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REVIEW

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Systemic and Central Immunity in Alzheimer's Disease: Therapeutic Implications

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SUMMARY

Clinical pharmaceutical trials aimed at modulating the immune system in Alzheimer's Disease have largely focused on either dampening down central proinflammatory innate immunity or have manipulated adaptive immunity to facilitate the removal of centrally deposited beta amyloid. To date, these trials have had mixed clinical therapeutic effects. However, a number of clinical studies have demonstrated disturbances of both systemic and central innate immunity in Alzheimer's Disease and attention has been drawn to the close communication pathways between central and systemic immunity. This paper highlights the need to take into account the potential systemic effects of drugs aimed at modulating central immunity and the possibility of developing novel therapeutic approaches based on the manipulation of systemic immunity and its communication with the central nervous system.

Introduction

In the past the parenchyma of the central nervous system (CNS) was considered an "immunologically privileged site" because the blood brain barrier (BBB) was thought to prevent the entry, or exit, of many molecules including antibodies from the periphery and to be devoid of macrophages and lymphocytes. However, it is clear that even in the presence of an intact BBB the CNS is capable of mounting inflammatory responses, albeit atypical, in response to tissue injury and infection [1].

Many aspects of innate immunity have been detected in the CNS and many cell types specific to the CNS, including microglial cells and astrocytes, are capable of performing these roles.

In the brain, microglia cells are considered "the CNS professional macrophages" [2]. Indeed microglial cells are, in essence, brain macrophages that entered the brain during embryogenesis [3] and like macrophages, they appear to survey their local environment looking for tissue damage or evidence of infection [4]. In the CNS microglial cells are largely downregulated with low or undetectable expression of cell surface antigens such as Major Histocompatability (MHC) class I and II molecules [5]. However, following an acute insult, such as a head injury or a CNS infection, resident microglia, like tissue macrophages, transform from their normal quiescent state to a morphologically different activation state that is characterized by the production of proinflammatory cytokines, such as Interleukin-1 (IL-1), Interleukin-6 (IL-6) and Tumour necrosis factor α (TNFα) and an upregulation or *de novo* synthesis of cell surface receptors or cytoplasmic antigens [6]. This involves a wide variety of receptors[7] but includes advanced glycoslyated end products (RAGE), the peripheral benzodiazepine receptor [8,9] and toll-like receptors (TLRs) with emerging data highlighting the importance of the TLRs in the regulation of the innate immune response [10]. This upregulation is tightly regulated at the translational level by antiinflammatory molecules such as Transforming growth factor 1β (TGF-1β) and Interleukin-10 (IL-10) [11] and also by interactions with neuronal cells. Thus, neurons are known to express ligands, for example CD200, that interact with receptors, for example CD200R, on the surface of microglia to generate a downregulated phenotype [3,12].

Astrocytes, unlike macrophages, are ectodermally derived. Their role in mediating CNS inflammation has been relatively neglected but they also have an important role in innate immunity, including cytokine production, complement and antigen presenting cell properties. In addition, because of their location in close contact with CNS resident cells and blood vessels they can also act to modify BBB permeability and thus support an adaptive immune response [13].

Adaptive immunity is not thought to be as important as innate immunity in the CNS. Thus, microglial cells are poor antigen presenting cells [14]. Lymphocytes are also not found in large numbers in the normal CNS and although activated T helper cells (T_H)

are able to enter the CNS those that fail to encounter antigen leave within 1–2 days of entry [15]. There are also few reports of B lymphocytes entering the normal CNS [16].

The Immune System in Alzheimer's Disease

The Systemic Immune System

Cross sectional studies have been variable in terms of establishing differences in serum or plasma markers of innate immunity between Alzheimer's Disease (AD) populations and age matched control groups. Some studies have found increases in plasma markers of pro-inflammatory cytokines (principally TNFα or IL6) in AD compared with controls [17–24] others have found no or mixed differences [25,26] and yet others reduced levels [27,28].

More consistent have been a number of studies that have suggested an association between peripheral blood indicators of systemic inflammation and the subsequent development of AD. Thus, inflammatory proteins in plasma, notably C reactive protein (CRP) and IL-6, have been found to be elevated 5 years before the clinical onset of dementia in a number of studies [29–31]. Indeed, one long-term follow-up study has suggested that a raised CRP is associated with a 3-fold increased risk of developing AD up to 25 years later [32]. However, care needs to be taken when interpreting systemic immune markers and their relationship with AD. Differences between plasma or serum markers of inflammation (e.g., serum CRP or cytokine concentrations) between an AD and a control group is likely to be subject to a plethora of other factors that will either exaggerate or conceal differences between these groups. Thus, there is a need to correct for established confounders, for example, medications (e.g., cholinesterase inhibitors) as well as other factors (time of sampling) that may alter peripheral markers of inflammation but which cannot be considered to be risk factors for the development of AD. However, and equally important, correcting for some established risk factors for AD (e.g., diabetes, obesity, atherosclerosis, vascular disease) may underestimate the role of systemic inflammation as a risk factor for the development of AD. An additional complication is that a number of comorbid inflammatory conditions may be difficult to detect or be largely asymptomatic (e.g., periodontitis; soft tissue injury).

An approach that helps to reduce variability due to uncontrollable environmental inflammatory trigger factors is to examine the ability of whole blood or peripheral blood mononuclear cells (PBMCs) to produce cytokines following a nonspecific mitogen, such as lipopolysaccharide (LPS) and phytohaemagglutinin (PHA) challenge. This, in effect, is a measure of an individual's intrinsic cytokine producing ability following a controlled stimulus. Using this approach a number of cross sectional studies [33–35] have shown an increase in the intrinsic production of proinflammatory cytokines in AD subjects compared with controls; although not all [36]. More recently, a prospective study [37] suggested that cognitively intact individuals in the top tertile of PBMC TNFα (or IL-1β) production have an approximately three times increased risk of developing AD compared with those in the lowest tertile.

The role of systemic adaptive immunity in the development or natural progression of AD has been underexplored and studies so far have produced mixed findings. Thus, whilst some comparisons of plasma samples in AD and control subjects have shown some evidence for an increase in antibody titres to beta amyloid (Aβ) in AD compared to control subjects [38,39] other studies have no significant increases or even decreases [40,41] with other studies [42] suggesting that serum antibodies for oligomeric preparations of Aβ1–42 decline with advancing AD.

The Central Immune System

Cerebrospinal Fluid

In theory because cerebrospinal fluid (CSF) bathes the brain and exchanges with the extracellular fluid it should contain molecules produced by neurones, astrocytes and microglia, and could therefore provide an indication of how these cells are altered in AD. However, peripheral biomarkers of inflammation may also gain access from the bloodstream and so they may not be specific for neuroinflammation. In addition, the action of inflammatory signals in the brain may be very localized and short lived without extensive diffusion into the CSF and so their absence cannot be equated with a lack of effect. Many studies have measured CSF levels of cytokines and other inflammatory markers in AD. Some studies [43,44] have shown evidence of increases in proinflammatory cytokines including IL-1β; IL-6 and TNFα in AD compared with control subjects. However, other studies [45,46] have found no significant differences.

Post Mortem Brain Studies

Disturbances of brain innate immunity in AD has been extensively reviewed elsewhere [10,47]. Direct antibody-independent activation of the alternative complement pathway by fibrillar Aβ [48] and decoration of dystrophic neurites with membrane attack complexes (MAC) [49] has been shown. ApoJ (clusterin), a complement defense protein, shows increases in the AD brain and is associated with senile plaques, possibly reflecting the need to protect against ongoing complement activation [50]. Furthermore, expression of class II MHC is increased on the surface of microglia cells in AD compared with control brain tissue [51]. Microglia aggregate more around amyloid-containing neuritic plaques than diffuse plaques in AD [52] and many different laboratories have shown that microglia, both *in vivo* and in culture, phagocytose exogenous fibrillar Aβ [53]. These interactions are modulated in part by TLR2, TLR4 and TLR9 [54–56] suggesting that the expression of these innate immune receptors might be a mechanism to prevent the accumulation of Aβ in the CNS that may be impaired in AD [10]. Indeed, it has been suggested that Aβ may be interpreted as an invading pathogen since bacteria produce similar amyloidogenic aggregates on their cell surface [7,57]. However, although phagocytosis of Aβ has generally been considered beneficial, there is also the possibility that this process may be harmful. Phagocytosis by peripheral macrophages is accompanied by the release of cytotoxic compounds. Moreover, phagocytosis by brain-derived macrophages in culture results in the release of potentially destructive reactive oxygen species [58], reactive nitrogen species [59], and TNF-α [60]. Interestingly, recent research has suggested

that Aβ, rather than being an inadvertent instigator of the innate immune reponse, might be acting as a bacteriocidal agent [61]. Thus, the accumulation of Aβ with age might represent a physiological defense reaction to infectious organisms.

Evidence for increased proinflammatory cytokines in AD brain has largely focused on studies of IL-1 with relatively few studies examining or showing elevation of IL-6 or TNFα levels [62]. IL-1 has been to shown to be over-expressed within cortical regions of the AD brain, as shown by elevated brain tissue IL-1 concentrations and by increased numbers of IL-1 immunoreactive microglia associated with AD plaques [63,64]. IL-1 overexpression also seems to occur early in plaque evolution. It is, for example, already evident in diffuse, non-neuritic Aβ deposits, and can be observed in autopsied brain samples from children with Down's syndrome [64]. Notably, IL-1 promotes the synthesis [65] of amyloid precursor protein (APP) and may therefore promote further amyloid production and deposition in plaques. Thus, IL-1 has been proposed to be the initiator of a cascade of self-perpetuating events resulting in the genesis and progression of neurodegeneration in AD [66]. However, it is important to note that the elevations of proinflammatory cytokines, where found in AD, are small compared with what might occur following a direct microbial challenge. As stated earlier this is likely to reflect the tight control of inflammation within the CNS by antiinflammatory molecules such as TGF-β1 [67].

The role of adaptive immunity within the CNS of AD subjects has received even less attention than the peripheral immune system. However, one recent study [68] of AD brain tissue suggests that the majority of neuritic plaques in AD brain tissue are decorated by IgG and have a corresponding increase in associated phagocytic microglia.

