Targeting Infectious Agents as a Therapeutic Strategy in Alzheimer's Disease: Rationale and Current Status

Tamas Fulop1*, Usma Munawara1, Anis Larbi2,3, Mathieu Desroches4,5, Serafim Rodrigues6,7, Michele Catanzaro1,8, Andrea Guidolin7, Abdelouahed Khalil1, François Bernier9, Annelise Barron10, Katsuiku Hirokawa11, Pascale B Beauregard12, David Dumoulin12, Jean-Philippe Bellenger13, Jacek M. Witkowski14, Eric Frost15

1Research Center on Aging, Geriatric Division, Department of Medicine, Faculty of Medicine and Health Sciences, University of Sherbrooke, Sherbrooke, Quebec, Canada

2Singapore Immunology Network (SIgN), Agency for Science Technology and Research (A*STAR), Immunos Building, Biopolis, Singapore, Singapore

3Department of Biology, Faculty of Science, University Tunis El Manar, Tunis, Tunisia

4MathNeuro Team, Inria Sophia Antipolis Méditerranée, France

5Université Côte d’Azur, Nice, France

6Ikerbasque, The Basque Foundation for Science, Bilbao, Spain

7BCAM - The Basque Center for Applied Mathematics, Bilbao, Spain

8Department of Drug Sciences, University of Pavia, Pavia, Italy

9Next Generation Science Institute, Morinaga Milk Industry Co., Ltd., Zama, Japan

10Department of Bioengineering, Stanford School of Medicine, Stanford, California, USA

11Institute of Health and Life Science, Tokyo Med. Dent. University, Tokyo and Nito-memory Nakanosogo Hospital, Department of Pathology, Tokyo, Japan

12Department of Biology, Faculty of Sciences, University of Sherbrooke, Sherbrooke, Quebec, Canada

13Department of Chemistry, Faculty of Sciences, University of Sherbrooke, Sherbrooke, Quebec, Canada

14Department of Pathophysiology, Medical University of Gdansk, Gdansk, Poland

15Department of Microbiology and Infectious diseases, Faculty of Medicine and Health Sciences, University of Sherbrooke, Sherbrooke, Quebec, Canada
*Corresponding authors information: Tamás Fülöp, M.D., Ph.D., Research Center on Aging, Faculty of Medicine and Health Sciences, University of Sherbrooke, 3001, 12th Avenue North, Sherbrooke, Quebec, Canada, J1H 5N4. Tel.: +1 819 780 2220; Fax: +1 819 829 7141; E-mail: Tamas.Fulop@Usherbrooke.ca.

Short title: Infection hypothesis of AD and therapeutic options
Abstract

Alzheimer’s disease (AD) is the most prevalent dementia in the world. Its cause(s) are presently largely unknown. The most common explanation for AD, now, is the amyloid cascade hypothesis, which states that the cause of AD is senile plaque formation by the Amyloid β peptide, and the formation of neurofibrillary tangles by hyperphosphorylated tau. A second, burgeoning theory by which to explain AD is based on the infection hypothesis. Much experimental and epidemiologic data support an involvement of infections in the development of dementia. According to this mechanism, the infection either directly, or via microbial virulence factors, precedes the formation of Amyloid β plaques. The amyloid β peptide, possessing antimicrobial properties, is beneficial at an early stage of AD, but becomes detrimental with the progression of the disease, concomitantly with alterations to the innate immune system at both the peripheral and central levels. Infection results in neuroinflammation, leading to and sustained by systemic inflammation, causing eventual neurodegeneration, and the senescence of the immune cells. The sources of AD-involved microbes are various body microbiome communities from the gut, mouth, nose, and skin. The infection hypothesis opens a vista to new therapeutic approaches, either by treating the infection itself, or modulating the immune system, its senescence, or the body’s metabolism, either separately, in parallel, or in a multi-step way.

