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REVIEW

Targeting Impaired Antimicrobial Immunity in the Brain for the Treatment of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is the most common form of dementia and aging is the most common risk factor for developing the disease. The etiology of AD is not known but AD may be considered as a clinical syndrome with multiple causal pathways contributing to it. The amyloid cascade hypothesis, claiming that excess production or reduced clearance of amyloid-beta (Aβ) and its aggregation into amyloid plaques, was accepted for a long time as the main cause of AD. However, many studies showed that Aβ is a frequent consequence of many challenges/pathologic processes occurring in the brain for decades. A key factor, sustained by experimental data, is that low-grade infection leading to production and deposition of Aβ, which has antimicrobial activity, precedes the development of clinically apparent AD. This infection is chronic, low grade, largely clinically silent for decades because of a nearly efficient antimicrobial immune response in the brain. A chronic inflammatory state is induced that results in neurodegeneration. Interventions that appear to prevent, retard or mitigate the development of AD also appear to modify the disease. In this review, we conceptualize further that the changes in the brain antimicrobial immune response during aging and especially in AD sufferers serve as a foundation that could lead to improved treatment strategies for preventing or decreasing the progression of AD in a disease-modifying treatment.

Keywords: Alzheimer's disease, mild cognitive impairment, neuroinflammation, antimicrobial immunity, brain, treatment

Introduction

Alzheimer's disease (AD) is the most frequent neurodegenerative disease leading to clinical dementia; however, the cause is still nebulous despite the important research effort invested to understand the disease. The most prevalent hypothesis is the amyloid cascade hypothesis, which states that the deposition of amyloid-beta (Aβ) as plaques is the cause of neurodegeneration. All clinical trials targeting this as the causal factor have failed, suggesting that we should understand the real, underlying, and treatable factors of this disease to find new treatment targets. For decades, alternative explanations for AD pathogenesis have been proposed, the most important being the vascular, the metabolic, the oxidative stress, and the infection hypotheses. In this review we describe the various putative causes of AD, with a special focus on the infection hypothesis. We also discuss how targeting the impaired antimicrobial defense of the brain may slow the progression or even prevent AD.

What is Alzheimer's Disease?

Clinically

The clinical manifestations of AD appear quite late in life as one of the most important risk factors for the late onset of AD is aging but the pathology of AD starts decades before that.[1,2] Several stages can be defined before the onset of full-blown clinical manifestation of the disease that involves memory and language changes resulting in altered everyday functions. The preclinical stage is characterized by the subjective memory complaint. There is still a controversy whether it exists but when it is present in a family occurrence context (ie, one parent is suffering from overt AD), it could have a certain prognostic value.[3] The most recognized prodromal stage called mild cognitive impairment (MCI) is when the cognitive problems may be revealed by tests, but the person is still functioning perfectly. However, not all patients will progress from the preclinical or prodromal stages to the full-blown disease state.[4] There should be a complex constellation of factors such as genetic, immunological, and environmental factors to progress from one stage to the other. These prodromal stages are the best time/targets for prevention or disease-modifying treatments; however, the lack of real biomarkers needs to be addressed before the development of any treatment.[5]

Pathologically

AD is a neurodegenerative disease with a very long development history that can last decades.[6] AD is likely a syndrome as it seems that many different causes can lead to its development. The initiating event is not precisely defined, nevertheless several events have been incriminated such as an acute brain injury (fall or sport trauma), a vascular injury, a metabolic injury, or infection.[7] The common action between each of these triggering events is an acute inflammation as well as the production of Aβ following the amyloidogenic processing of the cellular amyloid precursor protein (APP). This acute inflammation is at the very beginning a protective process, meant to contain the damaging effects of this injury.[8] The proper characteristic of this inflammation is to produce an immune reaction which will normally eliminate the damaging effects of the insult. This will mobilize the innate immune system first to produce pro-inflammatory cytokines as well as antimicrobial peptides. Usually with the blow-up of this inflammatory process, the insult will be resumed. However, because of genetic, environmental, metabolic reasons as well as the persistence of the insult, the acute inflammation is not completely resolved, but instead it may become chronic with the maintenance of the low-grade inflammatory signals which are the pro-inflammatory cytokines, free radicals, and antimicrobial peptides. This persistent chronic inflammatory process can lead, decades later, to AD with the characteristic pathological hallmarks including amyloid plaques, neurofibrillary tangles with intracellular hyperphosphorylated tau protein, synaptic loss and neuroinflammation.[9–12]

Immunosenescence and Inflammaging: A Nutshell Description

Immunity evolves with aging and it was suggested that changes in immune functions with the concomitant occurrence of inflammaging could be responsible for the age-related diseases such as cardiovascular diseases, neurodegenerative diseases, malignancies, and frailty syndrome.[13–18] Age-related immune functionality has been extensively investigated and the most important paradigm states that the decrease in T cell function characterizes immunosenescence.[19–23] The innate immune response is also affected.[24–26] Whether age-related immune changes act alone, or through inflammaging, is not clearly elucidated, as precise biomarkers of these phenomena are still missing.[27–32] As inflammation in AD mainly concern the innate immune system either in the brain or at the periphery, we will be mainly considering it below.

Innate Immunity in Aging: The Fate Keeper

The innate immune system is an ancestral immune response assuring the first line of defense against challenges coming from the inside or the outside, mainly pathogenic microorganisms and damaged cells.[33] It is a very fast and efficient reaction that determines the subsequent adaptive immune response.[34] The important factors of innate immunity are the various phagocytic cells including neutrophils (PMN), monocyte/macrophages, dendritic cells (DC) and natural killer (NK) cells,[35–38] as well as the most recent innate-like lymphocytes such as mucosal associated invariant T cells (MAIT).[39–41] It is important to mention that the number of pattern recognition receptors (PRR), danger receptors (DR) that sense the pathogen-associated molecular patterns (PAMPs) from pathogens, and damage-associated molecular patterns or alarmins (DAMPs) from damaged cells do not fluctuate

significantly during aging.[42–46] However, the signaling pathways such as MAPKs, PI3K-akt and JAK-STAT initiated by ligation of PRRs and DRs may be altered and lead to impaired NF-κB nuclear translocation during aging.[25,47–49] This alteration may significantly impact some cellular functions in all of the abovementioned cells including phagocytosis, intracellular killing, chemotaxis and free radical production.[50–52] In its prime, the innate immune system can return to a quiescent state after neutralizing these aggressions, but with the accumulation of stressors, periods of rest are less and less frequent. Thus, the innate immune cells become more permanently activated even at the "resting" state,[53–56] a concept that has been termed "trained innate memory".[57–60] Nevertheless, this permanent antigenic stimulation contributes to a state of low but significant secretion of pro-inflammatory mediators that participate to inflammaging[61–64] and lead to a disequilibrium between activation and inhibition. Thus, the innate cells are probably a cornerstone in driving the fate of immune responsiveness in old age resulting in inflammaging[27] and as such contributing to the development of AD.[65,66]

Inflammaging

Inflammaging is characterized by a peculiar presentation, being a sterile (allegedly) inflammatory status that is chronic, systemic, low grade and therefore subclinical for a long time. The level of cytokines often remains within the (high) normal range but is significantly more elevated in older adults than in younger individuals. This is why inflammaging is also referred to as low-grade inflammation. IL-6, TNFα and CRP are often cited in inflammaging-related studies generating a myeloid hypothesis that could explain the association between aging and a low-grade inflammatory state.[67,68] In the meantime, the anti-inflammatory mediators such as IL-10, IL-4, IL-13 may also be increased as a tentative measure to control this state.[61–69] Latent virus infections such as cytomegalovirus (CMV) infection, as well as commensal bacteria (eg bacteria in gut microbiome dysbiosis), may be reactivated and become harmful and contribute to inflammaging.[70–73] Indubitably, the finding that noninfectious agents can strongly contribute to the spreading of inflammatory processes has paved the way to extend the list of mechanisms that fuel inflammaging over time. The senescence-associated secretory phenotype (SASP), that can be acquired by different types of senescent cells, is currently considered as the main noninfectious trigger of inflammaging.[74–76] Senescent cells are in a state where they cannot divide, however, the activation of DNA damage-associated responses (DDR) leads these cells to a higher capacity of secretion of pro-inflammatory molecules defining the SASP.[77–79] Recent studies suggested also that exosomes secreted by senescent cells (and their cargo) participate to SASP[80] and can modulate immune system functions.[81] Studies also involved exosomes in AD as the means to propagate Aβ pathology, neuroinflammation and oxidative stress.[81–89]

Because of the abovementioned relationships, inflammaging is one of the most important links between aging and the age-related neurodegenerative diseases. Therefore, in this context, the production of Aβ represents most probably the consequence of the neuroinflammatory process induced by several chronic situations including chronic infection, as suggested by the AMP nature of Aβ.[90–95]

Do Chronic Infections Contribute to the AD Pathomechanism?