Brain Imaging Studies

The demonstration that the peripheral benzodiazepine receptor is upregulated in activated microglia [9] has led to the development of a ligand [11C](R)PK11195 that can be used to label these cells in the living brain using positron emission tomography (PET) [8]. In patients with AD, initial studies suggest that the signal from [11C](R)PK11195 binding to activated microglia correlates inversely with cognitive function [69]. Furthermore, as cognitive function declines over time the [11C](R)PK11195 signal increases without a change in the signal from a ligand detecting amyloid ([11C]PIB), consistent with the view that microglia are contributing to neuronal dysfunction.

Interactions Between Systemic and CNS Inflammation in AD

It is important to recognize that even in the face of an intact BBB the periphery and the CNS communicate inflammatory signals to one another. During a systemic infection a range of behaviors occur including lethargy, apathy, decreased social interaction, and poor concentration. These centrally derived behaviors are known collectively as "sickness behavior" and are not merely unpleasant side effects of infection; together they form an important, evolutionary conserved, homeostatic mechanism that allows the body to adapt to the infection or injury [70]. Four major routes of communication from the periphery have been proposed, all of which lead to the synthesis of cytokines and inflammatory mediators in the brain. First, inflammatory events in the thoracic and abdominal cavities are signaled to the brain through vagal-nerve sensory afferents, and in turn the vagal efferent outflow modifies these inflammatory events through acetylcholine secretion [71]. Second, circulating cytokines and other inflammatory mediators, for example, pathogen-associated molecular patterns (PAMPS) enter the blood and communicate directly with perivascular macrophages and other cells in the circumventricular organs, that lack a BBB, initiating the transcription of proinflammatory cytokines across the brain parenchyma [10]. Third, cytokines and other inflammatory mediators [72] interact with the induction of lipid mediators (e.g., prostaglandin E2) that communicate directly across the BBB [73]. Fourth, there may be direct entry of immune cells (monocytes and possibly bone marrow-derived microglial cells) from the periphery into the brain [74,75].

While communication between the systemic and central immune system can occur in the presence of an intact BBB, in AD there is also evidence for a breakdown in BBB permeability [76]. Increased permeability may be because of associated vascular pathology but may also be due to the degeneration of neurones and activation of glial cells causing changes to endothelial cell phenotype and transport properties [77].

Aetiological Considerations for Defective Immunity in AD

Genetics

In a small number of individuals, less than 0.1% of the total AD population, mutations in one of three genes, Presenilin 1, Presenilin 2 and APP or a duplication of the APP gene [78,79] are directly responsible for the development of largely early onset AD by altering APP processing so that Aβ deposition is greatly enhanced [80]. However, a majority (95%) of the cases of AD have an exponential growth in incidence after 65 years of age and are of late onset [81]. Until recently, the only established genetic risk factor for the development of late onset AD was Apolipoprotein (ApoE) e4. ApoE e4 influences the degree of activation and neurotoxin production of microglia cells to Aβ [82] and is also a risk factor in other chronic neurodegenerative conditions including Parkinson's disease that do not have Aβ plaques as a feature [83]. ApoE e4 phenotype may influence outcomes for a number of CNS and systemic infections [84–86] and, more recently, has been shown to be associated with an attenuation of the peripheral blood levels of CRP in nondemented subjects [87,88]. In addition, a large number of other genetic polymorphisms in proinflammatory genes, either alone or in association with ApoE e4, have also been implicated as risk factors for the development of AD. These include IL-1 [89]; IL-6 [90]; TNF-α [91–93] and α1-antichymotrypsin [94]. These findings have not, however, always been replicated, possibly due to the small individual effect size of these polymorphisms. However, more recently, two large-scale genome-wide association studies have been performed that have put the direct role of genetic variation in innate immunity on a clearer footing. These

two studies [95,96] both suggest that genes with important roles in immunity are genetic risk factors for the development of late onset AD. Both studies thus identified ApoJ and complement receptor 1 (CR1) the gene that encodes for the main receptor of the complement C3b protein. Further support for the increased expression of innate pro-inflammatory cytokine profiles in relatives of AD subjects has also been shown elsewhere [97].

Environmental Factors

In late onset AD, twin studies suggest a heritability of approximately 60% [98] with non-shared environmental risk factors playing an increasingly important role in the etiology of the disease with increasing age [99]. Research on the role of environmental infectious agents in the etiology of AD has largely followed the hypothesis that there are specific CNS pathogens (in an analogous fashion to established pathogens in other chronic neurodegenerative diseases, for example, Human Immunodeficiency Virus dementia or Creutzeld Jacob Disease) that have a direct influence on the pathogenesis of AD. Thus, Herpes simplex virus type 1, Chlamydophila pneumoniae and Borrelia burgdorferi have all been proposed as potential pathogens contributing to AD development. Each of these different pathogens have their own protagonists but there is a general paucity of consistent experimental evidence [100]. However, a wide variety of common systemic infections are a major cause of delirium in the elderly and delirium has been shown in a number of studies to be associated with an increased risk of developing dementia. Thus, in one study this increased risk was substantial with a cumulative incidence of 55% for the subsequent development of dementia in cognitively intact individuals after 1-year follow-up [101]. In addition, the risk of developing AD is also increased following the development of an infection in the absence of an obvious delirium. Thus, in a retrospective general practitioner database the presence of one or more infections over a 5-year follow-up period increased the odds of developing AD by around 2-fold. Risk increased with increasing age a finding that is consistent with the known decline of genetic risk with increasing age [102]. Other chronic inflammatory diseases, for example, depression [103], atherosclerosis [104], and obesity [105] have a clearer epidemiological basis for being proposed to be risk factors in the development of AD. For all of these risk factors the individual attributable risk is likely to be small [81,103,106]. However, their combined cumulative effects over time might be considerable. Thus, it is known that the accumulation of acute and chronic inflammatory events bombarding the immune system throughout life is accompanied by an age-dependent upregulation of the inflammatory response [107]. This suggests that increasing age, the biggest risk factor for the development of AD, could be considered to be a proxy for increased time of exposure to systemic inflammation.

We have hypothesized that the exposure of partially activated or "primed" microglial cells (arising from their chronic exposure to amyloid or degenerating neurones) to recurrent acute and chronic proinflammatory systemic signals, through one of the proposed communicating channels between the systemic and central innate immune system, may lead to a switch in phenotype and the production of a central proinflammatory cytokine profile that may act as a potent driver of neuronal degeneration [108]. A number of animal studies support this hypothesis [109,110]. In addition, we have recently shown that in AD subjects high serum levels of TNFα at baseline (top three quartiles compared with bottom quartile) and increases in serum TNFα associated with intermittent systemic infections are associated with a marked increase in the rate of cognitive decline in AD subjects over a 6-month period that is independent of the acute effects of delirium [111].

Therapeutic Strategies

Clinical pharmaceutical trials aimed at modulating the immune system in AD have largely focused on either dampening down central proinflammatory innate immunity or have manipulated adaptive immunity to facilitate the removal of centrally deposited beta amyloid. More recently, the possibility of developing novel therapeutic approaches based on the manipulation of systemic immunity and its communication with the CNS have been proposed.

Modulation of Central Innate Immunity

A number of existing drugs thought to have central modulatory effects have been examined as possible therapeutic targets in the treatment or development of AD. These include nonsteroidal anti-inflammatory drugs (NSAIDS), PPAR-γ agonists, statins, thalidomide, TNFα inhibitors, and other agents (Table 1).

NSAIDS

The incidence of AD in cohorts of older people taking NSAIDS has been examined in several large prospective studies [112]. The largest of these studies, the Baltimore Longitudinal study of Ageing, found a relative risk of AD of 0.35 for 10 years of NSAID use [113]. Case-control studies also suggest a reduced odds of developing AD in people taking NSAIDS regularly for long periods. Thus, a meta-analysis of the case-control studies carried out up to 1996 found that regular NSAID use was associated with a 2-fold reduction in the odds of developing AD (OR = 0.5; $P = 0.0002$) [114] and, furthermore, the largest case control study to date (49,349 cases and 196,850 matched controls) [115] showed a significant effect of NSAIDS after 5 years of regular use, with a combined OR of 0.76 (0.68–0.85).

There is notably some epidemiological evidence that the protective effect of NSAIDS is only found in ApoE e4 allele carriers. In the Cache County cohort NSAIDS were found to slow rates of cognitive decline in ApoE e4 allele carriers only [116] and a large prospective trial showed that NSAIDS reduced the risk of developing AD, but again only in e4 allele carriers [117].

Several clinical trials of NSAIDS have now been completed. A meta-analysis of three early trials of NSAIDS in patients with AD revealed no significant improvement in rates of cognitive decline [118]. Of these studies only one small study of indomethacin showed any significant benefit [119]. More recently a clinical trial of ibuprofen, while showing no significant effect overall, found some improvement in the rate of cognitive decline in a subgroup analysis of patients that were ApoE e4 allele carriers [120].

Table 1 Antiinflammatory agents for AD

Potential mechanisms of action	Clinical studies
NSAIDS COX inhibition causing reduced prostaglandin synthesis In vitro/animal models: Effects on amyloid pathways [47] PPAR-γ activation [195]	**Prevention:** Case-control/cohort studies: Modest reduction in risk [114, 115], greater risk reduction in ApoE e4 carriers [117] Clinical prevention trials: Overall no significant risk reduction[122] **Treatment:** Overall no significant benefit [118] COX2 inhibitors: No benefit [112] Some evidence of ibuprofen benefit in ApoE e4 carriers [120]
PPAR-γ agonists Decreased microglial activation in mouse model [128] Reduced COX-2 and iNOS expression [129]	**Treatment:** Overall no significant benefit [132]
RAGE Inhibitors Reduced generation of reactive oxygen species in response to Aβ [134,135] Reduced Aβ load in a mouse model [136]	**Treatment:** Phase II Study (n = 67): well tolerated, not powered to show treatment effect [137]
Statins Reduced Aβ-induced inflammation [140] Decreased lymphocyte traffic between CNS and periphery [141] Modulation of APP processing [139]	**Prevention:** Cochrane review of prevention trials revealed no significant risk reduction [142] **Treatment:** No evidence of benefit in meta-analysis of clinical treatment trials [143]
Thalidomide Reduced TNF-α levels and neurodegeneration in response to Aβ (mouse model) [148] Reduced reactive gliosis and inflammatory vascular pathology in response to Aβ (mouse model) [149]	**Treatment:** Phase II pilot study (n = 12): Too small to show changes in behaviour or cognition [150]
TNF-α Antagonists Reduced CNS inflammation [152] Intra-cerebral injection: reduced amyloid-associated neuropathology in 3xTgAD mice [152] Peripheral injection: Reduced behavioural deficits in PDAPP mouse model [190]	**Treatment:** Peripheral injection: Phase II pilot study (n = 9): Well tolerated, too small to show clinical benefit [189] Perispinal injection: Open-label, no control group, n = 15: improved cognitive scores in some subjects [153]
Omega-3 Fatty Acids Found in fish oils Reduced arachidonic acid metabolites Prevents oxidative damage in mouse model [196]. Several other putative neuro-protective and anti-amyloid effects [197].	**Prevention:** Epidemiological evidence that low levels of Omega-3 increase risk of AD [197]. **Treatment:** A preliminary study (n = 35) found some improvement in Clinician's Interview-Based Impression of Change Scale (CIBIC-plus) over the 24 week follow-up ($P = 0.008$) but no change in formal cognitive scores [198]. On-going trials
Curcumin The yellow pigment in turmeric. Possible effects on innate immunity resulting in less oxidative damage and increased amyloid clearance [199]. Decreases LPS-stimulated IL-1β and iNOS in a mouse model of AD [200].	**Treatment:** Exploratory trial (n = 30) showed no effect on cognition over 6 months [201]. On-going trials
Sodium valproate Short chain branched fatty acid, commonly used as an anticonvulsant, with antiinflammatory and neuroprotective effects [202]. Decreases LPS-induced microglia activation [203], although chronic use causes increased microglia activation [204].	**Treatment:** Anecdotal use for agitation in advanced dementia, but no clear evidence of benefit, and one Canadian trial showed worsening [205]. National Institute for Ageing (NIA) clinical trial is on-going (VALID study)