Key points:

1. Experimental and epidemiologic data support an involvement of infections in the development of Alzheimer’s Disease (AD) and the sources of AD-involved microbes are various body microbiome communities from the gut, mouth, nose, and skin;

2. The amyloid β peptide, possessing antimicrobial properties, is beneficial at an early stage of AD, but becomes detrimental with the progression of the disease;

3. Infection results in neuroinflammation, leading to and sustained by systemic inflammation, causing neurodegeneration, and the senescence of the immune cells preceding the clinical manifestations;

4. The infection hypothesis and the antimicrobial protection hypothesis of AD opens the way to new therapeutic approaches.
1. Introduction

Presently Alzheimer’s disease (AD) is one of the most important public health concerns (1). It remains the most common cause of dementia in the world (1-4). Despite huge scientific efforts and amounts of money invested we still do not know what is the cause of this disease or more appropriately defined as a syndrome (5-7). More than 1000 clinical trials have failed, and all ongoing attempts to identify treatment do not seem to be promising (8-10). The prevailing hypothesis to explain the pathomechanism(s) of AD puts the amyloid beta peptide (Aβ) at the center stage and is defined as the beta amyloid cascade hypothesis (11-13). All attempts to modulate by any means the concentration of Aβ in the patient brains have resulted so far in failure to improve the clinical status of patients suffering from any stage of AD. Thus, there is an urgent need to reconsider the causes of AD, which may and should lead to try to find new innovative preventing measures and treatments for AD (8-10). A new hypothesis has re-emerged which puts infection or microbial/microbiome challenge in the forefront of AD (5,14).

AD is a chronic disease and the pathophysiological processes leading ultimately to its overt symptoms are starting decades before the clinical manifestations may appear, triggered by age related changes (20,21), such as immune system modifications, inflammaging (increased levels of proinflammatory cytokines without overt signs of any inflammation), increase in gut leakage and microbiome shift (dysbiosis), as well as the appearance of senescent cells in the gut and the brain, will all favors the development of AD (5,7). This makes it very difficult to cure but, in the meantime, this may convey hope as it can be prevented in the “incubation period” preceding the appearance of cognitive decline to avoid the full-blown disease, if appropriate predictive biomarkers can be discovered. It is also of interest that this whole development from the emergence of the first clinical symptoms (MCI) to full-blown AD takes about 10 to 15 years. This time may also be used to slow down the progression or even cure it if the cause(s) of AD could be found.

2. What is the prevailing hypothesis and why it does not work?

Since the description of AD by Alois Alzheimer of extracellular Aβ plaques and intracellular hyperphosphorylated tau deposition, called neurofibrillary tangles, and unrelated or only indirectly related to the formation of Aβ, have become the pathological hallmarks of AD (24,25).

These findings gave rise to the amyloid hypothesis of AD. Since that time the majority of the AD scientific community has revolved around this hypothesis. Everything in AD research, clinical trials and ultimately in memory clinics has been oriented and driven by the Aβ hypothesis (27-29).

However, the lack of a significant progress toward the mechanistic understanding of AD call for a revaluation of the Aβ cascade hypothesis. The amyloid hypothesis states that the production of Aβ from its amyloid precursor protein (APP) in neurons and astrocytes by β-secretase (BACE) together with presenilin-containing complex called γ-secretase is the primary cause of AD (30-32). Thus, formation of Aβ is the starting point that initiates all the other observed pathological phenomena associated with AD and culminates in the deposition of amyloid plaques in the brain (13). It also triggers the intracellular deposition of hyperphosphorylated tau. Both these phenomena (formation of plaques and of neurofibrillary tangles) result in neurodegeneration (synapse degeneration and then neuronal cell death) and, more importantly, neuroinflammation (33-39). It has subsequently
been found that AD has many different genetic risk (susceptibility) factors such as ApoE4, TREM-2, TOMM40 (40-46).