The most popular hypothesis to explain the origin of AD proposes that deposition of Aβ in senile plaques leads to inflammation and neuron death.[96–98] However, attempts to decrease the Aβ load or to prevent its formation have had no effect on AD.[99,100] No cure whatsoever exists or seems to be on the horizon.[101,102] These facts together question the validity of this mainstream hypothesis.[103–105] Therefore, new and bold avenues of research need to be pursued to unravel new pathomechanisms leading to successful prevention and/or treatment of AD,[7,106] however integrating the unavoidable Aβ cascade hypothesis. Obviously, the most important risk factor for late onset AD is aging, which is associated with pro-inflammatory conditions that increases the risk of neurodegenerative disorders including AD.[107–109] Infection by particular microorganisms as a plausible pathomechanism had been voiced several years ago but did not receive significant attention. The demonstration by Wozniak et al of the presence of HSV-1 viral DNA[110–112] and by Miklossy and Miklossy and McGeer of the presence of spirochetes in the AD brain were too instrumental to consider infections as contributors to the pathogenesis of AD.[113–116] Furthermore, it is well recognized that periodontitis and gingivitis are linked to a higher risk of AD.[117–121] What could be the pathomechanism of this association and are specific pathogens involved? In this context, the role of *Porphyromonas gingivalis* as the master bacteria orchestrating the whole community of

microorganisms inside the mouth has been strongly evoked.[120,122] We and other groups have shown that Aβ is a powerful antimicrobial peptide secreted by neurons in response to an attack by microorganisms lends weight to this hypothesis.[90–92] However, none of these individual microorganisms has been linked irrefutably with the disease, therefore, we suggest that simultaneous or consecutive infection by several microorganisms fueled by inflammaging together lead to AD pathogenesis.[123–125] The most important common characteristic of all these microorganisms is their persistence and the inability of the brain and systemic immune system to clear them. This persistence creates a constant cycle of latency and reactivation that will activate microglia either periodically or constantly in the brain. Concomitantly with other risk factors such as genetics, diet, trauma, this can contribute to neuroinflammation and ultimately after several decades to neurodegeneration.[126,127]

Neuroinflammation, Inflammaging and Alzheimer's Disease

The infectious hypothesis provides a plausible stimulus for this neuroinflammation which is considered a hallmark of AD.[96,128–135] It also throws light on two other fundamental facts: (1) Neuroinflammation is not only the consequence of Aβ deposition (as stated by the amyloid hypothesis) but it is also the cause for Aβ deposition, and (2) Aβ is not only a "harmful" molecule that aggregates to form plaque and induce neuroinflammation, but it is also a basic element of the innate immune defense and thus a "beneficial" molecule,[13] at least at the beginning. Ultimately, as the reactivation of latent pathogens (HSV-1) and new infections become more frequent, the chronic production of Aβ increases, but its antimicrobial effect may be blunted by loss of active Aβ through its recruitment to plaque formation. Consequently, inflammation becomes chronic, endocytosis and clearance of Aß by microglia is overwhelmed, and ultimately the deposition proceeds and results in senile plaque formation.[124] The deposition of plaque may be the initiator of a chronic, harmful neuroinflammatory process that finally destroy the neighboring neurons. This process pursues unnoticed, then becomes visible clinically only when a threshold is crossed.

Local neuroinflammation may continue at a low level throughout life with little negative effect. However, when exacerbated by reactivation of infections combined with other insults such as oxidative stress, the acute inflammatory response results in unbalanced production of cytotoxic mediators difficult to control or stop.[27,136–141] Microbial metabolites may also fuel neuroinflammation. The enhanced neuroinflammatory process damages neurons and alters the blood-brain barrier (BBB). These mediators also induce peripheral inflammation and then return to further stimulate local neuroinflammation.[142–144] This progressive pro-inflammatory situation is exacerbated with age, creating a vicious cycle of local and systemic inflammatory responses leading to activation of cytotoxic microglia, unbalanced cytokine production, Aβ accumulation and irreversible brain damage.

Experimental Data Substantially Support the Infection Hypothesis of AD

The infection hypothesis was proposed decades ago when it became clear that there should be some triggering events at some points of the disease progression.[7,145–147] It is noteworthy that Oskar Fisher, in the same epoch as Alois Alzheimer, had already evoked this possibility.[148] Early evidence was done on HSV-1 viruses. The group lead by Ruth Itzhaki has identified the HSV-1 DNA in the plaques of fully developed AD brains.[149,150] An epidemiological Taiwanese study recently showed that HSV-1 antiviral treatments may interfere with the development of AD in contrast to those who did not get them.[151] The Lovheim group could make the association between the ApoE4 genotype, the susceptibility to HSV-1 infection and the occurrence of AD.[152] The virus could remain latent for many years, especially in the in neurons and in the trigeminal ganglia,[153,154] and then reactivate each time when the immune defense is diminished by stress, diseases, or other infections.[155,156] The virus can easily gain access to the brain by the trigeminus nerve and the olfactory system. Other herpes viruses like the HHV6 and HHV7 are also involved.[157] In this period of COVID-19, it has become evident that the brain might be affected either directly or indirectly by the respiratory SARS-CoV2 virus.[158] However, the long-term effects are unknown but may lead to AD-like neurodegenerative disease decades later.[159,160]

Concerning the bacteria which may be involved in triggering, strong evidence exist for *P. gingivalis*,[122] *Borrelia burgdorferi*[113,114] and *Chlamydia pneumoniae*.[161] All these bacteria themselves, their

remnant or products (LPS or gingipain) have been directly found in the brain.[122] *P. gingivalis* as a cornerstone bacterium can migrate from the mouth to the brain by the trigeminal nerve or the olfactive pathway.[162] Its presence in the brain of AD patients was recently demonstrated.[122] These bacteria were found directly in the amyloid plaques suggesting that the plaques may be a sort of biofilm.[114] Epidemiological studies also strongly suggest a correlation between periodontitis occurrence and AD.[163]

Another major source for the microbial contribution to AD is the gut–brain axis.[8,164–166] It is well known that when the gut microbiota is perturbed several psychological, psychiatric and cognitive problems, mostly acute, may arise.[167,168] These are mostly acute processes. The gut–brain axis provides a bidirectional communication via cytokines, hormones, and neurotransmitters.[169,170] In case of neurodegeneration, an alteration in the normal composition of the gut microbiota caused by infection, age or diet[171,172] may result in an inflammatory process in the brain by either direct migration of the pathological microbes to the brain,[173] via the vagus nerve,[166,174,175] or via the inflammatory products originating from these microorganisms such as LPS, lipoteichoic acid or *Escherichia coli* K99pili.[176–180] Evidence also suggests that the co-localization of LPS and other bacterial fragments in amyloid plaques[175,177] may contribute to the neuroinflammation.[181] It was also shown that production of short-chain fatty acids (SCFAs) by microbiota can activate brain microglia which causes neuroinflammation and neuronal damage in an AD model but may be also protective by decreasing BBB permeability.[182–184] Therefore, the (eubiotic) microbiome may have also protective effect on the brain neurons.[185] It should be strongly emphasized that the majority of the data discussed here were done in animal models, with the exception of the 2019 *P. gingivalis* results published by Dominy et al, which had human data.[122]

Brain Antimicrobial Immunity

The antimicrobial immunity of the brain is complex, and data are quite scarce. In the periphery, it is composed by natural defense lines, cells and mediators. In the context of the brain, the innate immunity has been the most studied because of the microglia existence and the Aβ-triggered neuroinflammation.[186] The relationship between the antimicrobial immunity and the infection hypothesis is becoming slowly unraveled.[145] This immunity seems very adequate and efficient at the beginning to eradicate the invaders, but considering the persistence of the aggressors it becomes more harmful.[187,188] In the context of AD, the innate immune system (via microglia) plays an important role in the neuroinflammation. We will mainly consider this part of the immunity in this review; however, we will also succinctly mention the adaptive part.