Table 1 Continued

Potential mechanisms of action	Clinical studies
Antibiotics Mutliple studies showing evidence for possible role of infective agents in AD [100].	**Treatment:** A trial of doxycycline and rifampicin in AD patients showed improved cognitive scores, despite no effect on Chlamydia burden [206]. A trial of Helicobacter pylori eradication showed improved cognitive scores at 2 years [207].
Cholinesterase inhibitors Commonly used symptomatic drugs in AD – may have antiinflammatory modes of action in addition to effects on cholinergic neurotransmission. Decrease Aβ-induced microglia activation [208]. Alpha-7 nicotinic receptor agonists prevent LPS-induced microglia activation [209].	**Treatment:** Good evidence of symptomatic benefit [210]. Possibility that some of the efficacy is due to anti-inflammatory effects regulated by alpha-7 nicotinic receptors [209].

A potentially pivotal primary prevention study (ADAPT) using either naproxen, celecoxib or placebo in nondemented people with a family history of AD trial was unfortunately stopped at 2 years because of fears about the cardiovascular risks of celecoxib [109]. Early reports suggested no benefit for naproxen after 2 years of treatment but more recently a 4-year follow-up study of the ADAPT cohort showed a significant protection effect for naproxen [121].

Trials using COX-2 specific NSAIDS have not shown any benefit in AD patients or in mild cognitive impairment [112] and primary prevention studies have also been negative. Indeed, in the ADAPT study the evidence gathered prior to the premature cessation of the trial revealed a worsening risk for the celecoxib arm [122] and another primary prevention study with rofecoxib was also negative [123].

A number of explanations have been put forward to explain these mixed clinical findings.

First, any central antiinflammatory effect of NSAIDS assumes that NSAIDS cross the BBB. However, penetration of NSAIDS into the brain is generally low; levels in the CSF are only 1–2% of the plasma levels required for a therapeutic effect in humans [124]. Ibuprofen and indomethacin, which interestingly show the most evidence for benefit in epidemiological studies, are the most lipophilic NSAIDS and are therefore likely to cross the blood-brain barrier more easily than other NSAIDS. Second, while the major antiinflammatory effects of NSAIDS is thought to be mediated through the inhibition of prostaglandins, a number of studies show that cerebral inflammation in AD is characterized by microglia activation, IL-1 and complement, rather than by elevated prostaglandin levels or increased COX expression [125]. Thus, while, elevated levels of prostaglandin E_2 (PGE_2) are found in the CSF of patients with AD [126], these elevated CSF PGE_2 levels decrease in AD patients as the severity of dementia increases [127]. Thus, any benefit that NSAIDS may have in AD because of a reduction in cerebral prostaglandin levels would be anticipated to reduce as the disease progressed and PGE_2 levels fell. Third, it may be that NSAIDS will only be effective if started early enough in the disease course. Hence the positive findings in the epidemiological, case control and long-term intervention studies may be a result of early disease intervention.

PPAR-γ Agonists

In addition to the use of NSAIDS other more specific agents aimed at stimulating PPAR-γ have been investigated. Rosiglitazone, a PPAR-γ agonist, is commonly used in diabetes and has been shown to reduce microglia activation in mouse models and reduce expression of COX-2 and iNOS [128,129]. In animal models rosiglitazone has been shown to improve learning and memory [130]. These encouraging findings led to a preliminary study in AD subjects ($N = 30$) that showed suggestions of improvements in memory and cognition [131]. This was followed by a large scale ($N = 511$) 6-month clinical trial in patients with mild-to-moderate AD patients [132]. No statistically significant differences on primary end points of cognition and global impression of change were detected overall between placebo and rosiglitazone although exploratory analyses suggested that ApoE e4 noncarriers exhibited cognitive and functional improvement in response to rosiglitazone, whereas ApoE e4 carriers showed no improvement and even some decline. These genetic findings are contrary to the findings with NSAIDS and clearly require confirmation.

RAGE Inhibitors

This area has been recently extensively reviewed elsewhere [133]. RAGE acts as a receptor for Aβ on neurons, microglia and astrocytes and increased expression of RAGE is observed in regions of the brain affected by Alzheimer's disease (AD)[134]. Interaction between Aβ and RAGE leads to cell stress with the generation of reactive oxygen species [135] and so therapeutic strategies aimed at reducing this interaction are an attractive therapeutic target. Interception of Aβ interaction with RAGE, by infusion of soluble RAGE, decreases Aβ content and amyloid load, as well as improving learning/memory and synaptic function, in a murine transgenic model of Aβ accumulation [136]. Thus, this data suggests that RAGE may be a therapeutic target for AD. A phase II study of a RAGE antagonist in 67 AD subjects has been reported as being well tolerated [137].

Statins

There has been considerable interest in statin therapy as a potential preventative or symptomatic treatment for AD [138]. Cholesterol modulates APP processing in cell culture and animal models and has been implicated in the production of Aβ [139]. However, statins also have various effects on the immune system that appear independent of any effect on cholesterol metabolism. Thus, inflammation stimulated by Aβ is reduced by statin therapy [140] and therapy also results in decreased lymphocyte trafficking from the periphery to the CNS [141].

Unfortunately, the clinical effects of statins are largely negative. Thus, while retrospective case-control studies indicated large reductions in AD risk among statin users, prospective studies have failed to find evidence of benefit. A Cochrane review of randomized, double-blind, placebo-controlled studies aimed at preventing AD concluded that there was no significant risk reduction [142]. A meta-analysis of trials that used statins as a treatment for existing AD also found no evidence of benefit [143].

Statin therapy does not therefore appear to be of any benefit in AD. This may in part be due to the short half life and high liver metabolism of most statins [144] or to the differing solubility of statins in lipids or water. Lipophilic statins (lovastatin, cerivistatin, simvastatin) cross the BBB and penetrate cell membranes more effectively and thus may be more efficient in the treatment of AD than the hydrophilic statins (atorvastatin, fluvastatin, pravastatin) [138]. However, cholesterol is necessary for synaptogenesis and neural homeostasis and so cholesterol reduction may have detrimental effects on neuronal survival during chronic neurodegenerative stress [145]. The antiinflammatory effect of statins may simply not be robust enough to prevent damaging inflammation. In this regard it is notable that statins may have too small an effect on Aβ burden to prevent inflammation in the brain [146]. It is also notable that there are conflicting reports about the effects of statins on the production of pro-inflammatory cytokines. Thus, one group has found reduced expression of inflammatory markers, including TNFα and Nitric Oxide [141], while another group has found evidence of activated microglia and increased TNFα expression [147].

Thalidomide

Thalidomide was first used in the late 1950s as an antiemetic. Despite its teratogenic effects there has been renewed interest in the powerful antiinflammatory effects of thalidomide in recent years and it is now used to treat inflammation in specific conditions such as multiple myeloma and erythema nodosum leprosum. One action of thalidomide is to decrease the stability of TNF-α mRNA [148]. Thalidomide has therefore been used in animal models to assess the effect of reduced TNF-α on neurodegeneration.

Intracerebral injection of Aβ causes up-regulation of mRNA for TNF-α and inducible nitric oxide synthase (iNOS), and subsequent neurodegeneration and behavioral change in mice. Thalidomide treatment in this animal model reduced TNF-α and prevented neurodegeneration [148]. Furthermore, Aβ-induced neurodegeneration is not seen in TNF-α (–/–) knock-out mice, supporting the hypothesis that neurodegeneration is dependent on TNF-α [148]. Thalidomide was also neuroprotective in another animal model of the inflamed AD brain, with reduced gliosis and vascular pathology and reduced levels of TNF-α [149].

There is only one small pilot study (n = 12) of thalidomide in patients with AD [150]. The trial was too small to show any change in behavior or cognition, although there was a nonsignificant trend toward lower serum levels of TNF-α. Thus, thalidomide reduces the activity of TNF-α and this may be neuroprotective in AD, but this hypothesis has not been properly tested in patients.

TNF-α Inhibition

Work in animal models has lent support to the hypothesis that reducing TNF-α levels will reduce neurodegeneration in AD. In an acute model of neuroinflammation, initiated by intracerebral injection of Aβ, an intracerebral injection of an anti-TNF-α antibody prevented the nitration of proteins in the hippocampus and the impairment of recognition memory induced by Aβ [148]. In a chronic systemic inflammation model in the 3xTgAD mouse model [151] chronic inhibition of soluble TNF signaling, using specifically engineered antibodies delivered intracerebrally, prevented amyloid-associated neuropathology in 3xTgAD mice and reduced the deposition of intraneuronal amyloid species [152]. Etanercept has also been given as a perispinal injection to a small number of patients with AD [153,154]. Cognitive scores has been reported as improved after administration of etanercept, but no control group was used in this open-label study and the number of subjects was low (n = 15).

Other Agents

There are several other anti-inflammatory agents currently under investigation (see Table 1).

