K. Lai, L. Lannfelt, H. Bradley, M. Rabe, A. Koyama, L. Reyderman, D. A. Berry, S. Berry, R. Gordon, L. D. Kramer, J. L. Cummings, *Alzheimers Res. Ther.* **2021**, *13*, 80.
[20] S. Salloway, M. Farlow, E. McDade, D. B. Clifford, G. Wang, J. J. Llibre-Guerra, J. M. Hitchcock, S. L. Mills, A. M. Santacruz, A. J. Aschenbrenner, J. Hassenstab, T. L. S. Benzinger, B. A. Gordon, A. M. Fagan, K. A. Coalier, C. Cruchaga, A. A. Goate, R. J. Perrin, C. Xiong, Y. Li, J. C. Morris, B. J. Snider, C. Mummery, G. M. Surti, D. Hannequin, D. Wallon, S. B. Berman, J. J. Lah, I. Z. Jimenez-Velazquez, E. D. Roberson, et al., *Nat. Med.* **2021**, *27*, 1187.
[21] A Mullard, *Nat. Rev. Drug Discovery* **2021**, *20*, 3.
[22] M. W. Salter, B Stevens, *Nat. Med.* **2017**, *23*, 1018.
[23] M. Ries, M Sastre, *Front. Aging Neurosci.* **2016**, *8*, 160.
[24] Y. Zhao, X. Wu, X. Li, L.-L. Jiang, X. Gui, Y. Liu, Y. Sun, B. Zhu, J. C. Piña-Crespo, M. Zhang, N. Zhang, X. Chen, G. Bu, Z. An, T. Y. Huang, H. Xu, *Neuron* **2018**, *97*, 1023.e7.
[25] K. Tahara, H.-D. Kim, J.-J. Jin, J. A. Maxwell, L. Li, K Fukuchi, *Brain J. Neurol.* **2006**, *129*, 3006.
[26] K. L. Richard, M. Filali, P. Prefontaine, S Rivest, *J. Neurosci.* **2008**, *28*, 5784.
[27] H. Keren-Shaul, A. Spinrad, A. Weiner, O. Matcovitch-Natan, R. Dvir-Szternfeld, T. K. Ulland, E. David, K. Baruch, D. Lara-Astaiso, B. Toth, S. Itzkovitz, M. Colonna, M. Schwartz, I. Amit, *Cell* **2017**, *169*, 1276.e17.
[28] Y. Wang, T. K. Ulland, J. D. Ulrich, W. Song, J. A. Tzaferis, J. T. Hole, P. Yuan, T. E. Mahan, Y. Shi, S. Gilfillan, M. Cella, J. Grutzendler, R. B. DeMattos, J. R. Cirrito, D. M. Holtzman, M. Colonna, *J. Exp. Med.* **2016**, *213*, 667.
[29] S. C. Hopp, Y. Lin, D. Oakley, A. D. Roe, S. L. DeVos, D. Hanlon, B. T. Hyman, *J. Neuroinflammation* **2018**, *15*, 269.
[30] C. E. G. Leyns, M. Gratuze, S. Narasimhan, N. Jain, L. J. Koscal, H. Jiang, M. Manis, M. Colonna, V. M. Y. Lee, J. D. Ulrich, D. M. Holtzman, *Nat. Neurosci.* **2019**, *22*, 1217.
[31] S.-H. Lee, W. J. Meilandt, L. Xie, V. D. Gandham, H. Ngu, K. H. Barck, M. G. Rezzonico, J. Imperio, G. Lalehzadeh, M. A. Huntley, K. L. Stark, O. Foreman, R. A. D. Carano, B. A. Friedman, M. Sheng, A. Easton, C. J. Bohlen, D. V. Hansen, *Neuron* **2021**, *109*, 1283.e6.

[32] S. M. Bemiller, T. J. McCray, K. Allan, S. V. Formica, G. Xu, G. Wilson, O. N. Kokiko-Cochran, S. D. Crish, C. A. Lasagna-Reeves, R. M. Ransohoff, G. E. Landreth, B. T. Lamb, *Mol. Neurodegener.* **2017**, *12*, 74.
[33] A. Lyons, R. J. Griffin, C. E. Costelloe, R. M. Clarke, M. A Lynch, *J. Neurochem.* **2007**, *101*, 771.
[34] A. Michelucci, T. Heurtaux, L. Grandbarbe, E. Morga, P Heuschling, *J. Neuroimmunol.* **2009**, *210*, 3.
[35] M. Sastre, J. Walter, S. M Gentleman, *J. Neuroinflammation* **2008**, *5*, 25.
[36] Y.-F. Liao, B.-J. Wang, H.-T. Cheng, L.-H. Kuo, M. S Wolfe, *J. Biol. Chem.* **2004**, *279*, 49523.
[37] C. Dempsey, A. Rubio Araiz, K. J. Bryson, O. Finucane, C. Larkin, E. L. Mills, A. B. Robertson, M. A. Cooper, L. A. J. O'Neill, M. A. Lynch, *Brain, Behav., Immun.* **2017**, *61*, 306.
[38] J. Koenigsknecht-Talboo, G. E Landreth, *J. Neurosci.* **2005**, *25*, 8240.
[39] E. Gerrits, N. Brouwer, S. M. Kooistra, M. E. Woodbury, Y. Vermeiren, M. Lambourne, J. Mulder, M. Kummer, T. Möller, K. Biber, W. F. A. den Dunnen, P. P. De Deyn, B. J. L. Eggen, E. W. G. M. Boddeke, *Acta Neuropathol.* **2021**, *141*, 681.