Blood–Brain Barrier

The BBB is the first line of defense against many noxious elements coming from the periphery including infectious agents (pathogens) and activated immune cells. The BBB is a semipermeable interface between the brain parenchyma and cerebral circulation consisting of endothelial cells, astrocytes, pericytes and a basal lamina. The BBB is predisposed to filtrate, retain and destroy the microorganisms.[189] Macrophages and endothelial cells as part of the BBB can eliminate the infectious agents. However, when the attacks become more frequent, an inflammatory process alters BBB permeability, leading microorganisms and their products to pass more freely from the blood into the brain.[190] Astrocytes are also part of the brain antimicrobial defense as they have a very important neuroprotective function by assuring the BBB integrity and as such decreasing the passage of inflammatory cells from the periphery.[191–193] However, when they become activated as A1 astrocytes they are mediating the neuroinflammation either themselves via the production of cytokines and chemokines[194] or by making the BBB more permeable to peripheral inflammatory mediators.[195]

Cellular Defense

As part of the innate immune system of the brain, microglia which are the macrophages of the brain are the most important cellular defense.[9,196,197] They are mostly from embryonic origin but some of them may originate from the monocytes getting to the brain.[198–200] Microglia very efficiently get rid of invaders and detect synaptic anomalies as they are always patrolling the brain.[194,201,202] At the same time, they are maintained in a quiescent state by their interaction with neurons via CXCR1[203] or CD200L.[204] When activated through different pathways including the TREM2-DAP12,[196,200,205] they can phagocytose and kill intracellularly all types of microorganisms. Interestingly, mutations in the TREM2

have been identified as risk factor for AD.[206] They are also able to migrate and proliferate and they exhibit two distinct phenotypes but are able to be very plastic.[207,208] The type 1 microglia are very pro-inflammatory and secrete pro-inflammatory cytokines to help clearing the aggressors, while the type 2 microglia are anti-inflammatory and are able to mitigate the inflammation and repair the tissue damages. Recently a third microglia type was described and called disease associated microglia (DAM)[209–212] and its functions are related to a stepwise activation manner implicating or not TREM2.[213,214] The DAM are somehow specific for the neurodegenerative state and participate at the beginning to the clearance of Aβ and later to neurodegeneration. However, most of the data concerning microglia in AD are in relation to Aβ peptide independently of its form (monomeric, polymeric, fibrillar or aggregated as plaques).[215,216] Through their activation via CD36, CD14, CD47 and TLRs (especially TLR4), microglia produce pro-inflammatory cytokines and chemokines.[217–219] The role of microglia is well established in various cerebral infections[220,221] however, there are no data related to the infection hypothesis of AD at the exception of one study that reported the relation between microglia and some changes of microbiota and its derivatives including LPS, as well as related to the genetic background such as ApoE4.[222] Therefore, it would be interesting to assess how microglia could behave at different stages of AD.

As the aggression in the brain persists microglia become more activated, producing chronically pro-inflammatory mediators that participate in the neuronal destruction.[196,223] Furthermore, they possess receptors which react to the overproduced Aβ.[224,225] The most important receptors are the TLRs, in particular TLR4,[199,226,227] which initiate intracellular signaling pathways leading to the activation of the NF-κB, the inflammasome and the antiviral molecular machinery.[228] At the end of this process, activated microglia become senescent and only produce pro-inflammatory neurotoxic mediators such as TNFα.[229–231] Morphologically senescent microglia show cytoplasmic hypertrophy and pseudopodia reduction[135,232,233] in contrast to the stationary microglia which can always scan the milieu for invaders with their extended pseudopodia.[234] These data point to the need of a timely regulation of the brain innate immune response to exploit the beneficial potential and decrease the inflammatory action.[197]

It is of note that the role of the adaptive immunity in the antimicrobial defense of the brain is much less understood than that of innate immunity.[235] In AD, the changes in the peripheral adaptive system are well established.[236,237] T cells can be found normally in meningeal, perivascular space and choroid plexus, but the resident T cells in the parenchyma are rare. When T and B cells can be found in brain parenchyma, it means that the BBB is compromised. However, recent studies found a small population of resident, tissue specific, memory $CD4^+$ and $CD8^+$ T cells in human brains.[238–241] Studies performed mainly in animal models suggested that T cells may modulate the microglia phenotype and activation state.[242–244] Most of the data on the adaptive immunity role in AD came from mouse models. They indicate that, when T cells are solicited because of the infection, they can enter the brain and contribute either to the neuroinflammation or to the antimicrobial defense of the brain.[245] The better understanding of their role is of the utmost importance for further immunotherapies in AD.

Soluble Mediators

The activated microglia and astrocytes secrete cytokines, chemokines and reactive oxygen species. Interleukin-1 (IL-1β), tumor necrosis factor-α (TNF-α), IL-6, IL-10, chemokines and free radicals are the most important. These mediators are very useful at the beginning of an infection as they drive the innate and the adaptive immune responses.[246] They prime the microglia for better anti-infectious response, stimulate antigen presenting cell differentiation and prime the adaptive immunity. During chronic stimulation, the production of these pro-inflammatory mediators becomes uncontrolled and leading to the constant activation of the innate immune system and to tissue destruction.[247] The activation of inflammasome via NLRP3 and NLRP1 in AD largely contribute to the production of pro-inflammatory cytokines of the IL-1 family.[228,248–250]

One of the most efficient antimicrobial and antiviral system in the brain is the interferon pathway leading to production and secretion of various interferons.[251–254] In the interferon family, the most important members are type I and type III acting on different receptors but with similar cellular effects.[255,256] The interferon regulatory factors (IRF3, IRF7) regulate IFN production.[257,258] A recent study by Romagnoli et al[154] found that

decreased mRNA levels of IRF7, MED23, IL28B and IFN-α were present in human AD brain hippocampus and temporal cortex samples, with a genetic background of the patients (eg ApoE ε4 and IRF7 A alleles) that could worsen mRNA levels and affect brain immune efficiency. Thus, in the early phase of the infection, this downregulation would favor the decrease of microglia and astrocyte activation and as such mitigate brain damage. While it becomes detrimental when the system cannot eradicate the aggression; the inflammation continues, and neurodegeneration is occurring. However, the exact role and contribution of this important antimicrobial defense pathway just starts to be elucidated as the recent COVID-19 disease revealed the gaps in our understanding especially with its neurological manifestations.

Antimicrobial peptides (AMP) are also part of the immune defense against pathogens. They can efficiently fight the infections. Aβ is not only a harmful by-product, but also could have important physiological roles.[33,35,259] The knowledge about the physicochemical properties by which Aβ may exert its antimicrobial action is emerging but still remains partially understood. It became evident that targeting Aβ at preclinical and prodromal stage may be very harmful as demonstrated by many clinical trials targeting Aβ. All the pharmacological attempts to block its production by inhibiting the BACE or by directly targeting any physical Aβ form will not lead to any clinical and cognitive improvement.[100–102] Therefore, this discovery gave a new impetus to the infection hypothesis of AD.[103] This also highlighted that in the brain there may be other antimicrobial peptides protecting against invasion. LL-37 and defensin-1 are well-known AMP[260] and several neuropeptides may also play this role including GLP1 and PACAP.[261,262] Furthermore, it was shown in 2017 by De Lorenzi et al that LL-37 can bind to Aβ peptide and form a nontoxic complex.[260]

Together the brain antimicrobial immune defense is very efficient but the concomitant chronic insults, inflammaging, genetic, epigenetic, and environmental factors lead to neuroinflammation resulting in neurodegeneration. Thus, it is very important to understand the upstream events resulting in neuroinflammation which lead to the final common step in the pathology of AD—the uncontrolled Aβ production initiating and maintaining a vicious chronic inflammatory circle which may serve target to treatments.

What About Interventions?

In the past decades, there have been numerous valuable randomized clinical trials (RCTs), mainly targeting Aβ. For example, the most recent ones—with solanezumab[263] or verubecestat[264] have been unsuccessful. Thus, we need new treatments targeting other pathomechanisms of the disease such as the neuroinflammation.[265,266]

By understanding the syndromic nature of AD, it would be very difficult to design just one treatment, but one pathological process seems to be common to all specific causes: neuroinflammation. An optimal treatment for AD could be an agent specifically targeting neuroinflammation. As we are specifically interested here in the antimicrobial defense in the brain, we will consider the fight against infections and inflammation in a chronic setting.[5] We will describe what treatment options exist and what is in the pipeline considering these pathological processes.