Modulation of Adaptive Immunity

In the amyloid cascade hypothesis for the pathogenesis of AD amyloid deposition in the brain is thought to be the initiating step, with subsequent inflammation, tau hyperphosphorylation and eventually neurodegeneration [80]. It follows that removal of amyloid and prevention of further amyloid deposition would be beneficial. Schenk and colleagues developed an anti-amyloid vaccine to test the hypothesis that immune-mediated removal of amyloid from the brain would reduce neurodegeneration. Systemic vaccination of transgenic mice that overexpressed human APP with Aβ_{1-42} produced high titres of antibodies directed against Aβ and reduced central Aβ deposition [155]. In a separate experiment, passive immunization with monoclonal antibodies to Aβ similarly reduced cerebral amyloid deposits implying that the beneficial effects of the vaccine were due to the generation of Aβ-specific antibodies [156].

Aβ-specific antibodies could reduce cerebral amyloid load in several ways. Opsonization of amyloid deposits by specific IgG antibodies allows phagocytosis by microglia [156]. Antiamyloid antibodies may directly bind to and dissolve amyloid deposits [157], with the resulting soluble oligomers being removed via the blood

stream [158]. Binding and sequestration of soluble amyloid species in the blood may provide a "peripheral sink" that draws soluble amyloid out of the brain parenchyma [159]. Antibodies may also prevent the toxic effects of soluble oligomers by binding them and preventing toxic interactions [160].

The success of the initial mouse vaccine studies led to human trials of AN1792, an antiamyloid vaccine, in 2001. Eighty patients were enrolled in the initial phase I trial. Fifty-three percent of the immunized participants developed detectable antibodies to Aβ [161]. The vaccine was altered slightly by the addition of the emulsifier polysorbate 80 and the subsequent larger phase II trial enrolled 372 patients [162]. This trial was halted after 18 out of 298 (6%) immunized patients developed symptoms of meningoencephalitis [163]. In the full analysis of the trial data, including the placebo group, there was no therapeutic effect on cognitive decline [162].

Post mortem examination of the vaccine-treated patients in the initial phase I trial revealed extensive plaque clearance from the cerebral cortex [164,165]. Microglia contained Aβ particles, implying phagocytosis as the method of clearance [165] and furthermore, the degree of plaque removal was associated with mean antibody response [166]. However, although postmortem examination of AN1792-treated patients showed sustained and significant reductions in amyloid deposits within the brain, there were, however, no long-term beneficial therapeutic effects. Thus, even immunized patients with almost complete plaque removal had severe end stage dementia at death, with no reduction in the time until severe dementia or survival time [166].

Antibody production by B-cell lymphocytes in response to vaccination is facilitated by Th2 helper T-cells. Animal models show that vaccination with Aβ_{1-42} produces a Th2 response that encourages B-cells to produce anti-Aβ antibodies [167]. However, postmortem examination of the patients enrolled in the AN1792 trial showed that some patients had evidence of a proinflammatory Th1 T-cell reaction around some cerebral blood vessels [164,165]. The T-cell response to the vaccine in humans was further examined in experiments using peripheral blood mononuclear cells (PBMCs) taken from immunized patients [167]. PBMCs from many participants produced IL-2 and IFNγ in response to challenge with Aβ, indicating a Th1 response. This excessive Th1-mediated response in some patients, possibly associated with the choice of adjuvant in the AN1792 trial, may have been the cause of the severe meningo-encephalitis seen in some patients [168].

The failure of the AN1792 vaccine has led to further work in mouse models with redesigned vaccines. These vaccines have been designed to reduce the risk of stimulating Th1 lymphocytes and to encourage a purely humoral immune response mediated by Th2 cells. Aβ_{1-42} is thought to have one major antibody binding site at the N-terminus and two major T-cell epitopes located at the central and C-terminal hydrophobic regions [160]. Newer vaccines, therefore, consist of short Aβ species containing the N-terminus region of Aβ_{1-42} with the T-cell epitopes either altered or deleted altogether [169]. Other groups are working on vaccines using adjuvants less likely to elicit a cytotoxic Th2 response. A predominantly humoral antibody response can also be achieved by altering the route of administration of a vaccine, for example, mucosal or transdermal [170–173]. DNA vaccines, which allow precise control of the immune reaction to the vaccine and have the advantage of not requiring adjuvants with unpredictable immune consequences, are also in development in animal models [174]. A DNA vaccine containing three copies of the Aβ B-cell epitope, a chemokine (MDC/CCL22) and a Th2-cell epitope to help drive a Th2 response, reduces AD pathology in a transgenic mouse model [175].

Even where the primary response to vaccination is antibody production rather than Th1-mediated inflammation there may be less desirable innate immune consequences. In a microglial cell culture model opsonization of amyloid with anti-Aβ IgG increased microglial chemotaxis and phagocytosis of the Aβ [176]. However, the phagocytosis was also associated with secretion of TNFα and IL-6 from microglial cells. Interestingly the authors found that the NSAID indomethacin reduced TNFα and IL-6 production in this model, without impairing Aβ clearance by the microglial cells [176]. It has therefore been suggested that NSAIDs might be a useful adjunct in clinical trials of Aβ vaccines [177].

Passive immunization reduces the risk of a Th1 cell-mediated inflammatory response. Animal models have demonstrated similar effects on amyloid burden as with antigenic vaccination [156] and several clinical trials are underway [160]. A phase II trial of bapineuzumab, a monoclonal antibody against Aβ, has now been completed [178]. Two hundred thirty-four patients were enrolled in the study and treated with infusions over 18 months. No significant differences were found in the primary efficacy tests of cognitive function and disability. However, a subgroup analysis showed some possible benefit in ApoE e4 noncarriers. A phase III trial is now underway that will examine the effect of ApoE status in more detail.

Amyloid vaccines are designed to break up amyloid plaques, and it is hoped that this will lead to reduced neurodegeneration. However, despite the promising results in animal studies human trials of both active and passive immunization have not yet demonstrated convincing clinical results for pre-determined clinical outcomes. Failure of these studies may be due to a number of factors. Once dementia is diagnosed neurodegeneration in AD is already well established. Interventions that reduce amyloid burden at this stage may be too late to significantly improve the disease. Breaking plaques up into soluble amyloid species may be more harmful than beneficial. Soluble amyloid oligomers are potentially more neurotoxic than amyloid sequestered in plaques. Increased cerebral amyloid angiopathy and consequent microhemorrhages have been observed in postmortem examination of subjects from the AN1792 trial [179]. This finding may be explained by a movement of amyloid from plaques to cerebral blood vessels in vaccinated patients, with a failure of adequate perivascular drainage [180]. The side effects of meningo-encephalitis in the AN1792 trial, and of vasogenic edema in the bapineuzumab trial, demonstrate the potential harm of unintended activation of proinflammatory pathways by vaccination.

More recently another approach has been to utilize intravenous immunoglobulin (IVIg) that is obtained from the pooled plasma of healthy human blood donors, and contains natural anti-amyloid antibodies. In a phase I safety and preliminary efficacy clinical trial, eight AD patients were treated with IVIg (Gammagard, Baxter Healthcare Corporation, Westlake Village, CA) for 6

months of therapy. Cognitive function stopped declining in seven patients and improved in six of the eight patients [181]. A randomized phase III trial is now under way. In another phase 1 safety and preliminary efficacy clinical trial five "clinically probable or possible" AD patients were treated with IVIg. A slight improvement was observed on neuropsychological testing at 6 months in all patients except one where the score did not change between baseline and at 6 months [182].

Modulation of Systemic Immunity

It follows from the earlier discussion around the close relationship between systemic and central innate immunity that a lack of consideration of the deleterious effects of systemic inflammation on cognitive outcomes might greatly influence treatment outcomes in a number of drug studies. Thus, the exclusion of co-morbid inflammatory disease in randomized placebo controlled trials of antiinflammatory agents will tend to reduce naturalistic cognitive decline in the placebo arm and mitigate against any beneficial effects in the treatment arm. Comorbid exclusion criteria in such studies might further explain why observational studies in populations with chronic inflammatory conditions might see more benefit to NSAIDS than randomized placebo control trials [7,108]. Furthermore, interventions aimed primarily at central immunity might have indirect consequences on systemic immunity that might lead to modulation of the desired central effects. Thus, for example, NSAID dosage used in clinical trials for AD subjects may have little effect on, [183] or may paradoxically cause an increased production of, proinflammatory cytokines such as TNF-α in the periphery [184–186]. This paradoxical increase in systemic TNF-α in response to NSAID treatment might thus mitigate any central effects. Similar considerations apply to statin therapy [187]. Conversely, the beneficial effects of some agents, for example, cholinesterase inhibitors and antibiotics, might be primarily due to their systemic effects on innate immunity rather than their central effects [100,188].

Direct modulation of systemic immunity as a way of modulating central immunity has largely focused on the modulation of adaptive immunity to remove central amyloid deposits and has already been discussed in detail. Direct manipulation of systemic innate immunity, as a therapeutic target in its own right, has been underexplored. Thus, to date, there has only been exploratory use of systemic anti-TNF in human subjects [189], although closer examination of the effects of systemic anti-TNF agents is warranted in view of the effective use of peripheral anti-TNF treatment in the PDAPP mouse model of AD [190] and the documented improvements in sickness behavior in humans taking anti-TNF agents [191]. Other systemic approaches will depend on increasing our understanding of the communicating pathways between systemic and central innate immune systems. Thus, manipulation of the inflammatory reflex has a number of potential applications in AD but no direct interventions have, as yet, been realized [192]. The finding that peripheral immune cells can be mobilized to the CNS [74] has raised the possibility that stimulation of bone marrow-derived microglia by systemic macrophage colony-stimulating factor might be beneficial in AD [193] as well other approaches including genetic engineering of bone marrow-derived microglial cells to favor a more neuroprotective phenotype [194]. What is clear is that our knowledge of the molecular communication between systemic and central immunity is in its infancy and there are many uncertainties [194].

Conflict of Interest

The authors have no conflict of interest.