[40] C. Ising, C. Venegas, S. Zhang, H. Scheiblich, S. V. Schmidt, A. Vieira-Saecker, S. Schwartz, S. Albasset, R. M. McManus, D. Tejera, A. Griep, F. Santarelli, F. Brosseron, S. Opitz, J. Stunden, M. Merten, R. Kayed, D. T. Golenbock, D. Blum, E. Latz, L. Buée, M. T. Heneka, *Nature* **2019**, *575*, 669.
[41] N. Maphis, G. Xu, O. N. Kokiko-Cochran, S. Jiang, A. Cardona, R. M. Ransohoff, B. T. Lamb, K. Bhaskar, *Brain* **2015**, *138*, 1738.
[42] M. Fá, D. Puzzo, R. Piacentini, A. Staniszewski, H. Zhang, M. A. Baltrons, D. D. Li Puma, I. Chatterjee, J. Li, F. Saeed, H. L. Berman, C. Ripoli, W. Gulisano, J. Gonzalez, H. Tian, J. A. Costa, P. Lopez, E. Davidowitz, W. H. Yu, V. Haroutunian, L. M. Brown, A. Palmeri, E. M. Sigurdsson, K. E. Duff, A. F. Teich, L. S. Honig, M. Sierks, J. G. Moe, L. D'Adamio, C. Grassi, et al., *Sci. Rep.* **2016**, *6*, 19393.
[43] C. A. Lasagna-Reeves, D. L. Castillo-Carranza, M. J. Guerrero-Muñoz, G. R. Jackson, *Biochemistry* **2010**, *49*, 10039.
[44] M. Rapoport, H. N. Dawson, L. I. Binder, M. P. Vitek, A Ferreira, *Proc. Natl. Acad. Sci.* **2002**, *99*, 6364.
[45] O. A. Shipton, J. R. Leitz, J. Dworzak, C. E. J. Acton, E. M. Tunbridge, F. Denk, H. N. Dawson, M. P. Vitek, R. Wade-Martins, O. Paulsen, M. Vargas-Caballero, *J. Neurosci.* **2011**, *31*, 1688.
[46] C. K. Combs, J. C. Karlo, S.-C. Kao, G. E Landreth, *J. Neurosci.* **2001**, *21*, 1179.
[47] J. Guadagno, P. Swan, R. Shaikh, S. P Cregan, *Cell Death Dis.* **2015**, *6*, 1779.
[48] G. Lopez-Castejon, D Brough, *Cytokine Growth Factor Rev.* **2011**, *22*, 189.
[49] Z. Z. Lieu, J. G. Lock, L. A. Hammond, N. L. La Gruta, J. L. Stow, P. A Gleeson, *Proc. Natl. Acad. Sci.* **2008**, *105*, 3351.
[50] M. Zhou, R. Xu, D. C. Kaelber, M. E Gurney, A. Bayer, *PLoS One* **2020**, *15*, 0229819.
[51] J. Butchart, L. Brook, V. Hopkins, J. Teeling, U. Puntener, D. Culliford, R. Sharples, S. Sharif, B. McFarlane, R. Raybould, R. Thomas, P. Passmore, V. H. Perry, C. Holmes, *Neurology* **2015**, *84*, 2161.
[52] F. Martinon, K. Burns, J Tschopp, *Mol. Cell* **2002**, *10*, 417.
[53] F. Martinon, V. Pétrilli, A. Mayor, A. Tardivel, J Tschopp, *Nature* **2006**, *440*, 237.
[54] P. Duewell, H. Kono, K. J. Rayner, C. M. Sirois, G. Vladimer, F. G. Bauernfeind, G. S. Abela, L. Franchi, G. Nuñez, M. Schnurr, T. Espevik, E. Lien, K. A. Fitzgerald, K. L. Rock, K. J. Moore, S. D. Wright, V. Hornung, E. Latz, *Nature* **2010**, *464*, 1357.
[55] M. T. Heneka, M. P. Kummer, A. Stutz, A. Delekate, S. Schwartz, A. Vieira-Saecker, A. Griep, D. Axt, A. Remus, T.-C. Tzeng, E. Gelpi, A. Halle, M. Korte, E. Latz, D. T. Golenbock, *Nature* **2013**, *493*, 674.
[56] M. T. Heneka, R. M. McManus, E Latz, *Nat. Rev. Neurosci.* **2018**, *19*, 610.
[57] M. S. J. Mangan, E. J. Olhava, W. R. Roush, H. M. Seidel, G. D. Glick, E Latz, *Nat. Rev. Drug Discovery* **2018**, *17*, 588.
[58] C. L. Evavold, J. Ruan, Y. Tan, S. Xia, H. Wu, J. C Kagan, *Immunity* **2018**, *48*, 35.
[59] E. Mulvihill, L. Sborgi, S. A. Mari, M. Pfreundschuh, S. Hiller, D. J Müller, *EMBO J.* **2018**, *37*, 98321.
[60] B. S. Franklin, L. Bossaller, D. De Nardo, J. M. Ratter, A. Stutz, G. Engels, C. Brenker, M. Nordhoff, S. R. Mirandola, A. Al-Amoudi, M. S. Mangan, S. Zimmer, B. G. Monks, M. Fricke, R. E. Schmidt, T. Espevik, B. Jones, A. G. Jarnicki, P. M. Hansbro, P. Busto, A. Marshak-Rothstein, S. Hornemann, A. Aguzzi, W. Kastenmüller, E. Latz, *Nat. Immunol.* **2014**, *15*, 727.