Prevention/treatment of Infections

The simplest intervention would be to find a prevention for the most important agents involved in the development of AD. We could develop efficient vaccines against the putative pathogens. The recent development of vaccines against SARS-CoV2 gives hope that we could develop a vaccine against the herpes virus HSV-1 and other Herpesviridae such as HHV6, HHV7 or CMV. If this is not possible, an intermittent secondary prevention treatment in all individuals, and more specifically in APOE4 homozygote carriers,[267,268] should be initiated with acyclovir, an antiviral treatment that shows almost no side effects. This assumption at least in a recent Taiwanese epidemiological study received strong support.[151] Therefore, strong arguments exist for the use of somehow intermittent antiviral treatment in individuals who are the most susceptible to carry lifelong infections with HSV-1, herpes zoster[269] or show signs of reactivation measured by IgM serum level. This is a cheap, affordable treatment with great potential. There is presently an ongoing phase II study with valacyclovir in mild AD patients.[270] It is of note that this treatment should be efficacious in the preclinical stage preventing its development or at the prodromal stage (MCI) delaying or preventing the progression to full AD. The results of the mentioned study should be known very soon (during 2021) which could hopefully

Table 1 Prevention Therapies (Potential Therapeutics for Modulating Inflammation/antimicrobial Immune Defense)

Agent	Class	Mechanism of Action	Trial	References
Vaccines	Infection	Antimicrobial		267, 268
Antivirals	Infection	Antiviral	Phase II valacyclovir	151, 269, 270
Penciclovir				112
Foscarnet				112
Bay57-1293				112
Bioflavanids				278
Antibiotics	Infection	Antibacterial		294
Minocycline				250, 365
Doxycycline				178, 365
Rifampin, ceftriaxone	Infection/inflammation	Increasing GLT-1		95, 271, 310, 338
Gingipain inhibitor	Infection	Gingipain inactivation	Phase III COR388	272–274
Mediterranean diet	Inflammation	Microbiome	Already available	178, 276–290
Holobiotics	Inflammation	Microbiome	Already available	164, 280, 282, 301–310
Prebiotics				165
Probiotics				165, 302, 311, 312
Postbiotics				278, 279, 313, 314
GV-971	Inflammation	Microbiome	Already available	292
Exercise	Inflammation	Innate immunity	Already available	293
NSAID	Inflammation	Innate/adaptive immunity	Phase I salsalate	320, 321
AMPs	Infection	Antimicrobial		90–92, 261, 262
Alz-OP1	Inflammation	Immune system	Phase III	360

change our present practice. There are other antiviral drugs which could become therapeutics in AD prophylaxis if appropriate clinical trials are carried out. Penciclovir, foscarnet, valacyclovir, Bay57-1293 and bioflavonoids derived from the leaves of *Ginkgo biloba* have been proposed for an eventual use in prevention or at least in stopping progression in AD (Tables 1 and 2). All these substances have demonstrated powerful antiviral activity in vitro and also in animal models, but data on their clinical trials are missing.

The same tactic may be also used for other pathogens like *P. gingivalis*. A vaccine neutralizing gingipain, toxic proteases from *P. gingivalis* could be efficient to prevent AD. Repeated courses of antibiotics may be also envisaged for bacteria, spirochetes, and chlamydia but all the different strategies using antibiotics have been unsuccessful in any RCTs carried out until now. Tetracycline antibiotics (minocycline or doxycycline) or rifampin were ineffective.[271] Even the reasons may be multiple (treatment time, dose, pathways used, brain transport), these failures unfortunately dried the antibiotic treatment pipeline for AD. Hope was revived with the development of potential gingipain inhibitors, as gingipain, is the virulence factor of *P. gingivalis* and plays a crucial role in the colonization of the host and in the inactivation of the antimicrobial defense of the host and as such ensures the pathogenicity and survival of *P. gingivalis*.[272,273] The developed gingipain inhibitors COR286, COR271 and COR388 were found to induce the bacterial death and reduce the bacterial burden in animal models.[274] Unfortunately, there is no epidemiological data for antibiotics lifelong use and AD development like it exists for antivirals or for nonsteroidal anti-inflammatory drugs (NSAIDs). This would be worthwhile to perform[275] but keeping in mind that a possible antimicrobial resistance may develop.

The occurrence of dysbiosis/pathobiont[276] may be prevented since the earliest period of life by a diet maintaining gut microbiota health.[8] In this context, a balanced anti-inflammatory diet such as the Mediterranean or the Asian diet may be successful candidates.[277–283] In contrast to the western diet, these

diets contain many beneficial products maintaining a balanced inflammatory milieu even during aging when the inflammaging is very frequent. Many components such as polyphenols, short chain fatty acids, flavonoids, proteins, vitamins B, curcumin and oligoelements (including selenium, copper, cobalt, magnesium) assure a healthy homeodynamic milieu decreasing the pro-inflammatory, pro-oxidant and epigenetic modulatory effects of the internal and external challenges.[178,280–292] These diets have not only the advantage to decrease the propensity for chronic inflammations, but also reinforce the adaptive immune response.[172,293–295] Recently GV-971, a new drug meant to regulate gut flora imbalance and reshape immune homeostasis, was approved in 2019 in China. GV-971 can prevent the infiltration of the peripheral immune cells into the brain, inhibit neuroinflammation and prevent the progression of AD.[296] Beside stabilizing the gut microbiota, it is reducing the increased circulating phenylalanine/isoleucine shown in AD patients and known to increase neuroinflammation. Together all these interventions alone or in a multimodal way considering their beneficial effects concur to improve cognitive functions in AD patients.

We should also mention the beneficial effect of regular physical activity. This has been shown to increase the cerebral flow, the production of antioxidants, and to reinforce our antimicrobial immunity. It is needless to say that most probably any of these interventions alone will be enough to prevent or treat the very early stages of AD, but a multimodal intervention combining all of them may be efficient. Some of these components were already involved in the original FINGER trial.[297] Together, as appealing as this antimicrobial therapeutic approach could be, the lack of real knowledge and insight into pathogenesis related to microbes preclude a judicious utilization of the antimicrobial agents.[298] More studies are needed to confirm their efficacy without any doubt on a long-term basis.

Mitigatory/modulatory Treatment of Neuroinflammation

There are many ways to intervene in the mitigation or modulation of neuroinflammation.[299] These may be pharmacological or nonpharmacological, direct or indirect interventions.[300–302] Among the nonpharmacological interventions, the diet and exercise are the most prominent but indirect measures. Multiple pharmacological means already exist to intervene at the neuroinflammation level such as the mentioned NSAIDs. Even controversial, this approach has been shown efficient when patients with rheumatoid arthritis have been treated and developed much less AD.[303] It is still questionable whether this effect is direct or indirect. Recently, it was shown that the blockade of peripheral myeloid EP2 (receptor of prostaglandin E2) restored the glucose metabolism, decreased the age-related inflammatory state, and reversed cognitive decline in aging mice.[304] These results suggest that regulating the immunometabolism of macrophages/microglia may have neuroinflammation modulatory action leading to better cognition.

Specific Dietary Components

Besides the general diet described above, some nutriments can be directly used to mitigate the neuroinflammation. The microbiota has been targeted by pre-, pro-, and postbiotics as potential complementary therapeutic approach for AD.[164,284,286,305–313] Of note, the probiotic may play a prominent role as they can efficiently regulate or even reset the alterations in various microbiota of the organism which could even have direct anti-inflammatory effect. Probiotics may restore the homeostatic equilibrium among pathogenic and beneficial microbes in the holobiota, especially decreasing bacteria that produce glutamate with excitotoxicity effects.[314] Few studies have investigated the use of multispecies probiotic treatment in AD with conflicting results. In one study, 12 weeks of probiotic treatment improved the cognitive status,[315] while in another the supplementation for one month changed the microbiome but had no effect on cognition.[316] A recent study found a significant improvement in cognition with a probiotic cocktail.[306] Two ways exist to manipulate the microbiota; the first, more futuristic, uses precision diets based on the specificities of each microbiome, while the other, already available, use bulk diet interventions to restore the healthy microbiome of an individual. Before we can define either the quantitative or qualitative microbial changes as well as the metabolic changes in AD, it will be difficult to implement a generalized microbiota modulating diet to modulate neuroinflammation in AD.[164]

Ketone (medium chain triglyceride) supplements have also been shown to improve the cognitive functions in MCI subjects.[317,318] Ketone bodies are known

to act on the microbiome by restoring its equilibrium, but more importantly by reducing the activation of the inflammasome which is one of the contributors to neuroinflammation. Recently, several case studies have been published on the use of ketogenic diet in APOE4 allele carrying MCI and mild AD individuals with a significant increase in their cognitive performance such as the significant increase of their score of MoCA test.[319–323] Involvement of vitamins like vitamin D and vitamins B may also modulate the inflammatory state of the brain by acting on the scavenger receptors.[324] Some oligoelements such as zinc may also regulate the chronic inflammation in the brain. Amino acids such as glycine or leucine may also be immunoregulatory by an anti-inflammatory effect leading to decreased microglia activation.[325] There is a long-lasting debate on the omega-3 docosahexaenoic acid (DHA) efficiency in the treatment of AD at different stages.[326] In a study on MCI patients, the combination of omega-3 supplementation with antioxidants, vitamin D3 and resveratrol showed beneficial effects on MMSE (mini mental state Examination) improvement via modulation of the innate immune response.[327,328]