References

1. Perry VH, Anthony DC, Bolton SJ, Brown HC. The blood-brain barrier and the inflammatory response. *Mol Med Today* 1997;**3**:335–341.
2. Aloisi F. Immune function of microglia. *Glia* 2001;**36**:165–179.
3. Ransohoff RM, Perry VH. Microglial physiology: Unique stimuli, specialized responses. *Annu Rev Immunol* 2009;**27**:119–145.
4. Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science* 2005;**308**:1314–1318.
5. Perry VH, Gordon S. Macrophages and microglia in the nervous system. *Trends Neurosci* 1988;**11**:273–277.
6. Kreutzberg GW. Microglia: A sensor for pathological events in the CNS. *Trends Neurosci* 1996;**19**:312–318.
7. Lucin KM, Wyss-Coray T. Immune activation in brain aging and neurodegeneration: Too much or too little? *Neuron* 2009;**64**:110–122.
8. Banati RB. Visualising microglial activation in vivo. *Glia* 2002;**40**:206–217.
9. Banati RB, Myers R, Kreutzberg GW. PK ('peripheral benzodiazepine')–binding sites in the CNS indicate early and discrete brain lesions: Microautoradiographic detection of [3H]PK11195 binding to activated microglia. *J Neurocytol* 1997;**26**:77–82.
10. Rivest S. Regulation of innate immune responses in the brain. *Nat Rev Immunol* 2009;**9**:429–439.
11. Bogdan C, Paik J, Vodovotz Y, Nathan C. Contrasting mechanisms for suppression of macrophage cytokine release by transforming growth factor-beta and interleukin-10. *J Biol Chem* 1992;**267**:23301–23308.
12. Barclay AN, Wright GJ, Brooke G, Brown MH. CD200 and membrane protein interactions in the control of myeloid cells. *Trends Immunol* 2002;**23**:285–290.
13. Farina C, Aloisi F, Meinl E. Astrocytes are active players in cerebral innate immunity. *Trends Immunol* 2007;**28**:138–145.
14. Hanisch UK, Kettenmann H. Microglia: Active sensor and versatile effector cells in the normal and pathologic brain. *Nat Neurosci* 2007;**10**:1387–1394.
15. Hickey WF, Hsu BL, Kimura H. T-lymphocyte entry into the central nervous system. *J Neurosci Res* 1991;**28**:254–260.
16. Pryce G, Santos W, Male D. An assay for the analysis of lymphocyte migration across cerebral endothelium in vitro. *J Immunol Methods* 1994;**167**:55–63.
17. Fillit H, Ding WH, Buee L, et al. Elevated circulating tumor necrosis factor levels in Alzheimer's disease. *Neurosci Lett* 1991;**129**:318–320.
18. Bermejo P, Martin-Aragon S, Benedi J, et al. Differences of peripheral inflammatory markers between mild cognitive impairment and Alzheimer's disease. *Immunol Lett* 2008;**117**:198–202.
19. Zuliani G, Ranzini M, Guerra G, et al. Plasma cytokines profile in older subjects with late onset Alzheimer's disease or vascular dementia. *J Psychiatr Res* 2007;**41**:686–693.
20. Bruunsgaard H, Andersen-Ranberg K, Jeune B, Pedersen AN, Skinhoj P, Pedersen BK. A high plasma concentration of TNF-alpha is associated with dementia in centenarians. *J Gerontol A Biol Sci Med Sci* 1999;**54**:M357–M364.
21. Licastro F, Pedrini S, Caputo L, et al. Increased plasma levels of interleukin-1, interleukin-6 and alpha-1-antichymotrypsin in patients with Alzheimer's disease: Peripheral inflammation or signals from the brain? *J Neuroimmunol* 2000;**103**:97–102.
22. Singh VK, Guthikonda P. Circulating cytokines in Alzheimer's disease. *J Psychiatr Res* 1997;**31**:657–660.
23. De Luigi A, Fragiacomo C, Lucca U, Quadri P, Tettamanti M, Grazia De Simoni M. Inflammatory markers in Alzheimer's disease and multi-infarct dementia. *Mech Ageing Dev* 2001;**122**:1985–1995.
24. Kamer AR, Craig RG, Pirraglia E, et al. TNF-alpha and antibodies to periodontal bacteria discriminate between Alzheimer's disease patients and normal subjects. *J Neuroimmunol* 2009;**216**:92–97.
25. van Duijn CM, Hofman A, Nagelkerken L. Serum levels of interleukin-6 are not elevated in patients with Alzheimer's disease. *Neurosci Lett* 1990;**108**:350–354.
26. Alvarez XA, Franco A, Fernandez-Novoa L, Cacabelos R. Blood levels of histamine, IL-1 beta, and TNF-alpha in patients with mild to moderate Alzheimer disease. *Mol Chem Neuropathol* 1996;**29**:237–252.
27. Cacabelos R, Alvarez XA, Franco-Maside A, Fernandez-Novoa L, Caamano J. Serum tumor necrosis factor (TNF) in Alzheimer's disease and multi-infarct dementia. *Methods Find Exp Clin Pharmacol* 1994;**16**:29–35.