[61] M. Monteleone, A. C. Stanley, K. W. Chen, D. L. Brown, J. S. Bezbradica, J. B. von Pein, C. L. Holley, D. Boucher, M. R. Shakespear, R. Kapetanovic, V. Rolfes, M. J. Sweet, J. L. Stow, K. Schroder, *Cell Rep.* **2018**, *24*, 1425.
[62] B. Zhou, D. W Abbott, *Cell Rep.* **2021**, *35*, 108998.
[63] M. Bruchard, C. Rebé, V. Derangère, D. Togbé, B. Ryffel, R. Boidot, E. Humblin, A. Hamman, F. Chalmin, H. Berger, A. Chevriaux, E. Limagne, L. Apetoh, F. Végran, F. Ghiringhelli, *Nat. Immunol.* **2015**, *16*, 859.
[64] A. Lučiūnaitė, R. M. McManus, M. Jankunec, I. Rácz, C. Dansokho, I. Dalgėdienė, S. Schwartz, F. Brosseron, M. T. Heneka, *J. Neurochem.* **2020**, *155*, 650.
[65] A. Halle, V. Hornung, G. C. Petzold, C. R. Stewart, B. G. Monks, T. Reinheckel, K. A. Fitzgerald, E. Latz, K. J. Moore, D. T. Golenbock, *Nat. Immunol.* **2008**, *9*, 857.
[66] N. Murphy, B. Grehan, M. A Lynch, *NeuroMol. Med.* **2014**, *16*, 205.
[67] C. Venegas, S. Kumar, B. S. Franklin, T. Dierkes, R. Brinkschulte, D. Tejera, A. Vieira-Saecker, S. Schwartz, F. Santarelli, M. P. Kummer, A. Griep, E. Gelpi, M. Beilharz, D. Riedel, D. T. Golenbock, M. Geyer, J. Walter, E. Latz, M. T. Heneka, *Nature* **2017**, *552*, 355.
[68] L. L. Friker, H. Scheiblich, I. V. Hochheiser, R. Brinkschulte, D. Riedel, E. Latz, M. Geyer, M. T. Heneka, *Cell Rep.* **2020**, *30*, 3743.e6.
[69] S. Ghosh, M. D. Wu, S. S. Shaftel, S. Kyrkanides, F. M. LaFerla, J. A. Olschowka, M. K. O'Banion, *J. Neurosci.* **2013**, *33*, 5053.
[70] J. Flores, A. Noël, B. Foveau, J. Lynham, C. Lecrux, A. C LeBlanc, *Nat. Commun.* **2018**, *9*, 3916.
[71] I.-C. Stancu, N. Cremers, H. Vanrusselt, J. Couturier, A. Vanoosthuyse, S. Kessels, C. Lodder, B. Brône, F. Huaux, J.-N. Octave, D. Terwel, I. Dewachter, *Acta Neuropathol.* **2019**, *137*, 599.
[72] M. Kitazawa, D. Cheng, M. R. Tsukamoto, M. A. Koike, P. D. Wes, V. Vasilevko, D. H. Cribbs, F. M. LaFerla, *J. Immunol.* **2011**, *187*, 6539.
[73] M. A Lynch, *Prog. Neurobiol.* **2020**, *184*, 101719.
[74] L.-P. Bernier, E. M. York, A. Kamyabi, H. B. Choi, N. L. Weilinger, B. A MacVicar, *Nat. Commun.* **2020**, *11*, 1559.
[75] G. Tondo, L. Iaccarino, S. P. Caminiti, L. Presotto, R. Santangelo, S. Iannaccone, G. Magnani, D. Perani, *Alzheimers Res. Ther.* **2020**, *12*, 50.
[76] S. H. Baik, S. Kang, W. Lee, H. Choi, S. Chung, J.-I. Kim, I. Mook-Jung, *Cell Metab.* **2019**, *30*, 493.e6.
[77] O. M. Finucane, J. Sugrue, A. Rubio-Araiz, M.-V. Guillot-Sestier, M. A Lynch, *Sci. Rep.* **2019**, *9*, 4034.
[78] A. McIntosh, V. Mela, C. Harty, A. M. Minogue, D. A. Costello, C. Kerskens, M. A. Lynch, *Brain Pathol.* **2019**, *29*, 606.
[79] R. Holland, A. L. McIntosh, O. M. Finucane, V. Mela, A. Rubio-Araiz, G. Timmons, S. A. McCarthy, Y. K. Gun'ko, M. A. Lynch, *Brain, Behav., Immun.* **2018**, *68*, 183.
[80] M.-V. Guillot-Sestier, A. R. Araiz, V. Mela, A. S. Gaban, E. O'Neill, L. Joshi, E. T. Chouchani, E. L. Mills, M. A. Lynch, *Commun. Biol.* **2021**, *4*, 711.

[81] A. J. Farrall, J. M Wardlaw, *Neurobiol. Aging* **2009**, *30*, 337.
[82] R. M. McManus, K. H. G. Mills, M. A Lynch, *J. Neuroimmune Pharmacol.* **2015**, *10*, 547.
[83] A. Carrano, J. J. M. Hoozemans, S. M. van der Vies, A. J. M. Rozemuller, J. van Horssen, H. E de Vries, *Antioxid. Redox Signaling* **2011**, *15*, 1167.