Anti-inflammatory Drugs/cytokines

There are presently no direct anti-inflammatory drugs recommended or used in AD. Epidemiological and observational studies strongly suggest a decreased relative risk of developing AD with nonselective NSAIDs,[329,330] however the RCT studies did not confirm these observations. One of the main problems is the timing of their utilization, since it cannot be to early neither too late. These treatments should not compromise the natural defense of the brain immune response but should act before the immune response could become harmful by becoming chronic. In this context, biomarkers would make the difference, however we currently do not have any of them in the pipeline to be targeted for intervention. The role of IL-10 which may be appealing to become an efficient target, however, its role was questioned as it can be inflammatory at some point of the AD development.[331] In contrast, if exposed to Il-1β, TGFβ1 or IL4, microglia may acquire an anti-inflammatory phenotype by expressing arginase-1 what will increase its phagocytic capacity towards Aβ.[332] Many omics and other high throughput-based studies were carried out without really much success to find target biomarkers but brought important scientific data for the future development.[333] Nevertheless, some anti-inflammatory treatment already exists in the pipeline and some others may become interesting.[313,334,335]

For a long time, the use of angiotensin receptor blockers (ARBs), including candesartan, telmisartan or losartan, showed a reduction of neuroinflammation, but only in animal models.[336] In humans there are mainly epidemiological evidence that ARBs may be efficient in AD treatment.[337] In the ONTARGET trial using telmisartan vs ACE inhibitor, the telmisartan group showed less decrease in MMSE than the control group.[338] However, it is difficult to establish what is the mechanism as the reduction of the hypertension recognized as a risk factor for AD could be also the cause of the ARB success.[339]

Another putative repurposed drug could be fasudil which is a selective inhibitor of rho kinase (ROCK) 1 and 2 and a powerful vasodilator.[340] This drug has anti-inflammatory properties that decrease the IL-1 and TNFα production in a rat model.[341] More studies are needed in humans to confirm these results. Another promising compound may be phenserine which is a cholinesterase inhibitor.[342] In preclinical models, this drug suppressed IL-1 production, to protect against free radicals and reduce excitotoxicity, resulting in decreased neuroinflammation.[343] A small phase II study showed good tolerability and some cognitive benefits but was very much underpowered.[344] Other drugs which may also have promising applications are disease-modifying antirheumatic drugs (DMARDs) which are used in other inflammatory diseases such as rheumatoid arthritis.[265,345]

Other repurposed molecules could be considered such as the β-lactam antibiotic ceftriaxone which increases the expression of astrocytic glutamate transporter 1 (GLT1) resulting in decreased excitotoxicity and neuroinflammation by detoxifying the brain from glutamate.[314,346] Ceftriaxone may also play an anti-inflammatory and antioxidant role.[347] This could open new avenues of investigations with similar compounds. It would be also interesting to study whether they have also direct antibacterial properties in AD. Other compounds found beneficial in PD, namely salbutamol and trifusal (platelet aggregation inhibitor), are antioxidant by blocking the cyclooxygenase 1 and anti-inflammatory by modulating among others, NF-κB. RCT human studies in different phases of AD are badly warranted with all these drugs. Considering the role of the pro-

Table 2 Disease-modifying Treatments (Potential Therapeutics for Modulating Inflammation/antimicrobial Immune Defense)

Agent	Class	Mechanism of Action	Trial	References
ARB	Inflammation	Antihypertensive	Phase III Telmisartan	327–330
Fasudil	Inflammation	Pro-inflammatory cytokines		331,332
Phenserine	Inflammation	Immune system	Phase II	333–335
DMARD Etanercept	Inflammation	Pro-inflammatory cytokines		336, 337 340, 341
Checkpoint inhibitors	Inflammation	Immune system	Planned	265, 343–345
Copexone	Inflammation	T cells	In use in MS	347
Rapamycine	Inflammation	mTOR	NCT04209110	348, 356
Thalidomide	Inflammation	Decreasing TNFα		349
Senolytics Metformin	Inflammation	Senescent cells		355, 356 355
Dratumumab	Inflammation	Anti-CD38	NCT04070378	363, 364
Lenalidomid	Inflammation	Pro-inflammatory cytokines	NCT04032626	349, 360
L-serine	Inflammation	Immune system	Phase II	360
Montelukast	Inflammation	Antileukotriene	Phase II	360
Sargramostim	Inflammation	GM-CSF	Phase II	360
GB301	Inflammation	Autologous Treg	NCT03865017, Phase II	265
AL002	Inflammation	TREM2 agonist	Phase I	360
Azeliragon	Inflammation	Antagonist-RAGE	Phase III	362
Masatinib	Inflammation	Tyrosine kinase	Phase III	360
XPro1595	Inflammation	AntiTNFα	NCT03943264	360

inflammatory cytokines, it would be legitimate to think that the drugs developed for other chronic inflammatory diseases could be beneficial for AD too. However earlier studies on anti-TNF treatment failed. A recent study indicated that patients with rheumatoid arthritis are at increased risk for AD but those using the etanercept had a lowered risk of AD.[348] These findings initiated a new study using etanercept as disease-modifying therapy (DMT) for AD.[349]

Reinforcement of the Antimicrobial Defense by Stimulating the Immune System (Immunomodulation)

An efficient approach could be to potentiate the initial immune and inflammatory responses in order to reinforce the antimicrobial defense. One of the first events in the immune fight against pathogens is the production of interferons (IFN) that modulate the inflammatory response, eradicate the pathogen, and prime the immune system to become more efficient. Anti-CSF-1R treatment may enhance the production of type-I IFN as demonstrated in cancer.[350] The production of other pro-inflammatory cytokines, the complement system and the free radical production may also be enhanced by this treatment. Sometimes drugs approved for other diseases (eg cancer) may be repurposed for other chronic inflammatory diseases such as AD. This could be the case for the tyrosine kinase inhibitors (eg dasatinib), immune checkpoint inhibitors (eg PD1, PD1L, CTLA-4) in non-T cells such as dendritic cells[351] which can increase the innate immune response and prime the adaptive immune response. In animal studies, checkpoint inhibitors enhanced the cognitive

performance[352–354] but this treatment appears nonconclusive in human studies.

Some immunomodulating agents may also be considered for AD treatment.[266] Copaxone used in multiple sclerosis to boost the T cell immune response could modulate the microglia response.[355] Rapamycin, an mTOR inhibitor used as anti-aging drug, could be considered as an immunomodulatory drug in case of AD as preclinical data showed that it can maintain BBB integrity and decrease Aβ pathology.[356] Thalidomide and its derivatives are immunomodulatory drugs decreasing TNFα levels and regulating microglia and astrocytes activation in preclinical studies.[357]

Importantly, the use of therapeutics enhancing the antimicrobial efficiency of the brain immune response should be very tightly controlled in power and time as prolonged stimulation will lead to chronic inflammation, cellular senescence, chronic neuroinflammation and neuronal/synaptic damage.

Geroprotectors and Senolytics

Aging, the most important risk factor for AD development, is associated with changes in the immune system which contribute to the decreased antimicrobial defense. It is conceivable that modulation of the immune changes with aging could be a viable strategy for AD prevention and treatment, and toward this approach, geroprotectors may be useful.[358] In animal studies, young blood was shown to influence the cognitive status[359] and the results from these studies served as a model for a human phase 1 clinical trial demonstrating the feasibility and the innocuity of a such treatment.[360] Identical considerations can be given to mTOR inhibitors which demonstrated immune modulating effects in older subjects by increasing the influenza vaccine efficacy.[361] IL-7 and thymosin β4 treatments were also proposed in this sense.[362,363] However, this type of treatment should be envisaged from very early ages giving the long-term development of AD. Therefore, each of the proposed treatments can be looked at from two possible points of view. One is prophylaxis, where the envisaged drugs, vaccines or other, would have to be applied to young populations, prior to the onset of any symptoms. The other would be aiming at stopping or at least delaying the disease progression when it is already manifested. The latter would likely be easier to be accepted, even if less effective, but new studies try to implement more the prevention type of interventions early at life.[362,363]

The use of senolytics at a precise timescale may also be rewarding since senescent cells via the SASP phenotype are suggested to be the major mediators of aging and inflammaging, and microglia and astrocytes may adopt a senescent phenotype over time. Among these senolytics, metformin, which is used in the treatment of type 2 diabetes, could be considered. A phase 3 clinical trial is underway to explore whether metformin can improve CNS glucose metabolism or decrease the senescent cell charge (NCT0062019; NCT01965756). In retrospective epidemiological studies, metformin showed a reduced risk of cognitive impairment.[364] Rapamycin and other agents modulating/inhibiting the mTOR pathway could act as senolytics.[365]

Disease Modifying Treatment: Present and Future

Currently, there is no DMT available for AD but the abovementioned treatments may become DMTs and there are more molecules in the pipeline.