28. Ray S, Britschgi M, Herbert C, et al. Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. *Nat Med* 2007;**13**:1359–1362.
29. Engelhart MJ, Geerlings MI, Meijer J, et al. Inflammatory proteins in plasma and the risk of dementia: The rotterdam study. *Arch Neurol* 2004;**61**:668–672.
30. Tilvis RS, Kahonen-Vare MH, Jolkkonen J, Valvanne J, Pitkala KH, Strandberg TE. Predictors of cognitive decline and mortality of aged people over a 10-year period. *J Gerontol A Biol Sci Med Sci* 2004;**59**:268–274.
31. Kuo HK, Yen CJ, Chang CH, Kuo CK, Chen JH, Sorond F. Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: Systematic review and meta-analysis. *Lancet Neurol* 2005;**4**:371–380.
32. Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: A 25-year follow-up of the Honolulu-Asia Aging Study. *Ann Neurol* 2002;**52**:168–174.
33. Reale M, Iarlori C, Gambi F, et al. Treatment with an acetylcholinesterase inhibitor in Alzheimer patients modulates the expression and production of the pro-inflammatory and anti-inflammatory cytokines. *J Neuroimmunol* 2004;**148**:162–171.
34. Huberman M, Sredni B, Stern L, Kott E, Shalit F. IL-2 and IL-6 secretion in dementia: Correlation with type and severity of disease. *J Neurol Sci* 1995;**130**:161–164.
35. Lombardi VR, Garcia M, Rey L, Cacabelos R. Characterization of cytokine production, screening of lymphocyte subset patterns and in vitro apoptosis in healthy and Alzheimer's Disease (AD) individuals. *J Neuroimmunol* 1999;**97**:163–171.
36. De Luigi A, Pizzimenti S, Quadri P, et al. Peripheral inflammatory response in Alzheimer's disease and multiinfarct dementia. *Neurobiol Dis* 2002;**11**:308–314.
37. Tan ZS, Beiser AS, Vasan RS, et al. Inflammatory markers and the risk of Alzheimer disease: The Framingham Study. *Neurology* 2007;**68**:1902–1908.
38. Mruthinti S, Buccafusco JJ, Hill WD, et al. Autoimmunity in Alzheimer's disease: Increased levels of circulating IgGs binding Abeta and RAGE peptides. *Neurobiol Aging* 2004;**25**:1023–1032.
39. Gruden MA, Davudova TB, Malisauskas M, et al. Autoimmune responses to amyloid structures of Abeta(25–35) peptide and human lysozyme in the serum of patients with progressive Alzheimer's disease. *Dement Geriatr Cogn Disord* 2004;**18**:165–171.
40. Baril L, Nicolas L, Croisile B, et al. Immune response to Abeta-peptides in peripheral blood from patients with Alzheimer's disease and control subjects. *Neurosci Lett* 2004;**355**:226–230.
41. Weksler ME, Relkin N, Turkenich R, LaRusse S, Zhou L, Szabo P. Patients with Alzheimer disease have lower levels of serum anti-amyloid peptide antibodies than healthy elderly individuals. *Exp Gerontol* 2002;**37**:943–948.
42. Britschgi M, Olin CE, Johns HT, et al. Neuroprotective natural antibodies to assemblies of amyloidogenic peptides decrease with normal aging and advancing Alzheimer's disease. *Proc Natl Acad Sci U S A* 2009;**106**:12145–12150.
43. Galimberti D, Venturelli E, Fenoglio C, et al. Intrathecal levels of IL-6, IL-11 and LIF in Alzheimer's disease and frontotemporal lobar degeneration. *J Neurol* 2008;**255**:539–544.
44. Tarkowski E, Blennow K, Wallin A, Tarkowski A. Intracerebral production of tumor necrosis factor-alpha, a local neuroprotective agent, in Alzheimer disease and vascular dementia. *J Clin Immunol* 1999;**19**:223–230.
45. Garlind A, Brauner A, Hojeberg B, Basun H, Schultzberg M. Soluble interleukin-1 receptor type II levels are elevated in cerebrospinal fluid in Alzheimer's disease patients. *Brain Res* 1999;**826**:112–116.
46. Blasko I, Lederer W, Oberbauer H, et al. Measurement of thirteen biological markers in CSF of patients with Alzheimer's disease and other dementias. *Dement Geriatr Cogn Disord* 2006;**21**:9–15.
47. Akiyama H, Barger S, Barnum S, et al. Inflammation and Alzheimer's disease. *Neurobiol Aging* 2000;**21**:383–421.
48. Bradt BM, Kolb WP, Cooper NR. Complement-dependent proinflammatory properties of the Alzheimer's disease beta-peptide. *J Exp Med* 1998;**188**:431–438.
49. Itagaki S, Akiyama H, Saito H, McGeer PL. Ultrastructural localization of complement membrane attack complex (MAC)-like immunoreactivity in brains of patients with Alzheimer's disease. *Brain Res* 1994;**645**:78–84.
50. Zlokovic BV, Martel CL, Mackic JB, et al. Brain uptake of circulating apolipoproteins J and E complexed to Alzheimer's amyloid beta. *Biochem Biophys Res Commun* 1994;**205**:1431–1437.
51. McGeer PL, Akiyama H, Itagaki S, McGeer EG. Immune system response in Alzheimer's disease. *Can J Neurol Sci* 1989;**16**(4 Suppl):516–527.
52. Frautschy SA, Yang F, Irrizarry M, et al. Microglial response to amyloid plaques in APPsw transgenic mice. *Am J Pathol* 1998;**152**:307–317.
53. Ard MD, Cole GM, Wei J, Mehrle AP, Fratkin JD. Scavenging of Alzheimer's amyloid beta-protein by microglia in culture. *J Neurosci Res* 1996;**43**:190–202.
54. Chen K, Iribarren P, Hu J, et al. Activation of Toll-like receptor 2 on microglia promotes cell uptake of Alzheimer disease-associated amyloid beta peptide. *J Biol Chem* 2006;**281**:3651–3659.
55. Richard KL, Filali M, Prefontaine P, Rivest S. Toll-like receptor 2 acts as a natural innate immune receptor to clear amyloid beta 1–42 and delay the cognitive decline in a mouse model of Alzheimer's disease. *J Neurosci* 2008;**28**:5784–5793.
56. Tahara K, Kim HD, Jin JJ, Maxwell JA, Li L, Fukuchi K. Role of toll-like receptor signalling in Abeta uptake and clearance. *Brain* 2006;**129**(Pt 11):3006–3019.
57. Hammer ND, Schmidt JC, Chapman MR. The curli nucleator protein, CsgB, contains an amyloidogenic domain that directs CsgA polymerization. *Proc Natl Acad Sci U S A* 2007;**104**:12494–12499.
58. Colton CA, Gilbert DL. Production of superoxide anions by a CNS macrophage, the microglia. *FEBS Lett* 1987;**223**:284–288.
59. Chao CC, Hu S, Molitor TW, Shaskan EG, Peterson PK. Activated microglia mediate neuronal cell injury via a nitric oxide mechanism. *J Immunol* 1992;**149**:2736–2741.
60. Van Der Laan LJ, Ruuls SR, Weber KS, Lodder IJ, Dopp EA, Dijkstra CD. Macrophage phagocytosis of myelin in vitro determined by flow cytometry: Phagocytosis is mediated by CR3 and induces production of tumor necrosis factor-alpha and nitric oxide. *J Neuroimmunol* 1996;**70**:145–152.
61. Soscia SJ, Kirby JE, Washicosky KJ, et al. The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. *PLoS One* 2010. doi:10.1371/journal.pone.0009505.
62. Wood JA, Wood PL, Ryan R, et al. Cytokine indices in Alzheimer's temporal cortex: No changes in mature IL-1 beta or IL-1RA but increases in the associated acute phase proteins IL-6, alpha 2-macroglobulin and C-reactive protein. *Brain Res* 1993;**629**:245–252.
63. Griffin WS, Sheng JG, Royston MC, et al. Glial-neuronal interactions in Alzheimer's disease: The potential role of a 'cytokine cycle' in disease progression. *Brain Pathol* 1998;**8**:65–72.
64. Griffin WS, Stanley LC, Ling C, et al. Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. *Proc Natl Acad Sci U S A* 1989;**86**:7611–7615.
65. Goldgaber D, Harris HW, Hla T, et al. Interleukin 1 regulates synthesis of amyloid beta-protein precursor mRNA in human endothelial cells. *Proc Natl Acad Sci U S A* 1989;**86**:7606–7610.
66. Griffin WS, Mrak RE. Interleukin-1 in the genesis and progression of and risk for development of neuronal degeneration in Alzheimer's disease. *J Leukoc Biol* 2002;**72**:233–238.
67. Boche D, Cunningham C, Docagne F, Scott H, Perry VH. TGFbeta1 regulates the inflammatory response during chronic neurodegeneration. *Neurobiol Dis* 2006;**22**:638–650.
68. Kellner A, Matschke J, Bernreuther C, Moch H, Ferrer I, Glatzel M. Autoantibodies against beta-amyloid are common in Alzheimer's disease and help control plaque burden. *Ann Neurol* 2009;**65**:24–31.
69. Edison P, Archer HA, Gerhard A, et al. Microglia, amyloid, and cognition in Alzheimer's disease: An [11C](R)PK11195-PET and [11C]PIB-PET study. *Neurobiol Dis* 2008;**32**:412–419.
70. Hart BL. Biological basis of the behavior of sick animals. *Neurosci Biobehav Rev* 1988;**12**:123–137.
71. Tracey KJ. The inflammatory reflex. *Nature* 2002;**420**:853–859.
72. Laflamme N, Rivest S. Effects of systemic immunogenic insults and circulating proinflammatory cytokines on the transcription of the inhibitory factor kappaB alpha within specific cellular populations of the rat brain. *J Neurochem* 1999;**73**:309–321.
73. Ek M, Engblom D, Saha S, Blomqvist A, Jakobsson PJ, Ericsson-Dahlstrand A. Inflammatory response: Pathway across the blood-brain barrier. *Nature* 2001;**410**:430–431.
74. D'Mello C, Le T, Swain MG. Cerebral microglia recruit monocytes into the brain in response to tumor necrosis factoralpha signaling during peripheral organ inflammation. *J Neurosci* 2009;**29**:2089–2102.
75. Soulet D, Rivest S. Bone-marrow-derived microglia: Myth or reality? *Curr Opin Pharmacol* 2008;**8**:508–518.
76. Farrall AJ, Wardlaw JM. Blood-brain barrier: Ageing and microvascular disease–systematic review and meta-analysis. *Neurobiol Aging* 2009;**30**:337–352.
77. Popescu BO, Toescu EC, Popescu LM, et al. Blood-brain barrier alterations in ageing and dementia. *J Neurol Sci* 2009;**283**:99–106.
78. Campion D, Dumanchin C, Hannequin D, et al. Early-onset autosomal dominant Alzheimer disease: Prevalence, genetic heterogeneity, and mutation spectrum. *Am J Hum Genet* 1999;**65**:664–670.
79. Rovelet-Lecrux A, Hannequin D, Raux G, et al. APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. *Nat Genet* 2006;**38**:24–26.
80. Hardy J. Alzheimer's disease: The amyloid cascade hypothesis: An update and reappraisal. *J Alzheimers Dis* 2006;**9**(3 Suppl):151–153.
81. Launer LJ, Andersen K, Dewey ME, et al. Rates and risk factors for dementia and Alzheimer's disease: Results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. *Neurology* 1999;**52**:78–84.
82. Barger SW, Harmon AD. Microglial activation by Alzheimer amyloid precursor protein and modulation by apolipoprotein E. *Nature* 1997;**388**:878–881.
83. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: A causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc Natl Acad Sci U S A* 2006;**103**:5644–5651.
84. Itzhaki RF, Wozniak MA. Herpes simplex virus type 1, apolipoprotein E, and cholesterol: A dangerous liaison in Alzheimer's disease and other disorders. *Prog Lipid Res* 2006;**45**:73–90.
85. Gerard HC, Wildt KL, Whittum-Hudson JA, Lai Z, Ager J, Hudson AP. The load of Chlamydia pneumoniae in the Alzheimer's brain varies with APOE genotype. *Microb Pathog* 2005;**39**:19–26.
86. Moretti EW, Morris RW, Podgoreanu M, et al. APOE polymorphism is associated with risk of severe sepsis in surgical patients. *Crit Care Med* 2005;**33**:2521–2526.