[84] C.-C. Liu, Y. Yamazaki, M. G. Heckman, Y. A. Martens, L. Jia, A. Yamazaki, N. N. Diehl, J. Zhao, N. Zhao, M. DeTure, M. D. Davis, L. M. Felton, W. Qiao, Y. Li, H. Li, Y. Fu, N. Wang, M. Wren, T. Aikawa, M.-L. Holm, H. Oue, C. Linares, M. Allen, M. M. Carrasquillo, M. E. Murray, R. C. Petersen, N. Ertekin-Taner, D. W. Dickson, T. Kanekiyo, G. Bu, *Alzheimer's Dement.* **2020**, *16*, 1372.
[85] B. D. Zipser, C. E. Johanson, L. Gonzalez, T. M. Berzin, R. Tavares, C. M. Hulette, M. P. Vitek, V. Hovanesian, E. G. Stopa, *Neurobiol. Aging* **2007**, *28*, 977.
[86] J. D. Sengillo, E. A. Winkler, C. T. Walker, J. S. Sullivan, M. Johnson, B. V Zlokovic, *Brain Pathol.* **2013**, *23*, 303.
[87] M. Merlini, E. P. Meyer, A. Ulmann-Schuler, R. M Nitsch, *Acta Neuropathol.* **2011**, *122*, 293.
[88] D. M. Wilcock, M. P. Vitek, C. A Colton, *Neuroscience* **2009**, *159*, 1055.
[89] A. P. Sagare, R. D. Bell, Z. Zhao, Q. Ma, E. A. Winkler, A. Ramanathan, B. V. Zlokovic, *Nat. Commun.* **2013**, *4*, 2932.
[90] H. Akiyama, K. Ikeda, H. Kondo, P. L McGeer, *Neurosci. Lett.* **1992**, *146*, 152.
[91] T. M. Berzin, B. D. Zipser, M. S. Rafii, V. Kuo-Leblanc, G. D. Yancopoulos, D. J. Glass, J. R. Fallon, E. G. Stopa, *Neurobiol. Aging* **2000**, *21*, 349.
[92] M. Fiala, Q. N. Liu, J. Sayre, V. Pop, V. Brahmandam, M. C. Graves, A. Gustavson, J. Sayre, E. Sofroni, T. Suarez, F. Chiappelli, G. Bernard, *Eur. J. Clin. Invest.* **2002**, *32*, 360.
[93] J. K. Ryu, J. G McLarnon, *J. Cell. Mol. Med.* **2009**, *13*, 2911.
[94] H. Kebir, K. Kreymborg, I. Ifergan, A. Dodelet-Devillers, R. Cayrol, M. Bernard, F. Giuliani, N. Arbour, B. Becher, A. Prat, *Nat. Med.* **2007**, *13*, 1173.
[95] A. Minagar, J. S Alexander, *Mult. Scler. Houndmills Basingstoke Engl.* **2003**, *9*, 540.
[96] L. C. D. Smyth, J. Rustenhoven, T. I.-H. Park, P. Schweder, D. Jansson, P. A. Heppner, S. J. O'Carroll, E. W. Mee, R. L. M. Faull, M. Curtis, M. Dragunow, *J. Neuroinflammation* **2018**, *15*, 138.
[97] D. Jansson, J. Rustenhoven, S. Feng, D. Hurley, R. L. Oldfield, P. S. Bergin, E. W. Mee, R. L. M. Faull, M. Dragunow, *J. Neuroinflammation* **2014**, *11*, 104.
[98] R. O. Weller, E. Djuanda, H.-Y. Yow, R. O Carare, *Acta Neuropathol.* **2009**, *117*, 1.
[99] R. O. Carare, M. Bernardes-Silva, T. A. Newman, A. M. Page, J. Nicoll, A. R. , V. H. Perry, R. O. Weller, *Neuropathol. Appl. Neurobiol.* **2008**, *34*, 131.
[100] C. E. Johanson, J. A. Duncan, P. M. Klinge, T. Brinker, E. G. Stopa, G. D Silverberg, *Cerebrospinal Fluid Res.* **2008**, *5*, 10.
[101] A. Louveau, I. Smirnov, T. J. Keyes, J. D. Eccles, S. J. Rouhani, J. D. Peske, N. C. Derecki, D. Castle, J. W. Mandell, K. S. Lee, T. H. Harris, J. Kipnis, *Nature* **2015**, *523*, 337.
[102] J. Smolders, K. M. Heutinck, N. L. Fransen, E. B. M. Remmerswaal, P. Hombrink, I. J. M. ten Berge, R. A. W. van Lier, I. Huitinga, J. Hamann, *Nat. Commun.* **2018**, *9*, 4593.
[103] B. Engelhardt, R. M Ransohoff, *Trends Immunol.* **2005**, *26*, 485.
[104] M. T. de Graaf, P. Smitt, R. L. Luitwieler, C. van Velzen, P. D. M. van den Broek, J. Kraan, J. W. Gratama, *Cytometry B Clin. Cytom.* **2011**, *80*, 43.
[105] G. Lueg, C. C. Gross, H. Lohmann, A. Johnen, A. Kemmling, M. Deppe, J. Groger, J. Minnerup, H. Wiendl, S. G. Meuth, T. Duning, *Neurobiol. Aging* **2015**, *36*, 81.
[106] J. Rogers, J. Luber-Narod, S. D. Styren, W. H Civin, *Neurobiol. Aging* **1988**, *9*, 339.
[107] M Hartwig, *Neuroreport* **1995**, *6*, 1274.