If we consider the composition of the microbiome to explain AD pathogenesis, we should also ponder why many older subjects do not acquire AD. These individuals might possess in their gut bacteria that are metabolically and immunologically active which may produce either beneficial small molecules specifically targeting the brain. The issue is worth investigation by last-generation techniques such as artificial intelligence, transcriptomic, systems biology and complex system approach which would allow us to probe this question.[366]

Another treatment avenue to explore is the AMP antimicrobial characteristics.[90–93] Protein analysis comparing known AMPs and Aβ confirmed structural homology between Aβ and a specific family of bacteriocins.[367] Bacteriocins are traditionally synthesized by bacteria against other bacteria.[368] Aβ also has structural similarities with another AMP called LL-37. This implies that both can efficiently destroy microbes but also form cytotoxic soluble oligomers and insoluble fibrils.[92] Thus, it is conceivable that in the future, Aβ structure and properties may serve as a template for advanced computational models to develop new more powerful specific AMPs.

Small molecules targeting neuroinflammation (ie Masitinib, ALZT-OP1, COR388, telmisartan, sumifilam, neflamapimod, azeliragon, DNL758 and GC021109) are

in phase 3 clinical trials. Except for ALZT-OP1, all these molecules target the mild-to-moderate stages of AD. ALZT-OP1 targets the early stage of the disease with results being available between 2020 and 2024.[369] A recent article by Cummings et al[370] reviewed the AD drug development pipeline and stated that among the drugs in development many are disease-modifying agents or repurposed drugs. Four drugs targeting the inflammation/infection/immunity (17.6% of all agents) are currently in phase 3 clinical trials. The first is ALZT-OP1 (cromolyn + ibuprofen) aiming to increase the clearance of Aβ by modulating the microglia activation; the next is azeliragon, a RAGE antagonist, aiming to reduce Aβ load and neuroinflammation in the brain;[371] the third is masitinib, a tyrosine kinase inhibitor, aiming to reduce the Aβ charge and tau phosphorylation; and the last is COR388, a bacterial protease inhibitor targeting gingipain, aiming to reduce neuroinflammation and hippocampal neurodegeneration. Other potential candidates did not seem to lead to conclusive results and were halted.[335]

There are also several phase 2 clinical trials targeting inflammation/infection/immunity, including four using biologics and seven small molecules. One is using curcumin and aerobic yoga to exploit their antioxidant and anti-inflammatory properties and target neuroinflammation. Daratumumab (NCT04070378) is a monoclonal antibody targeting CD38 which is expected to have immunomodulatory effects by decreasing the microglial activity. CD38 is a glycoprotein found on the surface of many immune cells including $CD4^+$, $CD8^+$, B lymphocytes and natural killer (NK) cells. CD38 also functions in cell adhesion, signal transduction and calcium signaling. The CD38 role is controversial and depends on the cell types, the aggression and the moment of the immune stimulation. However, it may play a determinant role in the modulation of inflammatory processes such as in neuroinflammation.[372,373] Dasatinib and quercetin are respectively a tyrosine kinase inhibitor and a flavonoid antioxidant, with strong senolytic activity. They both can decrease inflammation and increase immune response. To downmodulate the immune system, GB301 is a trial comprising of isolating autologous Tregs from AD patients, expanding them and reinjecting them expecting the promotion of immune homeostasis and decrease of neuroinflammation. Lenalidomid, an antineoplastic and immunomodulatory molecule, is expecting to reduce the pro-inflammatory cytokines TNFα, IL-6 and IL-8 and to modulate both the innate and the adaptive immune responses to decrease neuroinflammation (NCT04032626). L-serine, a naturally occurring dietary amino-acid decreasing neuroinflammation, is expected to play a role in brain neuron preservation, similar to montelukast, a leukotriene receptor antagonist that reduces inflammatory pathways and neuronal injury. Sargramostim (GM-CSF) is expected to modulate neuroinflammation by stimulating the right immune response that will remove Aβ and improve synaptic functions. The infection/inflammation modulating agents rifaximin (antibiotic) and valacyclovir (antiviral) studies have been already discussed. All these studies are expected to be completed in the coming years with the hope that some of them may be pushed to phase 3 trials and ultimately become a disease-modifying drug.

There are also some potential drugs in phase 1 trials, including AL002 (monoclonal antibody targeting TREM2 receptors), AL003 (monoclonal antibody targeting SIGLEC-3: CD33), J1J-40346527 (CSF-1R antagonist), salsalate (NSAID), rapamycin (NCT042009110 the CARPEDIEM) and XPro1595 (TNF inhibitor: NCT03943264). They are all designed to mitigate neuroinflammation either by decreasing the microglia activation or increasing microglia functionality for Aβ phagocytosis and clearance.

The discovery that MMP13 and PI3K participate in Aβ production at a later stage of the neuroinflammation could stimulate the use of multistage treatment involving the mitigation of neuroinflammation and the modulation of the MMP13 pathway. This can also apply to many unique treatments that could be more efficient in combination using multi-hit targets. Among all these molecules mentioned above, none of them have proven a substantial efficacy during the trials but we should wait until the completion of these trials to know whether any of them could become a disease-modifying treatment.

Ways to Find New Treatments for AD: What Could Help to Accelerate the DMT Discovery?

To develop new treatments, we could investigate the molecular pathways underlying the pathogenesis of the disease, but it is not presently the case for AD. Another possibility is the combinatorial chemistry which can lead to the discovery of new molecules. Nowadays, one promising way is to repurpose or reorient drugs toward the treatment of AD as many of them are already

being used in practice for other indications and revealed to be harmless.

An alternative pathway to drug development, as it was also revealed in the search for COVID-19 treatment, is via the use of computational methods and artificial intelligence (AI).[374] In particular, an interesting and novel direction is computational drug design under the infection hypothesis and antimicrobial protection hypothesis of AD.[7,95] From the experimental side, receptor-ligand binding assays will be required to quantify binding affinity and kinetics, conformations of targets, binding thermodynamics between Aβ, AMPs and glycoproteins of AD-related microorganisms. This should also include nuclear magnetic resonance, surface plasmon resonance and isothermal titration calorimetry. These experimental data would provide invaluable information to narrow down the drug search space during the computational screening of novel AMPs. Moreover, these computations and experiments should be coupled to research strategies that shy away from transgenic animal models that do not recapitulate human AD. This is possible due to recent technological leaps in stem cell research, which enable lab-grown human mini-brains that reproduce the hallmarks of AD.[375,376] The mini-brains (as an alternative AD model) allow for testing of various invivo-based hypotheses and to gather complementary and complex information that perhaps is missed in transgenic animal models. For example, biofilm experiments, neural tissue based on multiomics data from patients and deceased frozen brains can in principle be recreated in mini-brains and tested. Altogether, this framework provides clear targets for the design of AMPs with high-therapeutic efficacy against AD. Indeed, since Aβ is a powerful antimicrobial peptide that targets and neutralizes AD pathogens, then it is reasonable to consider the development of a cocktail of novel and more powerful AMPs based on Aβ template and possibly other peptides (eg LL-37) but without their negative physical-chemical properties. Taking all this together, we can envisage a multistage closed-loop framework between in silico drug screening and drug testing in mini-brains as follows: stage one should involve data mining in existing databases, antimicrobial activity prediction via rational design[377] and quantitative structure–activity relationship (QSAR) should generate analogs with improved activity. This step should also incorporate novel computational methods based on topological data analysis (TDA), which enable us to extract topological and geometrical invariants from candidate molecules (see[378] for a brief introduction to TDA). The overall aim of this stage is to extract the microscopic structure/features of a molecule characterized by physical-chemical descriptors (polarizability, dipole moment, number of atoms, hydrophobicity, toxicity, etc) and uniquely map it to macroscopic experimental observables (ie activity of the molecule, for example, binding kinetic and thermodynamic parameters). With TDA one can go beyond and include geometrical and topological features of the molecule associated with primary, secondary, tertiary structures (and more) of the molecule. Stage two, should consider state-of-the-art molecular simulations to determine the mechanism of action of AMPs (in particular Aβ) against AD pathogens. Stage three, should combine information gained from steps 1 and 2, and with further determination of physical-chemical descriptors of the generated analogs and Aβ, these can be used to train and screen potential AMP candidates via advanced machine learning. This step should include optimization by means of an evolutionary algorithm, which runs in closed-loop process by bootstrapping the experimental assay (eg mini-brain) to the peptide synthesis process and further interactive in silico prediction by machine learning. During this stage the screened AMPs should be tested against user-desired property (eg IC_{50}), as well as multiomics analysis. In this way AMP sequences can be ranked in terms of the desired property and those of poorest quality are rejected, allowing a new population to be selected. The added value of multiomics is that it departs from traditional experimental studies, which are usually carried out to isolate the effects of a single mechanism and not to investigate the interactions of many mechanisms. This leads to a set of results that are conflicting, difficult to interpret or understand the interactions of the underlying mechanisms leading to the pathogenesis of a disease. Overall, the proposed closed-loop framework based on advanced data analysis and state-of-the-art in silico drug screening provides a systematic and holistic screening of AMPs with high-therapeutic efficacy against AD pathogens. Moreover, it has the potential of accelerating drug design and reducing the overall cost of drug development, which aligns with the National Alzheimer's Project Act that articulates the

ultimate goal of preventing or effectively treating AD by the year 2025.[379]