However, as appealing as this hypothesis may appear, many observations made over decades have spoken against it. One of the most important, yet constantly overlooked details is that these hallmarks exist in the brain of 20 to 30% of non-demented healthy elderly, while in contrast almost identical proportion of patients suffering from AD do not have these hallmarks (5,47). Evidence suggesting a role for events preceding and precipitating deposition of Aβ-containing plaques emerged almost a decade ago from the laboratory of Dr Tanzi, who had demonstrated the antimicrobial properties of Aβ and first described it as an antimicrobial protein (AMP) (48). These crucial observations were later confirmed by other laboratories finding that Aβ acts as AMP against many different microorganisms (49,50), which establishes the Antimicrobial Protection Hypothesis of AD. Moreover, several different microorganisms have been demonstrated in the brain of AD patients (51-62). Nevertheless, the most important argument against the Aβ hypothesis of AD origins from the failure, as already mentioned, of almost all trials which directly targeted Aβ accumulation through vaccination or monoclonal antibodies or its production by the beta secretase (BACE) inhibitors (63,64). An additional finding supports the antimicrobial role of Aβ generated in the brain, as a decrease in Aβ production with the emergence some type of infections in the brain occasionally occurred (65). Thus, based on these facts the infection hypothesis of AD pathogenesis was developed and slowly conceptualized and finally clearly published in a recent editorial (14). Other hypotheses aiming at explanation of mechanisms leading to AD have also been advanced (67-69).

3. Other existing theories

It should be mentioned that over the years a few researchers have promoted different ideas about AD etiology. Among them was the vascular hypothesis which appeared in the 90s (69). A study in nuns (The Nun study) demonstrated that even if, pathologically, amyloid plaques could be detected in the brain, the clinical diagnosis of AD was established only when these lesions were accompanied by atherosclerotic lesions in the brain regardless of the age of the nun (70). Later it was shown that ischemia and shear stress were also able to generate the production of Aβ (71,72). These ideas, were integrated as risk factors for AD such as hypertension (73,74).

Another theory, the mitochondrial cascade hypothesis authored by Swerdlow (76), has proposed that mitochondrial dysfunction resulting from aging, genetic predisposition or environmental factors results in the production of reactive oxygen species (ROS) which damage brain cell functions resulting in typical AD pathology. The mitochondrial cascade hypothesis, similarly, to the Aβ hypothesis, is not an alone-standing causative factor for neurodegeneration but requires internal or external stresses acting on various brain cells such as neurons, microglia and astrocytes. All infections stimulate ROS production and may interact directly with mitochondria perturbing mtDNA and mitochondrial homeostasis (fission, fusion, mitophagy) leading to mitochondrial dysfunction (68). Thus, this hypothesis can be easily integrated to the infectious hypothesis.

3. What evidence supports the infectious hypothesis for AD?
There are numerous epidemiological and experimental discoveries that support that AD may be an infectious disease. Already many years ago, epidemiologic evidence has linked the treatment of Rheumatoid arthritis (RA) to the prevention of AD. McGeer et al (81) showed that RA patients who are receiving anti-inflammatory treatment develop AD much less often than others. This observation was confirmed by an updated Meta-Analysis from cohort studies (83). 16 cohort studies including 236,022 participants, published between 1995 and 2016, were included in this systematic review. Current evidence suggests that NSAID exposure might be significantly associated with reduced risk of AD, but again the need for prospective studies with individual NSAID is badly needed. Initially, this protection was suggested to be linked to the decrease in the neurotoxic effect of Aβ-induced neuroinflammation (82). However, more recently, RA was linked to the mouth bacterial pathogen P. gingivalis (83-87). Thus, the question may arise whether the treatment of RA inflammation which indirectly also decreased AD progression by reducing neuroinflammation could somehow treat the common root, namely an infectious origin.

Epidemiologically, the first and strongest evidence was brought to the community by dentists (88-91). They observed that people who suffer from periodontitis develop AD much more often than those who do not present this alteration in the mouth (92,93). Since these epidemiological observations there are numerous experimental data supporting the link between periodontitis induced systemic inflammation, oral dysbiosis and altered immune response and AD (94-104). It should be mentioned that some studies could not confirm these associations (105). Increased AD incidence was linked to the presence of biofilms produced by the cornerstone bacteria P. gingivalis (94), however recently other bacteria were involved such as Treponema denticola and Tannerella forsythia (95). The bacterial effect might be direct via entering to the brain by the olfactory bulb or indirect via their virulence products that stimulate the production of Aβ making structure resembling to biofilm in the brain called senile amyloid plaques (79,89,91). Indeed, it was recently postulated that amyloid plaques are biofilms (95). This was recently supported by a study demonstrating the presence of one of the most important virulence factors, gingipain, in the brain of healthy and AD patients (61). This latter group showed also by qPCR the presence of P. gingivalis in the brain of healthy subjects as well as in the brain of patients suffering from AD (61). Our unpublished data also demonstrated by qPCR the presence of P. gingivalis in the AD brain (manuscript in preparation).