[108] P. L. McGeer, H. Akiyama, S. Itagaki, E. G McGeer, *J Neurol. Sci. J. Can. Sci. Neurol.* **1989**, *16*, 516.
[109] A. Parachikova, M. G. Agadjanyan, D. H. Cribbs, M. Blurton-Jones, V. Perreau, J. Rogers, T. G. Beach, C. W. Cotman, *Neurobiol. Aging* **2007**, *28*, 1821.
[110] T. Pirttilä, S. Mattinen, H Frey, *J. Neurol. Sci.* **1992**, *107*, 160.
[111] T. Town, J. Tan, R. A. Flavell, M Mullan, *Neuromolecular Med.* **2005**, *7*, 255.
[112] M. Merlini, T. Kirabali, L. Kulic, R. M. Nitsch, M. T. Ferretti, *Neurodegener. Dis.* **2018**, *18*, 49.
[113] T. Togo, H. Akiyama, E. Iseki, H. Kondo, K. Ikeda, M. Kato, T. Oda, K. Tsuchiya, K. Kosaka, *J. Neuroimmunol.* **2002**, *124*, 83.
[114] M. S. Unger, E. Li, L. Scharnagl, R. Poupardin, B. Altendorfer, H. Mrowetz, B. Hutter-Paier, T. M. Weiger, M. T. Heneka, J. Attems, L. Aigner, *Brain, Behav., Immun.* **2020**, *89*, 67.
[115] D. Gate, N. Saligrama, O. Leventhal, A. C. Yang, M. S. Unger, J. Middeldorp, K. Chen, B. Lehallier, D. Channappa, M. B. De Los Santos, A. McBride, J. Pluvinage, F. Elahi, G. Kyin-Ye Tam, Y. Kim, M. Greicius, A. D. Wagner, L. Aigner, D. R. Galasko, M. M. Davis, T. Wyss-Coray, *Nature* **2020**, *577*, 399.
[116] R. M. McManus, M. T Heneka, *Lancet Neurol.* **2020**, *19*, 285.
[117] E. Zotova, V. Bharambe, M. Cheaveau, W. Morgan, C. Holmes, S. Harris, J. W. Neal, S. Love, J. A. R. Nicoll, D. Boche, *Brain J. Neurol.* **2013**, *136*, 2677.
[118] R. M. McManus, S. C. Higgins, K. H. G. Mills, M. A Lynch, *Neurobiol. Aging* **2014**, *35*, 109.
[119] R. M. McManus, O. M. Finucane, M. M. Wilk, K. H. G. Mills, M. A Lynch, *J. Neuroimmune Pharmacol.* **2017**, *12*, 670.
[120] R. J. Kelly, A. M. Minogue, A. Lyons, R. S. Jones, T. C. Browne, D. A. Costello, S. Denieffe, C. O'Sullivan, T. J. Connor, M. A. Lynch, *J. Alzheimer's Dis.* **2013**, *37*, 63.
[121] C. Laurent, G. Dorothée, S. Hunot, E. Martin, Y. Monnet, M. Duchamp, Y. Dong, F.-P. Légeron, A. Leboucher, S. Burnouf, E. Faivre, K. Carvalho, R. Caillierez, N. Zommer, D. Demeyer, N. Jouy, V. Sazdovitch, S. Schraen-Maschke, C. Delarasse, L. Buée, D. Blum, *Brain J. Neurol.* **2017**, *140*, 184.
[122] S. Jimenez, D. Baglietto-Vargas, C. Caballero, I. Moreno-Gonzalez, M. Torres, R. Sanchez-Varo, D. Ruano, M. Vizuete, A. Gutierrez, J. Vitorica, *J. Neurosci.* **2008**, *28*, 11650.
[123] C. Späni, T. Suter, R. Derungs, M. T. Ferretti, T. Welt, F. Wirth, C. Gericke, R. M. Nitsch, L. Kulic, *Acta Neuropathol. Commun.* **2015**, [cited 2019 Nov 26], *3*, Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4642668/.
[124] T. C. Browne, K. McQuillan, R. M. McManus, J.-A. O'Reilly, K. H. G. Mills, M. A Lynch, *J. Immunol. Baltim. Md.* **2013**, *190*, 2241.
[125] A. Monsonego, V. Zota, A. Karni, J. I. Krieger, A. Bar-Or, G. Bitan, A. E. Budson, R. Sperling, D. J. Selkoe, H. L. Weiner, *J. Clin. Invest.* **2003**, *112*, 415.
[126] M. Saresella, E. Calabrese, I. Marventano, F. Piancone, A. Gatti, M. G. Calvo, R. Nemni, M. Clerici, *J. Alzheimer's Dis.* **2010**, *21*, 927.
[127] M. Saresella, E. Calabrese, I. Marventano, F. Piancone, A. Gatti, E. Farina, R. Alberoni, M. Clerici, *Neurobiol. Aging* **2012**, *33*, 624.e11.
[128] S.-M. Man, Y.-R. Ma, D.-S. Shang, W.-D. Zhao, B. Li, D.-W. Guo, W.-G. Fang, L. Zhu, Y.-H. Chen, *Neurobiol. Aging* **2007**, *28*, 485.
[129] Y.-J. Liu, D.-W. Guo, L. Tian, D.-S. Shang, W.-D. Zhao, B. Li, W.-G. Fang, L. Zhu, Y.-H. Chen, *Neurobiol. Aging* **2010**, *31*, 175.