Below, we briefly compare Aβ42 (in an apolar microenvironment[380]) and LL-37[381] to provide a glimpse of only a very small part of the proposed closed-loop computational framework in order to sway the AD community about the validity of this research pathway. A key part of screening novel AMPs will involve comparing AMPs and search for new amino acid sequences with improved physical-chemical properties. One step in this direction is to employ traditional primary amino acid sequence alignments and secondary protein alignment (ie 3D structural superposition), as shown in Figure 1 (left panels **A**–**E**), which compares Aβ42 and LL-37. Panel A, depicts the 3D secondary structures of Aβ42 in an apolar environment, which appear to depict formation of α-helices (see[380]). Panel B shows LL-37 and panel C illustrates the 3D alignment and superposition of the two peptides, showing that they possess similarities in their secondary structures. Panel D shows primary sequence alignment and indicates a minor level of amino acid sequence homology between the two peptides. However, by performing sequence alignment followed by 3D structural superposition (of secondary structures) we observe that there is a significant portion of their amino acid sequence that aligns. In Figure 1 (right panels **A**–**E**) we use TDA to characterize the topological invariants of the two peptides. For the sake of brevity, we will not explain the method in great detail but rather refer the reader to our recent article that gives an insight of TDA and how it can be applied to high-dimensional and multiscale data.[371] However, in brief, TDA extracts topological and geometrical features that persist across spatial scales (hence beyond classical network analysis). These persistent features correspond to invariances of the data and are summarized in specific diagrams as shown in Figure 1 (right panel, **A** and **B**). These invariances can in principle be related to primary, secondary, tertiary (and so on) structures of proteins. In Figure 1 (right panel,

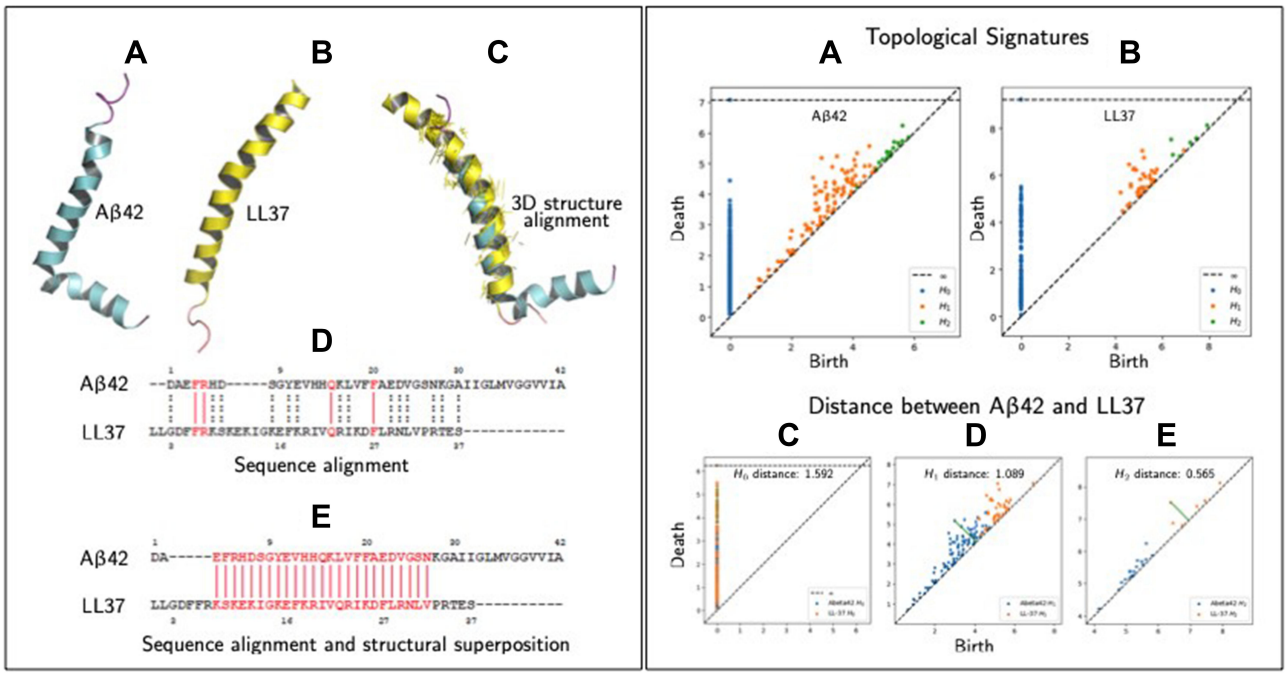

Figure 1 Similarities measures between peptides (specifically Aβ42 and LL-37). Left panel, (**A**) 3D structure of Aβ42 in an apolar environment; data from PDB (RCSB Protein Data Bank, http://www.rcsb.org, PDB ID 1IYT) shown using PyMol software. (**B**) 3D structure of human host defense cathelicidin LL-37 (RCSB Protein Data Bank, PDB ID 2K6). (**C**) Structural superposition/alignment of 3D structures of Aβ42 and LL-37 represented in blue and yellow colors, respectively. The yellow colored lines represent actual alignments the algorithm has predicted shown using PyMol. (**D**) Sequence alignment of Aβ42 and LL-37 using the Clustal Omega shareware (http://expasy.org/proteomics). Identical amino acid residues are indicated by vertical solid red lines and amino acids possessing similar properties, by dashed vertical dotted black lines. (**E**) Sequence alignment of Aβ42 and LL-37 using PyMol alignment plugin using method "super" whose algorithms can be looked at (http://pymolwiki.org/index.php/Align). Vertical red lines represent the sequence that gets aligned/superimposed in the 3D structure as shown in (**C**). Right panel, (**A**) Topological signatures of Aβ42, which persist (birth/death) across scales. The invariants (H0,1,2) are computed with RIpser software (https://ripser.scikit-tda.org/en/latest/), where the input is the peptide as a point cloud. In this case we generated the point cloud in which each point represents one the centroid of the amino acid residue. (**B**) Topological signatures of LL-37. (**C**–**E**) Compares three topological signatures of Aβ42 and LL-37 using bottleneck distances, which shows some level of topological similarities.

C–E) we compare the topological invariances of Aβ42 and LL-37 via an appropriate distance called bottleneck distance. The results show that there is some level of topological similarities between these two peptides and we envisage that such information could be used as input features to machine learning algorithms to screen for new AMPs.