Yet another bit of information associating the development of AD with bacterial infections is the role of calreticulin (CRT) and galectin-3 in the brain. The decreased expression of calreticulin in the neurons of AD patients was first demonstrated almost 2 decades ago (96). CRT is a multifunctional protein, which has since been associated with a chaperone function for the APP; thus, the more CRT is present in the neuron the more stable the APP becomes and less Aβ is produced resulting in its aggregates (plaques) (97). On the other hand, CRT production is upregulated by Aβ oligomers, at least in vitro (98). Serum levels of CRT are considered a negative biomarker of AD development and progression (99). This may make sense, as CRT has been very recently shown to be secreted also by activated macrophages and microglia and to act as opsonin facilitating the phagocytosis of bacteria invading the brain (albeit so far only in a rat model) (100). Thus, we could envisage/propose a schematics where an infection leads to production and release of Aβ which aggregates and upregulates the production and secretion of CRT which
binds/opsonizes bacteria for microglia-executed phagocytosis; thus, more intracerebral infection could lead to decreased levels of CRT (as it would be used up by opsonisation and phagocytosis).

Very recently a study in Taiwan showed that those suffering from herpes simplex-1 (HSV-1) infection and treated with antiviral drugs will have reduced incidence of AD (101). This retrospective cohort study from Taiwan showed the 10-year incidence of dementia in a group of 8362 subjects aged 50 years or over who were newly diagnosed with HSV-1 or HSV-2 infection was 2.56-fold greater than that in the control group (95% CI, 2.351–2.795; P < 0.001). More strikingly, anti-herpetic medication reduced the risk of developing dementia by approximately 91%. These results strongly support a potential causative link between HSV-1 infection and AD, mainly in genetically susceptible subjects (45). This observation suggests that AD is linked somehow to viral infections (62,102-104). However, this still does not clearly demonstrate whether HSV-1 is the cause or the consequence of AD, but highly suggests that HSV-1 may be also involved in its pathogenesis. Interestingly, decades ago, Ithzhaki et al have shown experimentally that HSV-1 DNA is present in the plaques of persons suffering from AD (52). This indicated that virus infection may play a role in the development of AD and that the secretion of Aβ may be a reactive phenomenon to control infection. It may have some antimicrobial peptide (AMP) effect or may be a general acute phase reaction to a strong stress as many other peptides in the organism during aggression, such as LL-37 are affected (105,106). Very recently the Lovheim group demonstrated in a large population-based cohort study supported by cross sectional and longitudinal results an association between HSV-1 carriage and declining episodic memory function, most interestingly among ApoEε4 carriers while the other alleles such as ε2 and ε3 did not show such association (46). Therefore, the Lovheim group (45,46) for the first time showed, that the host genetic background interacts with HSV1 carriage to increase the risk for developing AD in a prospective epidemiological material. The primary strengths of their studies include a large number of cases with closely matched controls from the same population, combined with thorough clinical AD diagnosis. These studies further confirmed the interaction between APOEε4 heterozygosity (APOEε2/ε4 or ε3/ε4) and HSV1 carriage which increased the risk of AD by approximately fivefold, whereas the presence of only one factor did not. A calculated GRS, based on nine additional risk genes (ABCA7, BIN1, CD33, CLU, CR1, EPHA1, MS4A4E, NECTIN2, and PICALM), also interacted with anti–HSV1 IgG for increased risk of subsequent AD. The present findings suggest that the APOEε4 allele and other AD genetic risk factors might potentiate the risk of developing HSV1- associated AD. These data could provide new insights into the possible mechanisms by which the genetic susceptibility of ApoE4 may be involved in the development of AD. Another very recent study in a cohort at Bordeaux in France further confirmed these relationships between ApoE4 and HSV-1 being a strong risk factor for AD development (107). This study further suggests a role for HSV-1 in AD development among subjects with a genetic susceptibility factor, the APOE4 allele (107).