[130] D. Goldeck, A. Larbi, M. Pellicanó, I. Alam, I. Zerr, C. Schmidt, T. Fulop, G. Pawelec, *PLoS One* **2013**, *8*, 66664.
[131] M. Reale, C. Iarlori, C. Feliciani, D Gambi, *J. Alzheimer's Dis.* **2008**, *14*, 147.
[132] M. Pellicanò, M. Bulati, S. Buffa, M. Barbagallo, A. Di Prima, G. Misiano, P. Picone, M. Di Carlo, D. Nuzzo, G. Candore, S. Vasto, D. Lio, C. Caruso, G. Colonna-Romano, *J. Alzheimer's Dis.* **2010**, *21*, 181.

[133] L. Cartier, O. Hartley, M. Dubois-Dauphin, K.-H Krause, *Brain Res. Brain Res. Rev.* **2005**, *48*, 16.
[134] P. L. McGeer, S. Itagaki, H. Tago, E. G McGeer, *Neurosci. Lett.* **1987**, *79*, 195.
[135] L. S. Perlmutter, S. A. Scott, E. Barrón, H. C Chui, *J. Neurosci. Res.* **1992**, *33*, 549.
[136] T. Togo, H. Akiyama, H. Kondo, K. Ikeda, M. Kato, E. Iseki, K. Kosaka, *Brain Res.* **2000**, *885*, 117.
[137] K. McQuillan, M. A. Lynch, K. H. G Mills, *Brain, Behav., Immun.* **2010**, *24*, 598.
[138] F. Baglio, M. Saresella, M. G. Preti, M. Cabinio, L. Griffanti, I. Marventano, F. Piancone, E. Calabrese, R. Nemni, M. Clerici, *Front. Aging Neurosci.* **2013**, *5*, 81.
[139] M. Fiala, J. Lin, J. Ringman, V. Kermani-Arab, G. Tsao, A. Patel, A. S. Lossinsky, M. C. Graves, A. Gustavson, J. Sayre, E. Sofroni, T. Suarez, F. Chiappelli, G. Bernard, *J. Alzheimer's Dis.* **2005**, *7*, 221.
[140] N. L. Monson, S. J. Ireland, A. J. Ligocki, D. Chen, W. H. Rounds, M. Li, R. M. Huebinger, C. M. Cullum, B. M. Greenberg, A. M. Stowe, R. Zhang, *J. Cereb. Blood Flow Metab.* **2014**, *34*, 30.
[141] T. J. Oberstein, L. Taha, P. Spitzer, J. Hellstern, M. Herrmann, J. Kornhuber, J. M. Maler, *Front. Immunol.* **2018**, *9*, https://www.frontiersin.org/articles/10.3389/fimmu.2018.01213/full.
[142] M. Saresella, E. Calabrese, I. Marventano, F. Piancone, A. Gatti, M. Alberoni, R. Nemni, M. Clerici, *Brain, Behav., Immun.* **2011**, *25*, 539.
[143] F. Ciccocioppo, P. Lanuti, L. Pierdomenico, P. Simeone, G. Bologna, E. Ercolino, F. Buttari, R. Fantozzi, A. Thomas, M. Onofrj, D. Centonze, S. Miscia, M. Marchisio, *Sci. Rep.* **2019**, *9*, 1.
[144] A. Faridar, A. D. Thome, W. Zhao, J. R. Thonhoff, D. R. Beers, B. Pascual, J. C. Masdeu, S. H. Appel, *Brain Commun.* **2020**, *2*, fcaa112.
[145] C. Dansokho, D. Ait Ahmed, S. Aid, C. Toly-Ndour, T. Chaigneau, V. Calle, N. Cagnard, M. Holzenberger, E. Piaggio, P. Aucouturier, G. Dorothée, *Brain J. Neurol.* **2016**, *139*, 1237.
[146] C. Dansokho, P. Aucouturier, G Dorothée, *Brain J. Neurol.* **2017**, *140*, 39.
[147] A. Larbi, G. Pawelec, J. M. Witkowski, H. M. Schipper, E. Derhovanessian, D. Goldeck, T. Fulop, *J. Alzheimer's Dis.* **2009**, *17*, 91.
[148] M. Pellicanò, A. Larbi, D. Goldeck, G. Colonna-Romano, S. Buffa, M. Bulati, G. Rubino, F. Iemolo, G. Candore, C. Caruso, E. Derhovanessian, G. Pawelec, *J. Neuroimmunol.* **2012**, *242*, 52.
[149] K. Schindowski, A. Eckert, J. Peters, C. Gorriz, U. Schramm, T. Weinandi, K. Maurer, L. Frölich, W. E. Müller, *Neuromolecular Med.* **2007**, *9*, 340.
[150] L. Speciale, E. Calabrese, M. Saresella, C. Tinelli, C. Mariani, L. Sanvito, R. Longhi, P. Ferrante, *Neurobiol. Aging* **2007**, 1163.
[151] L. A. Panossian, V. R. Porter, H. F. Valenzuela, X. Zhu, E. Reback, D. Masterman, J. L. Cummings, R. B. Effros, *Neurobiol. Aging* **2003**, *24*, 77.
[152] R. M. McManus, M. T Heneka, *Alzheimer's Res. Ther.* **2017**, *9*, 14.
[153] H. C. Gérard, U. Dreses-Werringloer, K. S. Wildt, S. Deka, C. Oszust, B. J. Balin, W. H. Frey, E. Z. Bordayo, J. A. Whittum-Hudson, A. P. Hudson, *FEMS Immunol. Med. Microbiol.* **2006**, *48*, 355.