Given the context of infection hypothesis and antimicrobial protection hypothesis of AD we also computed the antimicrobial and antiviral activity of Aβ42 and LL-37, as shown in Tables 3 and 4 respectively. Specifically, in Table 3, we find that various amino-acid subsequences of Aβ42 show antimicrobial activity. However, so far, we found that only a subsequence that overlaps between the Turn and C-terminus region of Aβ42 has antiviral activity. Note that previous studies have suggested that the C-terminus region of Aβ42 has also some similarity with a virus fusion domain.[380] Although these results are under an

Table 3 Antibacterial and Antiviral Activity of Aβ42

	Method	Amino-acid Sequence	Start Position	Score	Antibacterial Activity
1	**N Terminus**	GYEVHHQKLVFFAED	9	1.025	✓
		DAEFRHDSGYEVHHQ	1	0.698	✓
		GSNKGAIIGLMVGGV	25	0.687	✓
2	**C Terminus**	GIIAGKNSGVDEAFF	10	0.280	✓
		GVMLGIIAGKNSGVD	6	0.142	✓
		FVLKQHHVEYGSDHR	24	0.129	✓
3	**NC Terminus**	YEVHHQKLVFFAEDVFFAEDVGSNKGAIIG	10	0.803	✓
		HDSGYEVHHQKLVFFDVGSNKGAIIGLMVG	6	0.572	✓
		KGAIIGLMVGGVVIADAEFRHDSGYEVHHQ	28	0.147	✓
4	**Full Sequence**	DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA	1	1.306	✓

Amino acid subsequence	**Alignment model**	**Composition model**	**Physicochemical model**	**AVP Motif – Antiviral activity**
KGAIIGLMVGGVVIA	Non-AVP	44.35	47.01	✓

Notes: For the antibacterial we used the AntiBP2 software (https://webs.iiitd.edu.in/raghava/antibp2/) that uses neural networks and support vector machines (SVM) to predict the amino-acid subsequence of a peptide with antibacterial activity. AntiBP2 utilizes four datasets to train their models: N-terminus based, C-terminus based, N+C terminus based and amino acid composition method. These four methods are SVM trained on 4 different datasets compiled using N, C, NC and full composition peptides respectively. For the antiviral activity we employ the AVPpred software (http://crdd.osdd.net/servers/avppred/), which computes various features (ie motifs and alignment followed by amino acid composition and physicochemical properties during fivefold cross validation using SVM. In particular, we fragment the amino sequence into subsequences of lengths 15 while taking the overlap length to be 14 and finally the subsequences of length 15 are processed by AVPred. In this case, we find that a subsequence contained in the turn and C-terminus of Aβ42 does indeed have antiviral activity.

Table 4 Antibacterial LL-37

#	Method	Amino Acid Sequence	Start Position	Score	Antibacterial Activity
1.	**N Terminus**	GKEFKRIVQRIKDFL	14	1.601	✓
		KEKIGKEFKRIVQRI	10	0.559	✓
		IVQRIKDFLRNLVPR	20	0.324	✓
2.	**C Terminus**	VLNRLFDKIRQVIRK	6	0.430	✓
		RKFEKGIKEKSKRFF	19	0.314	✓
		FDKIRQVIRKFEKGI	11	0.082	✓
3.	**NC Terminus**	QRIKDFLRNLVPRTELGDFFRKSKEKIGKE	22	0.237	✓
		KSKEKIGKEFKRIVQEFKRIVQRIKDFLRN	8	0.082	✓
		RIVQRIKDFLRNLVPFFRKSKEKIGKEFKR	19	0.017	✓
4.	**Full Sequence**	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES	1	1.474	✓

Notes: We find via AntiBP2 software that various amino acid subsequences have antibacterial activity. However, we could not determine antiviral activity with the AVPpred software and thus more work is required.

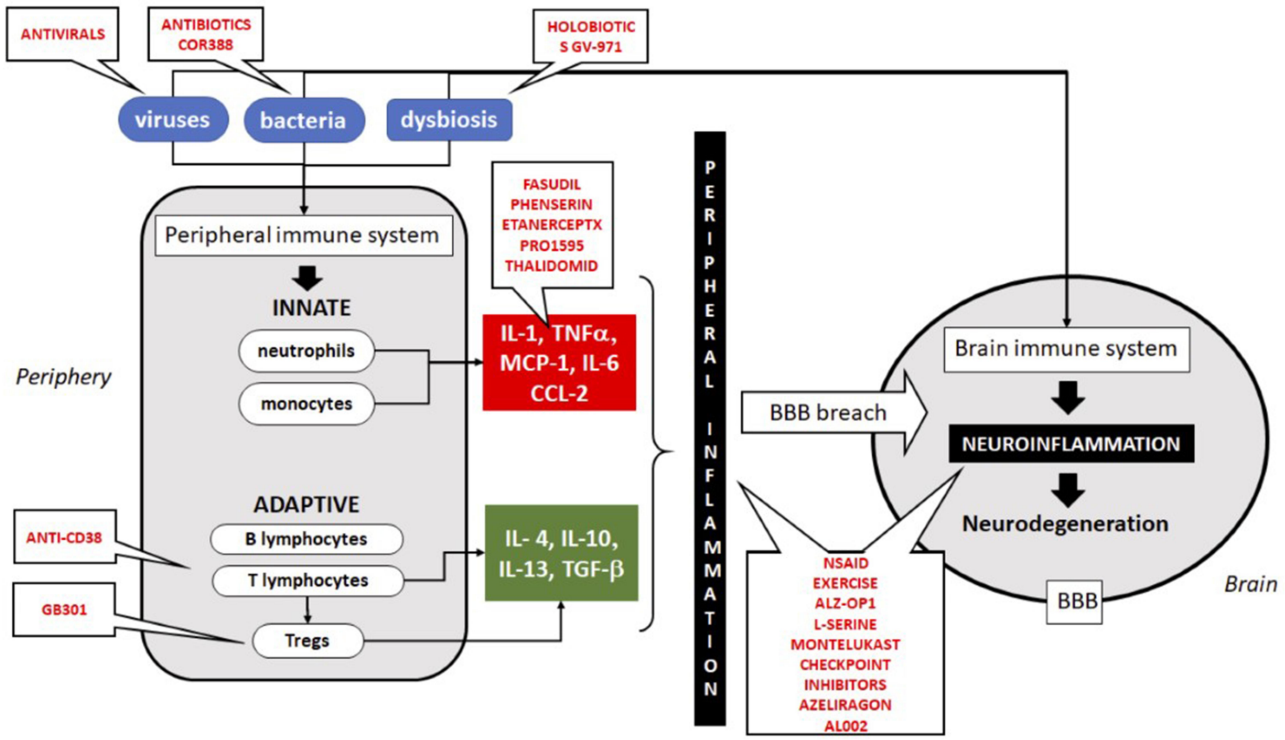

Figure 2 Schematic illustration of the immune system implication in neuroinflammation and neurodegeneration and the targets for treatment. All treatments in trial are in red.
Abbreviations: IL, interleukins; MCP-1, monocyte chemotactic protein-1; BBB, blood–brain barrier; NSAID, non-steroid anti-inflammatory drugs.

apolar environment, we cannot dismiss the possibility that microenvironments may be formed in the brain due to different conditions and thus these results may inform future AMPs design. Table 4 outlines the antimicrobial activity of various amino acid subsequences of LL-37. However, we were unable to compute the antiviral activity but this could possibly be related to the fact existing online databases need to be updated with novel AMPs that have been found to have antiviral properties.

Conclusions

It is clear that AD cannot be linked to any specific microbe. According to the emerging infection hypothesis, this is a polymicrobial induced inflammatory disease in which these microbes may play a role in the initiation and the progression of AD; see Figure 2 and Table 5 for a summary. If we successfully link at least a subgroup of AD subjects to underlying chronic or recurrent infections, this could open the way to treat at a preclinical stage of AD to delay or stop the progression. There are several candidates for these treatments but at the end of the road a very few are chosen. However, those chosen could make the difference by decreasing microbial load and reinforcing the immune defense at an early stage.

Furthermore, considering the pathogenesis of AD and its more syndromic nature, it is currently impossible to predict neither the real target nor the moment of an individualized treatment. It is conceivable that more than one treatment could be efficacious which would result in a multimodal intervention, possibly sequentially in time. New ways of thinking are necessary to reinvent the therapeutical approach of AD. Several obstacles should be overcome in designing new drugs such as crossing the BBB, maintaining their activities, and delivering them to the right place. Naturally occurring substances such as flavonoids should be evaluated as well.

We should also be very cautious to use the mice models as templates for humans. There are some similarities, but other models should be used such as 3D brain organoid cultures from human induced pluripotent stem cells (iPSCs). They are also powerful cellular, molecular, genetic, epigenomic techniques to unravel the pathogenetic basis of the disease from human samples. The use of AI techniques is also in constant evolution and could help modeling and find new compounds with potential DMT activities. All these new

Table 5 Summary of the Interventions at the Level of the Periphery and in the Brain

Periphery	Interventions	Brain
Innate immune response Virus Bacteria Dysbiosis Cellular debris	 Antiviral Antibiotics Probiotics Antisenolytics	Innate immune response Virus Bacteria
Cells Monocytes Neutrophils	 Anti-TLRs Antioxidants	Cells Microglia Astrocytes
Soluble mediators Pro-inflammatory cytokines Anti-inflammatory cytokines Chemokines	 Anticytokines Antichemokines	Soluble mediators Pro-inflammatory cytokines Anti-inflammatory cytokines Chemokines
Adaptive immune response T cells B cells Treg Th17 Antibodies	 Anti-T cells Anti-Treg	Adaptive immune response T cells B cells Treg Th17 Antibodies

ways of thinking may lead to promising treatments to alleviate this terrible human disease.

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Disclosure

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