Almost at the same time Miklossy and others have demonstrated the presence of other microbes, such as the spirochete Treponema burgdorferi, in blood, in cerebrospinal fluid and brain tissue (78,107,108). They also hypothesized that this bacterium may produce a biofilm that would constitute the amyloid plaque, protecting bacteria from various stress in the brain (109). Balin et al. have demonstrated the existence of Chlamydia pneumoniae in plaques (59). They later observed
that systemic infection with *Chlamydia pneumonia* in turn increased the occurrence of AD (60). All these data have converged to promote and justify the development of the infectious hypothesis stating that accumulation Aβ is not the primary cause of AD, but itself the consequence of infection. Aβ would then play its pathogenic role as stated by the amyloid hypothesis (5,110).

Subsequently, the demonstration of *Treponema* in plaques reinforced the infectious hypothesis. In the sexually transmitted infection syphilis, caused by *Treponema pallidum*, the tertiary stage is accompanied by a particular dementia status (111). This occurs also in most cases several decades after the primary infection (112). This is a very important similitude as this makes plausible the role of a bacterium of the genus *Treponema* in the pathogenesis of AD. Furthermore, another virus, HIV, has been associated with neurodegenerative disorders (HAND) (113,114). This a neurodegenerative disorder related to HIV infection previously led to a severe form of dementia (115). Since the efficacious treatment of HIV by antiretroviral therapy (cART), the patients live much longer with the virus reaching old age; their neurocognitive disorder has become much milder in its clinical manifestations (116-118). In these patients HAND resembles the AD more and more, even including production of Aβ in response to the virus (119,120). Interestingly, HIV suppresses production of Aβ at early stages of the infection as a protection against the AMP role of Aβ which reinforces its AMP role (121).

The latest microorganisms abundantly found post-mortem in the brain of AD patients are pathogenic fungi (122). The most important species were *C. albicans* and the *Malassezia* sp. (123,124). We do not know how fungi may be involved in the development of AD and this needs further investigations.

All this experimental evidence points toward the involvement of microbes in the pathogenesis of AD (14). These results also indicate that it would be very difficult to identify one microorganism as the unique cause. It was suggested that AD is a polymicrobial disease (123,126). Nevertheless, one bacterium may to be more important than the others namely *P. gingivalis*. Its cornerstone role in periodontitis where it orchestrates the formation of biofilms could be duplicated in AD. In support of this theory, a recent paper found *P. gingivalis* virulence factor gingipain in the post-mortem brain of AD patients (61). All the experimental data gathered so far suggest a causality between infections and AD (126).

Before further describing the putative pathomechanism that could explain how microorganisms may induce AD, we will describe the changes in the immune system which is a necessary corollary to allow infection to promote AD development and may be target for future treatments.

**The innate and adaptive immune system in AD**

The immune system has the role to defend the organism against external and internal challenges (127,128). In many circumstances, the immune system may be activated for a longer period than necessary when a challenge is maintained for a long time or is reactivated from time to time (129). This means that inflammation which plays a beneficial role in acute infection may become chronic and detrimental to the host organism and even generate disease (129).
In the case of AD, neuroinflammation is a fundamental part of its pathogenesis (13,21,33,130-133). According to the amyloid hypothesis, neuroinflammation is generated and maintained chronically by Aβ (13). In the infectious hypothesis it is the result of the penetration of the microbes or their products into the brain and meant to help in the elimination of the aggression, at least at the beginning of the aggression (20). However, as infection becomes chronic, neuroinflammation also becomes chronic and destructive (49,50). Neuroinflammation in AD is characterized by microglial and astrocyte activation, inflammasome activation via NLRP3, complement activation and altered cytokine production shifted towards pro-inflammatory cytokines such as IL-1β, TNFα and IL-6 (134). All these characteristic features of neuroinflammation may be found typically during infection also (135).