[154] B. J. Balin, H. C. Gérard, E. J. Arking, D. M. Appelt, P. J. Branigan, J. T. Abrams, J. A. Whittum-Hudson, A. P. Hudson, *Med. Microbiol. Immunol.* **1998**, *187*, 23.
[155] Z. Al-Atrache, D. B. Lopez, S. T. Hingley, D. M Appelt, *BMC Neurosci.* **2019**, *20*, 6.
[156] C. S. Little, C. J. Hammond, A. MacIntyre, B. J. Balin, *Neurobiol. Aging* **2004**, *25*, 419.
[157] G. R. Riviere, K. H. Riviere, K. S Smith, *Oral Microbiol. Immunol.* **2002**, *17*, 113.
[158] S. Poole, S. K. Singhrao, L. Kesavalu, M. A. Curtis, S Crean, *J. Alzheimer's Dis.* **2013**, *36*, 665.
[159] J. Miklossy, K. Khalili, L. Gern, R. L. Ericson, P. Darekar, L. Bolle, J. Hurlimann, B. J. Paster, *J. Alzheimer's Dis.* **2005**, *6*, 639.
[160] A. R. Kamer, E. Pirraglia, W. Tsui, H. Rusinek, S. Vallabhajosula, L. Mosconi, L. Yi, P. McHugh, R. G. Craig, S. Svetcov, R. Linker, C. Shi, L. Glodzik, S. Williams, P. Corby, D. Saxena, M. J. de Leon, *Neurobiol. Aging* **2015**, *36*, 627.
[161] N. Ishida, Y. Ishihara, K. Ishida, H. Tada, Y. Funaki-Kato, M. Hagiwara, T. Ferdous, M. Abdullah, A. Mitani, M. Michikawa, K. Matsushita, *npj Aging Mech. Dis.* **2017**, *3*, 15.
[162] V. Ilievski, P. K. Zuchowska, S. J. Green, P. T. Toth, M. E. Ragozzino, K. Le, H. W. Aljewari, N. M. O'Brien-Simpson, E. C. Reynolds, K. Watanabe, *PLoS One* **2018**, *13*, 0204941.
[163] Y. Ding, J. Ren, H. Yu, W. Yu, Y Zhou, *Immun. Ageing* **2018**, *15*, 6.
[164] K. Honjo, R. van Reekum, N. Verhoeff, *Alzheimer's Dement J.* **2009**, *5*, 348.
[165] R. F. Itzhaki, W. R. Lin, D. Shang, G. K. Wilcock, B. Faragher, G. A Jamieson, *Lancet London Engl.* **1997**, *349*, 241.
[166] D. M. Cairns, N. Rouleau, R. N. Parker, K. G. Walsh, L. Gehrke, D. L Kaplan, *Sci. Adv.* **2020**, *6*, eaay8828.
[167] G. De Chiara, R. Piacentini, M. Fabiani, A. Mastrodonato, M. E. Marcocci, D. Limongi, G. Napoletani, V. Protto, P. Coluccio, I. Celestino, D. D. Li Puma, C. Grassi, A. T. Palamara, *PLoS Pathog.* **2019**, *15*, 1007617.
[168] I. Carbone, T. Lazzarotto, M. Ianni, E. Porcellini, P. Forti, E. Masliah, L. Gabrielli, F. Licastro, *Neurobiol. Aging* **2014**, *35*, 122.
[169] S. C Castle, *Clin. Infect. Dis.* **2000**, *31*, 578.
[170] S. T. Engelhart, L. Hanses-Derendorf, M. Exner, M. H Kramer, *J. Hosp. Infect.* **2005**, *60*, 46.
[171] A. Natalwala, R. Potluri, H. Uppal, R Heun, *Dement Geriatr Cogn Disord* **2008**, *26*, 499.
[172] C. Holmes, M. El-Okl, A. L. Williams, C. Cunningham, D. Wilcockson, V. H Perry, *J. Neurol. Neurosurg. Psychiatry* **2003**, *74*, 788.
[173] C. Holmes, C. Cunningham, E. Zotova, J. Woolford, C. Dean, S. Kerr, D. Culliford, V. H. Perry, *Neurology* **2009**, *73*, 768.
[174] S. L. Tyas, J. Manfreda, L. A. Strain, P. R Montgomery, *Canada Int. J. Epidemiol.* **2001**, *30*, 590.
[175] R. Verreault, D. Laurin, J. Lindsay, G De Serres, *CMAJ Can Med. Assoc. J. Assoc. Med. Can* **2001**, *165*, 1495.
[176] N. Aytan, J.-K. Choi, I. Carreras, V. Brinkmann, N. W. Kowall, B. G. Jenkins, A. Dedeoglu, *Sci. Rep.* **2016**, *6*, 24939.
[177] I. Carreras, N. Aytan, J.-K. Choi, C. M. Tognoni, N. W. Kowall, B. G. Jenkins, A. Dedeoglu, *Sci. Rep.* **2019**, *9*, 10972.
[178] L. Mao, H. Jin, M. Wang, Y. Hu, S. Chen, Q. He, J. Chang, C. Hong, Y. Zhou, D. Wang, X. Miao, Y. Li, B. Hu, *JAMA Neurol.* **2020**, *77*, 683.