87. Judson R, Brain C, Dain B, Windemuth A, Ruano G, Reed C. New and confirmatory evidence of an association between APOE genotype and baseline C-reactive protein in dyslipidemic individuals. *Atherosclerosis* 2004;**177**:345–351.
88. Eiriksdottir G, Aspelund T, Bjarnadottir K, et al. Apolipoprotein E genotype and statins affect CRP levels through independent and different mechanisms: AGES-Reykjavik Study. *Atherosclerosis* 2006;**186**:222–224.
89. Nicoll JA, Mrak RE, Graham DI, et al. Association of interleukin-1 gene polymorphisms with Alzheimer's disease. *Ann Neurol* 2000;**47**:365–368.
90. Papassotiropoulos A, Bagli M, Jessen F, et al. A genetic variation of the inflammatory cytokine interleukin-6 delays the initial onset and reduces the risk for sporadic Alzheimer's disease. *Ann Neurol* 1999;**45**:666–668.
91. McCusker SM, Curran MD, Dynan KB, et al. Association between polymorphism in regulatory region of gene encoding tumour necrosis factor alpha and risk of Alzheimer's disease and vascular dementia: A case-control study. *Lancet* 2001;**357**:436–439.
92. Perry RT, Collins JS, Wiener H, Acton R, Go RC. The role of TNF and its receptors in Alzheimer's disease. *Neurobiol Aging* 2001;**22**:873–883.
93. Alvarez V, Mata IF, Gonzalez P, et al. Association between the TNFalpha-308 A/G polymorphism and the onset-age of Alzheimer disease. *Am J Med Genet* 2002;**114**:574–577.
94. Kamboh MI, Sanghera DK, Ferrell RE, DeKosky ST. APOE*4-associated Alzheimer's disease risk is modified by alpha 1-antichymotrypsin polymorphism. *Nat Genet* 1995;**10**:486–488.
95. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet* 2009;**41**:1088–1093.
96. Lambert JC, Heath S, Even G, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* 2009;**41**:1094–1099.
97. van Exel E, Eikelenboom P, Comijs H, et al. Vascular factors and markers of inflammation in offspring with a parental history of late-onset Alzheimer disease. *Arch Gen Psychiatry* 2009;**66**:1263–1270.
98. Gatz M, Reynolds CA, Fratiglioni L, et al. Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry* 2006;**63**:168–174.
99. Khachaturian AS, Corcoran CD, Mayer LS, Zandi PP, Breitner JC. Apolipoprotein E epsilon4 count affects age at onset of Alzheimer disease, but not lifetime susceptibility: The Cache County Study. *Arch Gen Psychiatry* 2004;**61**:518–524.
100. Holmes C, Cotterell D. Role of infection in the pathogenesis of Alzheimer's disease: Implications for treatment. *CNS Drugs* 2009;**23**:993–1002.
101. Rahkonen T, Luukkainen-Markkula R, Paanila S, Sivenius J, Sulkava R. Delirium episode as a sign of undetected dementia among community dwelling elderly subjects: A 2 year follow up study. *J Neurol Neurosurg Psychiatry* 2000;**69**:519–521.
102. Dunn N, Mullee M, Perry VH, Holmes C. Association between dementia and infectious disease: Evidence from a case-control study. *Alzheimer Dis Assoc Disord* 2005;**19**:91–94.
103. Andersen K, Lolk A, Kragh-Sorensen P, Petersen NE, Green A. Depression and the risk of Alzheimer disease. *Epidemiology* 2005;**16**:233–238.
104. Casserly I, Topol E. Convergence of atherosclerosis and Alzheimer's disease: Inflammation, cholesterol, and misfolded proteins. *Lancet* 2004;**363**:1139–1146.
105. Balakrishnan K, Verdile G, Mehta PD, et al. Plasma Abeta42 correlates positively with increased body fat in healthy individuals. *J Alzheimers Dis* 2005;**8**:269–282.
106. Biessels GJ, Kappelle LJ. Increased risk of Alzheimer's disease in Type II diabetes: Insulin resistance of the brain or insulin-induced amyloid pathology? *Biochem Soc Trans* 2005;**33**(Pt 5):1041–1044.
107. Licastro F, Candore G, Lio D, et al. Innate immunity and inflammation in ageing: A key for understanding age-related diseases. *Immun Ageing* 2005. doi:10.1186/1742-4933-2-8.
108. Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. *Nat Rev Immunol* 2007;**7**:161–167.
109. Cunningham C, Wilcockson DC, Campion S, Lunnon K, Perry VH. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. *J Neurosci* 2005;**25**:9275–9284.
110. Cunningham C, Campion S, Lunnon K, et al. Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. *Biol Psychiatry* 2009;**65**:304–312.
111. Holmes C, Cunningham C, Zotova E, et al. Systemic inflammation and disease progression in Alzheimer disease. *Neurology* 2009;**73**:768–774.
112. McGeer PL, McGeer EG. NSAIDs and Alzheimer disease: Epidemiological, animal model and clinical studies. *Neurobiol Aging* 2007;**28**:639–647.
113. Stewart WF, Kawas C, Corrada M, Metter EJ. Risk of Alzheimer's disease and duration of NSAID use. *Neurology* 1997;**48**:626–632.
114. McGeer PL, Schulzer M, McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: A review of 17 epidemiologic studies. *Neurology* 1996;**47**:425–432.
115. Vlad SC, Miller DR, Kowall NW, Felson DT. Protective effects of NSAIDs on the development of Alzheimer disease. *Neurology* 2008;**70**:1672–1677.
116. Hayden KM, Zandi PP, Khachaturian AS, et al. Does NSAID use modify cognitive trajectories in the elderly? The Cache county study. *Neurology* 2007;**69**:275–282.
117. Szekely CA, Breitner JCS, Fitzpatrick AL, et al. NSAID use and dementia risk in the cardiovascular health study – Role of APOE and NSAID type. *Neurology* 2008;**70**:17–24.
118. de Craen AJM, Gussekloo J, Vrijsen B, Westendorp RGJ. Meta-analysis of nonsteroidal antiinflammatory drug use and risk of dementia. *Am J Epidemiol* 2005;**161**:114–120.
119. Rogers J, Kirby LC, Hempelman SR, et al. Clinical trial of indomethacin in Alzheimer's disease. *Neurology* 1993;**43**:1609–1611.
120. Pasqualetti P, Bonomini C, Dal Forno G, et al. A randomized controlled study on effects of ibuprofen on cognitive progression of Alzheimer's disease. *Aging Clin Exp Res* 2009;**21**:102–110.
121. Breitner JC. A bi-directional effect of naproxen on the pathogenesis of Alzheimer's Disease: Clinical and biological evidence from a randomised primary prevention trial. *Clinical trials on Alzheimer's disease*. October 29th30th 2009. Las Vegas.
122. ADAPT-Research-Group,Lyketsos CG, Breitner JC, et al. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. *Neurology* 2007;**68**:1800–1808.
123. Imbimbo BP. An update on the efficacy of non-steroidal anti-inflammatory drugs in Alzheimer's disease. *Expert Opin Invest Drugs* 2009;**18**:1147–1168.
124. Gasparini L, Ongini E, Wenk G. Non-steroidal anti-inflammatory drugs (NSAIDs) in Alzheimer's disease: Old and new mechanisms of action. *J Neurochem* 2004;**91**:521–536.
125. Akiyama H, Barger S, Barnum S, et al. Inflammation and Alzheimer's disease. *Neurobiol Aging* 2000;**21**: 383–421.
126. Montine TJ, Sidell KR, Crews BC, et al. Elevated CSF prostaglandin E2 levels in patients with probable AD. [see comment]. *Neurology* 1999;**53**:1495–1498.
127. Combrinck M, Williams J, De Berardinis MA, et al. Levels of CSF prostaglandin E2, cognitive decline, and survival in Alzheimer's disease. *J Neurol, Neurosurg Psychiatry* 2006;**77**:85–88.
128. Storer PD, Xu J, Chavis J, Drew PD. Peroxisome proliferator-activated receptor-gamma agonists inhibit the activation of microglia and astrocytes: Implications for multiple sclerosis. *J Neuroimmunol* 2005;**161**:113–122.
129. Cuzzocrea S, Pisano B, Dugo L, et al. Rosiglitazone, a ligand of the peroxisome proliferator-activated receptor-gamma, reduces acute inflammation. *Eur J Pharmacol* 2004;**483**:79–93.
130. Landreth G, Jiang Q, Mandrekar S, Heneka M. PPARgamma agonists as therapeutics for the treatment of Alzheimer's disease. *Neurotherapeutics* 2008;**5**:481–489.
131. Watson GS, Cholerton BA, Reger MA, et al. Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: A preliminary study. *Am J Geriatr Psychiatry* 2005;**13**:950–958.
132. Risner ME, Saunders AM, Altman JF, et al. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics J* 2006;**6**:246–254.
133. Yan SD, Bierhaus A, Nawroth PP, Stern DM. RAGE and Alzheimer's disease: A progression factor for amyloid-beta-induced cellular perturbation? *J Alzheimers Dis* 2009;**16**:833–843.
134. Miller MC, Tavares R, Johanson CE, et al. Hippocampal RAGE immunoreactivity in early and advanced Alzheimer's disease. *Brain Res* 2008;**1230**:273–280.
135. Takeuchi M, Yamagishi S. Possible involvement of advanced glycation end-products (AGEs) in the pathogenesis of Alzheimer's disease. *Curr Pharm Des* 2008;**14**:973–978.
136. Cho HJ, Son SM, Jin SM, et al. RAGE regulates BACE1 and Abeta generation via NFAT1 activation in Alzheimer's disease animal model. *FASEB J* 2009;**23**:2639–2649.
137. Sabbagh M, Bell J, Agro A, Aisen P, Galasko D. P4-389: An oral antagonist of the receptor for advanced glycation end products (RAGE) is safe and well-tolerated in the treatment of Alzheimer's disease: Results form a phase II study. *Alzheimers Dis*. 2008;**4**:T788.
138. McGuinness B, Passmore P. Can statins prevent or help reat Alzheimer's disease? *J Alzheimers Dis* 2010;**20**:925–933.
139. Reid PC, Urano Y, Kodama T, Hamakubo T. Alzheimer's disease: Cholesterol, membrane rafts, isoprenoids and statins. *J Cell Mol Med* 2007;**11**:383–392.
140. Cordle A, Koenigsknecht-Talboo J, Wilkinson B, et al. Mechanisms of statin-mediated inhibition of small G-protein function. *J Biol Chem* 2005;**280**:34202–34209.
141. Stuve O, Youssef S, Steinman L, et al. Statins as potential therapeutic agents in neuroinflammatory disorders. *Curr Opin Neurol* 2003;**16**:393–401.
142. McGuinness B, Craig D, Bullock R, et al. Statins for the prevention of dementia. *Cochrane Database Syst Rev* 2009:CD003160.
143. Zhou B, Teramukai S, Fukushima M, Zhou B, Teramukai S, Fukushima M. Prevention and treatment of dementia or Alzheimer's disease by statins: A meta-analysis. *Dement Geriatr Cogn Disord* 2007;**23**:194–201.
144. Lennernas H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors. Similarities and differences. *Clin Pharmacokinet* 1997;**32**:403–425.
145. Thiele C, Hannah MJ, Fahrenholz F, Huttner WB. Cholesterol binds to synaptophysin and is required for biogenesis of synaptic vesicles. *Nat Cell Biol* 2000;**2**:42–49.
146. Wolozin B, Manger J, Bryant R, Cordy J, Green RC, McKee A. Re-assessing the relationship between cholesterol, statins and Alzheimer's disease. *Acta Neurol Scand Suppl* 2006;**185**:63–70.
147. Bi X, Baudry M, Liu J, et al. Inhibition of geranylgeranylation mediates the effects of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase

inhibitors on microglia. *J Biol Chem* 2004;**279**:48238–48245.
148. Alkam T, Nitta A, Mizoguchi H, et al. Restraining tumor necrosis factor-alpha by thalidomide prevents the amyloid beta-induced impairment of recognition memory in mice. *Behav Brain Res* 2008;**189**:100–106.
149. Ryu JK, McLarnon JG, Ryu JK, McLarnon JG. Thalidomide inhibition of perturbed vasculature and glial-derived tumor necrosis factor-alpha in an animal model of inflamed Alzheimer's disease brain. *Neurobiol Dis* 2008;**29**:254–266.
150. Burke W, Bohac D, Cotter R, Zheng JL, Potter J, Gendelman H. A 26 week double blind, placebo-controlled study of the efficacy of thalidomide in the treatment of Alzheimer's disease. *Neurobiol Aging* 2002;**23**:353.
151. Kitazawa M, Oddo S, Yamasaki TR, Green KN, LaFerla FM. Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer's disease. *J Neurosci* 2005;**25**:8843–8853.
152. McAlpine FE, Lee JK, Harms AS, et al. Inhibition of soluble TNF signaling in a mouse model of Alzheimer's disease prevents pre-plaque amyloid-associated neuropathology. *Neurobiol Dis* 2009;**34**:163–177.
153. Tobinick E. Perispinal etanercept for neuroinflammatory disorders. *Drug Discovery Today* 2009;**14**:168–177.
154. Tobinick EL, Gross H. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. *J Neuroinflammation* 2008. doi:10.1186/1742-2094-5-2.
155. Schenk D, Barbour R, Dunn W, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse.[see comment]. *Nature* 1999;**400**:173–177.
156. Bard F, Cannon C, Barbour R, et al. Peripherally administered antibodies against amyloid beta-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nat Med* 2000;**6**:916–919.
157. Solomon B, Koppel R, Frankel D, Hanan-Aharon E. Disaggregation of Alzheimer beta-amyloid by site-directed mAb. *Proc Natl Acad Sci U S A* 1997;**94**:4109–4112.
158. Zlokovic BV. Clearing amyloid through the blood-brain barrier. *J Neurochem* 2004;**89**:807–811.
159. DeMattos RB, Bales KR, Cummins DJ, Dodart JC, Paul SM, Holtzman DM. Peripheral anti-A beta antibody alters CNS and plasma A beta clearance and decreases brain A beta burden in a mouse model of Alzheimer's disease. [see comment]. *Proc Natl Acad Sci U S A* 2001;**98**:8850–8855.
160. Wisniewski T, Konietzko U, Wisniewski T, Konietzko U. Amyloid-beta immunisation for Alzheimer's disease. *Lancet Neurol* 2008;**7**:805–811.
161. Bayer AJ, Bullock R, Jones RW, et al. Evaluation of the safety and immunogenicity of synthetic Abeta42 (AN1792) in patients with AD. [see comment]. *Neurology* 2005;**64**:94–101.
162. Gilman S, Koller M, Black RS, et al. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. *Neurology* 2005;**64**:1553–1562.
163. Orgogozo JM, Gilman S, Dartigues JF, et al. Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization.[see comment]. *Neurology* 2003;**61**:46–54.
164. Nicoll JA, Wilkinson D, Holmes C, Steart P, Markham H, Weller RO. Neuropathology of human Alzheimer disease after immunization with amyloid-beta peptide: A case report. *Nat Med* 2003;**9**:448–452.
165. Nicoll JA, Barton E, Boche D, et al. Abeta species removal after abeta42 immunization. *J Neuropathol Exp Neurol* 2006;**65**:1040–1048.
166. Holmes C, Boche D, Wilkinson D, et al. Long-term effects of Abeta42 immunisation in Alzheimer's disease: Follow-up of a randomised, placebo-controlled phase I trial. *Lancet* 2008;**372**:216–223.
167. Pride M, Seubert P, Grundman M, et al. Progress in the active immunotherapeutic approach to Alzheimer's disease: Clinical investigations into AN1792-associated meningoencephalitis. *Neurodegenerative Dis* 2008;**5**:194–196.
168. Monsonego A, Imitola J, Petrovic S, et al. Abeta-induced meningoencephalitis is IFN-gamma-dependent and is associated with T cell-dependent clearance of Abeta in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* 2006;**103**:5048–5053.
169. Lemere CA, Lemere CA. Developing novel immunogens for a safe and effective Alzheimer's disease vaccine. *Prog Brain Res* 2009;**175**:83–93.
170. Hara H, Monsonego A, Yuasa K, et al. Development of a safe oral Abeta vaccine using recombinant adeno-associated virus vector for Alzheimer's disease. *J Alzheimer's Dis* 2004;**6**:483–488.
171. Lemere CA, Maron R, Selkoe DJ, Weiner HL. Nasal vaccination with beta-amyloid peptide for the treatment of Alzheimer's disease. *DNA Cell Biol* 2001;**20**:705–711.
172. Weiner HL, Lemere CA, Maron R, et al. Nasal administration of amyloid-beta peptide decreases cerebral amyloid burden in a mouse model of Alzheimer's disease. [see comment]. *Ann Neurol* 2000;**48**:567–579.
173. Giunta B, Fernandez F, Nikolic WV, et al. Inflammaging as a prodrome to Alzheimer's disease. *J Neuroinflammation* 2008. doi:10.1186/1742-2094-5-51.
174. Okura Y, Matsumoto Y, Okura Y, Matsumoto Y. Recent advance in immunotherapies for Alzheimer disease: With special reference to DNA vaccination. *Human Vaccines* 2009;**5**:373–380.
175. Movsesyan N, Ghochikyan A, Mkrtichyan M, et al. Reducing AD-like pathology in 3xTg-AD mouse model by DNA epitope vaccine – a novel immunotherapeutic strategy. *PLoS ONE* 2008. doi:10.1371/journal.pone.0002124.
176. Strohmeyer R, Kovelowski CJ, Mastroeni D, Leonard B, Grover A, Rogers J. Microglial responses to amyloid beta peptide opsonization and indomethacin treatment. *J Neuroinflammation* 2005. doi:10.1186/1742-2094-2-18.
177. Rogers J. The inflammatory response in Alzheimer's disease. *J Periodontol* 2008;**79**(8 Suppl):1535–1543.
178. Salloway S, Sperling R, Gilman S, et al. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. *Neurology* 2009;**73**:2061–2070.
179. Ferrer I, Boada Rovira M, Sanchez Guerra ML, Rey MJ, Costa-Jussa F. Neuropathology and pathogenesis of encephalitis following amyloid-beta immunization in Alzheimer's disease. *Brain Pathol* 2004;**14**:11–20.
180. Boche D, Nicoll JA, Boche D, Nicoll JAR. The role of the immune system in clearance of Abeta from the brain. *Brain Pathol* 2008;**18**:267–278.
181. Relkin NR, Szabo P, Adamiak B, et al. 18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease. *Neurobiol Aging* 2009;**30**:1728–1736.
182. Dodel RC, Du Y, Depboylu C, et al. Intravenous immunoglobulins containing antibodies against beta-amyloid for the treatment of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2004;**75**:1472–1474.
183. Dubois RN, Abramson SB, Crofford L, et al. Cyclooxygenase in biology and disease. [see comment]. *FASEB J* 1998;**12**:1063–1073.
184. Oh-ishi S, Utsunomiya I, Yamamoto T, Komuro Y, Hara Y. Effects of prostaglandins and cyclic AMP on cytokine production in rat leukocytes. *Eur J Pharmacol* 1996;**300**:255–259.
185. Sacco S, Agnello D, Sottocorno M, et al. Nonsteroidal anti-inflammatory drugs increase tumor necrosis factor production in the periphery but not in the central nervous system in mice and rats. *J Neurochem* 1998;**71**:2063–2070.
186. Spinas GA, Bloesch D, Keller U, Zimmerli W, Cammisuli S. Pretreatment with ibuprofen augments circulating tumor necrosis factor-alpha, interleukin-6, and elastase during acute endotoxinemia. *J Infect Dis* 1991;**163**:89–95.
187. Stankovic G, Sparks DL, Stankovic G, Sparks DL. Change in circulating C-reactive protein is not associated with atorvastatin treatment in Alzheimer's disease. *Neurol Res* 2006;**28**:621–624.
188. Tabet N. Acetylcholinesterase inhibitors for Alzheimer's disease: Anti-inflammatories in acetylcholine clothing! *Age Ageing* 2006;**35**:336–338.
189. Bohac D, Burke W, Cotter R, Zheng J, Potter J. A 24-week randomized, double-blind, placebo-controlled study of the efficacy and tolerability of TNFR: Fc (etanercept) in the treatment of dementia of the Alzheimer type. *Neurobiol Aging* 2002;**23**:315.
190. Giuliani F, Vernay A, Leuba G, et al. Decreased behavioral impairments in an Alzheimer mice model by interfering with TNF-alpha metabolism. *Brain Res Bull* 2009;**80**:302–308.
191. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: Double-blind placebo-controlled randomised phase III trial. *Lancet* 2006;**367**:29–35.
192. Tracey KJ. Reflex control of immunity. *Nat Rev Immunol* 2009;**9**:418–428.
193. Boissonneault V, Rivest S. The hematopoietic cytokine M-CSF as a cure for Alzheimer's disease. *Med Sci (Paris)* 2009;**25**:666–668.
194. Yong VW, Rivest S. Taking advantage of the systemic immune system to cure brain diseases. *Neuron* 2009;**64**:55–60.
195. Combs CK, Johnson DE, Karlo JC, Cannady SB, Landreth GE. Inflammatory mechanisms in Alzheimer's disease: Inhibition of beta-amyloid-stimulated proinflammatory responses and neurotoxicity by PPARgamma agonists. *J Neurosci* 2000;**20**:558–567.
196. Cole GM, Lim GP, Yang F, et al. Prevention of Alzheimer's disease: Omega-3 fatty acid and phenolic anti-oxidant interventions. *Neurobiol Aging* 2005;**26**(Suppl 1):133–136.
197. Cole GM, Ma QL, Frautschy SA. Omega-3 fatty acids and dementia. *Prostaglandins Leukot Essent Fatty Acids* 2009;**81**:213–221.
198. Chiu CC, Su KP, Cheng TC, et al. The effects of omega-3 fatty acids monotherapy in Alzheimer's disease and mild cognitive impairment: A preliminary randomized double-blind placebo-controlled study. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;**32**:1538–1544.
199. Garcia-Alloza M, Borrelli LA, Rozkalne A, Hyman BT, Bacskai BJ. Curcumin labels amyloid pathology in vivo, disrupts existing plaques, and partially restores distorted neurites in an Alzheimer mouse model. *J Neurochem* 2007;**102**:1095–1104.
200. Begum AN, Jones MR, Lim GP, et al. Curcumin structure-function, bioavailability, and efficacy in models of neuroinflammation and Alzheimer's disease. *J Pharmacol Exp Ther* 2008;**326**:196–208.
201. Baum L, Lam CW, Cheung SK, et al. Six-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with Alzheimer disease. *J Clin Psychopharmacol* 2008;**28**:110–113.
202. Zhang Z, Zhang ZY, Fauser U, Schluesener HJ. Valproic acid attenuates inflammation in experimental autoimmune neuritis. *Cell Mol Life Sci* 2008;**65**:4055–4065.
203. Peng GS, Li G, Tzeng NS, et al. Valproate pretreatment protects dopaminergic neurons from LPS-induced neurotoxicity in rat primary midbrain cultures: Role of microglia. *Brain Res Mol Brain Res* 2005;**134**:162–169.
204. Sobaniec-Lotowska ME. A transmission electron microscopic study of microglia/macrophages in the hippocampal cortex and neocortex following chronic exposure to valproate. *Int J Exp Pathol* 2005;**86**:91–96.
205. Herrmann N, Lanctot KL, Rothenburg LS, Eryavec G. A placebo-controlled trial of valproate for agitation and

aggression in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2007;**23**:116–119.
206. Loeb MB, Molloy DW, Smieja M, et al. A randomized, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease. *J Am Geriatr Soc* 2004;**52**:381–387.
207. Kountouras J, Boziki M, Gavalas E, et al. Eradication of Helicobacter pylori may be beneficial in the management of Alzheimer's disease. *J Neurol* 2009;**256**:758–767.
208. Moon JH, Kim SY, Lee HG, Kim SU, Lee YB. Activation of nicotinic acetylcholine receptor prevents the production of reactive oxygen species in fibrillar beta amyloid peptide (1–42)-stimulated microglia. *Exp Mol Med* 2008;**40**:11–18.
209. Suzuki T, Hide I, Matsubara A, et al. Microglial alpha7 nicotinic acetylcholine receptors drive a phospholipase C/IP3 pathway and modulate the cell activation toward a neuroprotective role. *J Neurosci Res* 2006;**83**:1461–1470.
210. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology* 1998;**50**:136–145.