Indeed, in AD, neuroinflammation is sustained mainly by the systemic and the local innate immune system. Systematically, the activated innate peripheral immune cells such as NK cells, neutrophils and monocytes are on the one hand able to cross the blood brain barrier and create destruction in the brain directly or on the other hand by their products such as the pro-inflammatory cytokines or chemokines which cross the blood brain barrier (BBB) and act on resident brain innate immune cells such as microglia and astrocytes as demonstrated in humans and in animal models of sepsis (136-140). Furthermore, Bu et al have shown in an association study that the systemic infectious burden measured by anti-microbial antibodies increased the risk of AD (142). This study points again towards the polymicrobial nature of AD. Thus, peripheral infections, inflammation and stress were linked to microglial activation via the NfκB/NLRP3 pathway via pro-inflammatory cytokines (143-145). Together these data suggest that systemic immune activation has central effects and vice versa (91,146,96,97).

The brain has a powerful innate system composed of microglia (brain macrophages), astrocytes and even neurons. They may destroy microorganisms or produce efficient anti-microbial peptides, the most important being the cathelicidin (LL-37) (147-149). Microglia, in response to stress (pathogen associated molecular patterns or damage-associated molecular patterns), develop an inflammatory response and secrete pro-inflammatory cytokines (147-149). Importantly, microglia may also modulate astrocyte reactivity by IL-1alpha, TNF and C1q, such stimulated astrocytes may acquire a pro-inflammatory A1 phenotype (150,151). These “good” innate cells may be turned into “bad” cells by several microbial products including LPS and gingipains, resulting in their dysfunction of eliminating invaders and decreasing the Aβ burden, in the activation of their senescence and in increasing their attack against neurons (134,152,153,104). In summary, under microbial pressure, the brain innate immune system deviates from a defensive to a killing role, resulting in neuroinflammation, senescence and neuronal death. Again, one trigger suspected to play a pathogenic role in AD are microbes and their products such as LPS.

The demonstration by Soscia et al that the Aβ is an AMP gave a new impetus to the infectious hypothesis (48). They have tested Aβ against bacteria and fungi and found it more powerful than even LL-37. More recently others and we have demonstrated that like LL-37, Aβ may also inactivate viruses including HSV-1 (50), influenza (154), and retroviruses (121). It was also shown that when HSV-1 infected them, neurons were able to secrete substantial amounts of Aβ which inhibited HSV-1 infection of other neurons (155). This indicates that Aβ is not only a pathological peptide as supposed originally but has a well-defined physiological role and is produced under very
well-defined conditions. Moreover, Aβ was more powerful than IFN type I. Recently, an interesting finding showed that Aβ may also have anticancer properties (156) as well as BBB repair properties (157). The most important cells producing Aβ are neurons and astrocytes. This is not surprising as the latter together with microglia play a crucial role in the brain host defense either clearing waste or secreting defensins (158,159).

The role of Aβ as an AMP has since been tested in many animal and experimental models. It was shown in a murine model of Salmonella enterica and S. typhimurium infection that endogenous as well as exogenous Aβ could prevent infection in the brain (160,161). These authors hypothesized that the mechanism of action of Aβ is by formation of amyloid aggregates (plaques) using the microbial surface (162). This led to the formulation of the “antimicrobial protection hypothesis” (80). However, they never linked biofilm formation to plaque formation as had been hypothesized by Miklossy (57). Together these data again strongly support the notion that Aβ is a newly recognized member of the large AMP family combatting infections in humans.

All these findings provide answer to why would evolution promote, even select for, an enzymatic system (β- and γ-secretase) if the result had no pro-survival value and – as believed - was only detrimental (leading to AD). Now, based on the convincing observations described above, we can say that generation of Aβ has a clear pro-survival role.

The adaptive immune system also showed important changes in AD (163). Naïve T cells decreased and CD8+ memory T cells increased. This situation is identical to what is observed during normal aging and to chronic infections, independent of age, such as CMV infections (164,165). This suggests that just like the innate immune system, the adaptive immune system is also chronically stimulated and its capacity to fight infections is not always efficient (166). Thus, the immune system shows similar properties in AD patients to those found in many other chronic infectious diseases with, of course, specificities related to its typical to its localization in the brain.