[179] X. Yang, Y. Yu, J. Xu, H. Shu, J. Xia, H. Liu, Y. Wu, L. Zhang, Z. Yu, M. Fang, T. Yu, Y. Wang, S. Pan, X. Zou, S. Yuan, Y. Shang, *Lancet Respir. Med.* **2020**, *8*, 475.
[180] J. Helms, S. Kremer, H. Merdji, R. Clere-Jehl, M. Schenck, C. Kummerlen, O. Collange, C. Boulay, S. Fafi-Kremer, M. Ohana, M. Anheim, F. Meziani, *N. Engl. J. Med.* **2020**, *382*, 2268.
[181] M. Heming, X. Li, S. Räuber, A. K. Mausberg, A.-L. Börsch, M. Hartlehnert, A. Singhal, I.-N. Lu, M. Fleischer, F. Szepanowski, O. Witzke, T. Brenner, U. Dittmer, N. Yosef, C. Kleinschnitz, H. Wiendl, M. Stettner, G. Meyer zu Hörste, *Immunity* **2021**, *54*, 164.e6.
[182] A. Hampshire, W. Trender, S. R. Chamberlain, A. E. Jolly, J. E. Grant, F. Patrick, N. Mazibuko, S. C. R. Williams, J. M. Barnby, P. Hellyer, M. A. Mehta, *EClinicalMedicine* **2021**, 101044.
[183] S. R. Bornstein, K. Voit-Bak, T. Donate, R. N. Rodionov, R. R. Gainetdinov, S. Tselmin, W. Kanczkowski, G. M. Müller, M. Achleitner, J. Wang, J. Licinio, M. Bauer, A. H. Young, S. Thuret, N. Bechmann, R. Straube, *Mol. Psychiatry* **2021**, https://doi.org/10.1038/s41380-021-01148-4.

[184] B. D. Paul, M. D. Lemle, A. L. Komaroff, S. H Snyder, *Proc. Natl. Acad. Sci.* **2021**, *118*, 2024358118.
[185] M Newman, *BMJ* **2021**, n1559.
[186] A. Paniz-Mondolfi, C. Bryce, Z. Grimes, R. E. Gordon, J. Reidy, J. Lednicky, E. M. Sordillo, M. Fowkes, *J. Med. Virol.* **2020**, *92*, 699.
[187] L. Bauer, B. Lendemeijer, L. Leijten, C. W. E. Embregts, B. Rockx, S. A. Kushner, F. M. S. de Vrij, D. van Riel, mSphere [Internet], **2021**, *6*, https://journals.asm.org/doi/10.1128/mSphere.00270-21, (accessed: September 2021).
[188] M. G. Andrews, T. Mukhtar, U. C. Eze, C. R. Simoneau, Y. Perez, M. A. Mostajo-Radji, S. Wang, D. Velmeshev, J. Salma, G. R. Kumar, A. A. Pollen, E. E. Crouch, M. Ott, A. R. Kriegstein, *Neuroscience* **2021**, http://biorxiv.org/lookup/doi/10.1101/2021.01.17.427024.
[189] J. F. Fullard, H.-C. Lee, G. Voloudakis, S. Suo, B. Javidfar, Z. Shao, C. Peter, W. Zhang, S. Jiang, A. Corvelo, H. Wargnier, E. Woodoff-Leith, D. P. Purohit, S. Ahuja, N. M. Tsankova, N. Jette, G. E. Hoffman, S. Akbarian, M. Fowkes, J. F. Crary, G.-C. Yuan, P. Roussos, *Genome Med.* **2021**, *13*, 118.
[190] A. C. Yang, F. Kern, P. M. Losada, M. R. Agam, C. A. Maat, G. P. Schmartz, T. Fehlmann, J. A. Stein, N. Schaum, D. P. Lee, K. Calcuttawala, R. T. Vest, D. Berdnik, N. Lu, O. Hahn, D. Gate, M. Windy McNerney, D. Channappa, I. Cobos, N. Ludwig, W. J. Schulz-Schaeffer, A. Keller, T. Wyss-Coray, *Nature* **2021**, *595*, 565.
[191] M.-H. Lee, D. P. Perl, G. Nair, W. Li, D. Maric, H. Murray, S. J. Dodd, A. P. Koretsky, J. A. Watts, V. Cheung, E. Masliah, I. Horkayne-Szakaly, R. Jones, M. N. Stram, J. Moncur, M. Hefti, R. D. Folkerth, A. Nath, *N. Engl. J. Med.* **2021**, *384*, 481.
[192] M. S. Woo, J. Malsy, J. Pöttgen, S. Seddiq Zai, F. Ufer, A. Hadjilaou, S. Schmiedel, M. M. Addo, C. Gerloff, C. Heesen, J. Schulze Zur Wiesch, M. A. Friese, *Brain Commun.* **2020**, *2*, fcaa205.
[193] N. Dunn, M. Mullee, V. H. Perry, C Holmes, *Alzheimer's Dis. Assoc. Disord.* **2005**, *19*, 91.

**Róisín McManus** obtained her Ph.D. from Trinity College Dublin, Ireland, in 2015 and is now a senior postdoctoral scientist at the German Center for Neurodegenerative Diseases (DZNE) in Bonn, Germany. With over 12 years of research experience in the field of neuroimmunology, her long-term interest is in the consequences of neuroinflammation during aging and Alzheimer's disease. Her current research uses preclinical models to unravel the novel pathways under the control of the NLRP3 inflammasome that contributes to the progression of dementia and Alzheimer's disease and importantly addresses how these mechanisms can be targeted therapeutically.