Furthermore, this constant stimulation of the immune system via what is called inflammaging, results in the exhaustion of the immune cells resulting in an increase of cellular senescence which is also evident in microglial cells (167). This cellular senescence, via the senescence associated secretory phenotype (SASP) further supports and amplifies the notion of inflammaging (168-171). SASP of microglia and astrocytes is sustained by the activation of two main intracellular inflammatory pathways which are intimately linked with the NFkB and the inflammasome pathways (172-174). The NOD receptor pathway via NLRP3 mediates the production of IL-1beta, IL-18 and caspase-1 which increase in AD brains. Moreover, IL-1beta has been shown to contribute to the permeability of the BBB favoring the passage of microorganisms and their by-products (7,175,176). These pathways may not only induce senescence but also what is called pyroptosis which is an inflammation triggered programmed cell death, especially in microglia (177).

The all of the body systems and cells, the immune system necessitates substantial amounts of energy in order to function properly (178). There are two ways to generate ATP from glucose: the aerobic glycolysis (converting glucose to lactate) or the oxidative phosphorylation (OXPHOS). Very reactive cells even in the presence of oxygen chose the aerobic glycolysis as a very rapid way to generate energy. Not only healthy cells or organs e.g. brain (179) use aerobic glycolysis, but also malignant cells (180). Microbes and even LPS may convert cells to the use of aerobic glycolysis
Not only this gives energy advantage to the immune cells, but also the produced lactate may react with its receptor GPR81 to generate more ATP used by neurons (182). The capacity to use aerobic glycolysis for energy production is decreased in aged and senescent cells. Thus, microbes have a dual, opposing role in energy metabolism; on one hand they stimulate cells to the reprogramming and on the other hand favor the mitochondrial OXPHOS impairing neuronal and immune functions (183-185).

What is the pathomechanism microorganism(s) use to cause AD?

We suggest two pathways for microbes to induce AD that are not mutually exclusive.

The first involves direct migration of the microorganisms to the brain via the olfactory bulb and crossing the permeabilized blood brain barrier (BBB) composed mainly of astrocytes, endothelial cells and pericytes (186,187). For a long-time the brain was considered a privileged organ as it was protected by a well sealed BBB, however it has been shown that even at the early stage of AD the BBB becomes more permeable (188). This also may occur during the process of aging (189) as well as during systemic inflammatory responses elicited by microbial infections such as viruses, bacteria with or without direct brain infection (190,191). Microbes have evolved to be able to make the BBB permeable partly by subverting pericytes and/or endothelial cells by inducing either their apoptosis or by using the complement system receptor 3 (CR3) to their advantage to make their way to the brain (192-194). The neurons would respond by producing Aβ and try to destroy the invasive microbes (48-50). In the meantime, the microglia and astrocytes are also stimulated and produce antimicrobial peptides, pro-inflammatory cytokines, free radicals, and proteases to destroy the microorganism (159,197,198). Moreover, the complement system is activated, and this favors phagocytosis (199). Finally, the adaptive immune system is also activated either to produce cytotoxic effector CD8+ T cells or antibodies via B cells (200). Thus, in a normal situation, the invading microorganism may be totally eliminated or imprisoned in biofilm, seen as plaques, which protect the microbial community from destruction (95). This process may occur, during the decades preceding clinical manifestations of AD, and many reactivation or reinfection cycles may lead to chronic neuroinflammation and plaque deposition resulting in massive neuronal death.

Another non mutually exclusive pathway may be the passage not of the entire microorganism but only its virulence factors such as LPS, gingipains, extracellular RNAs, arginine deiminase (61,201,202,101,103,104) or other. These substances may occur permanently in the organism and originate from any of the microbial communities/reservoirs of the organism such as gut microbiome, mouth, or neurobiome (203-207). These microbial products or metabolites may mediate their deleterious actions by being incorporated in extracellular vesicles (EVs) (208). Indeed, many microorganisms including P. gingivalis are also able to release EVs containing gingipain, fimbriae which will modulate intestinal permeability as well as the function of the innate immune system thus favoring an inflammatory status (209,103,210). In this way these by-products will stimulate the immune system with the production of inflammatory mediators which will chronically induce the same processes as the direct presence of the microorganism itself (211,212).

As mentioned, these microbes or their virulence products may originate from various microbial reservoirs in the body. The most important microbial reservoir in humans is in the gut, which leads to the notion of the gut-brain axis. This means that there is a constant communication between the
gut and the brain and vice versa during the whole life (210-213). Indeed, the direct presence of microbes and/or their by-products have been demonstrated in the brain of AD patients, but interestingly also in the brain of healthy aged subjects, hence the notion of neurobiome (61). The studies of the gut microbiome in aged people showed a tendency towards an increase in Gram-negative bacteria (214) which was also shown in MCI patients (215). This becomes even more problematic when the immune system manifests some maladaptation with aging which permits the clinical development of AD through the translocation of microbes which are normally commensal (dysbiosis) (216-218) and are contained within the gut by the local immune system inducing a tolerogenic state (219). It has also been demonstrated that dysbiosis of the gut microbiome may promote various inflammatory disorders which have provoked microglial activation during the development of AD (220-223). Thus, this suggests that the gut microbiome or better, its dysbiosis, is involved in regulating microglial activation and neuroinflammation in AD.

Another important axis for the development of AD could be the mouth-brain axis involving mainly *P. gingivalis* (224,225). *P. gingivalis* produces various virulence factors such as LPS, flagella and toxic proteases called gingipains (226). The LPS may activate astrocytes and transform them to the proinflammatory A1 phenotype by stimulating TLR-4 (227). Gingipains have been found in the brain of healthy subjects and AD patients and proposed to be involved in the pathophysiology of AD (61). In periodontitis these virulence factors mainly gingipains (lysin-gingipain and Arginine gingipain A/B) have been shown to play a role in host colonization, inactivation of the host immune response, iron and nutrient acquisition (228,229). Gingipains may also activate various innate receptors such as TREM1, TREM2, TLR-4, CR1 and NLRP3 (230-233) which may result in the activation of the inflammasome (234). This activation in turn facilitates plaque formation and may amplify the inflammatory reaction via release of ASC specks (235,236). Interestingly, the activation of this inflammasome results in pyroptosis which eliminates the cell infected by *P. gingivalis* and limits replication of this bacteria (237). Furthermore, this phenomenon does not always require the presence of live *P. gingivalis* but released gingipains may penetrate cells and have similar effects (238,239). These processes involving the mentioned receptors, the inflammasome, and *P. gingivalis* or its gingipains will ultimately kill neurons, favor amylloid plaque deposition and IL-1β release. This will further help to permeabilize the BBB. Gingipains are also able to cleave IgG1 and IgG3 mainly by gingipain K and in this way the adaptive branch of the immune defense of the organism can be compromised (240,241). Another important virulence factor of *P. gingivalis* is peptidylarginine deiminase (PPAD) which catalyzes the citrullination of both bacterial and host proteins (242,243). PPAD helps *P. gingivalis* evade destruction by neutrophils by impairing phagocytosis and bacteria induced NETosis (242). Furthermore, when PPAD citrullinates cationic antimicrobial peptides such as LP9, it efficiently neutralizes them. Gingipains can also deactivate them by proteolytic degradation (244,245) which may be followed by PPAD citrullination of exposed arginine residues. All of these products from *P. gingivalis* help it to evade from both the innate and adaptive immune system. It is of note that direct the role of *P. gingivalis* and its products in the development and progression of AD, even if they have been found in human brain of AD patients, will require further studies.

Inflammmaging is sustained by the disbalance between the innate and adaptive immune systems together with the senescence of the cells constituting the CNS including neurons, microglia and
astrocytes. This concomitant process of inflammaging, programmed cellular senescence and dysbiosis further favors the leakage of the gut resulting in the passage of bacteria (pathogenic and/or commensals) (251) and their products into the brain including those which may contribute to AD such as the curli (252).

One other recently described phenomenon which can lead to sustained neuroinflammation is the mechanism of trained innate immunity (253). This process captures the constant inflammatory state seen in the innate immune system during aging, AD and other chronic diseases (129). Once monocytes have been activated, any new unrelated stimulation will result in higher response from these cells (254). This is a sort of memory of the innate immune system resulting in the maintenance of a basic constant activation in cells like microglia in which will likely contribute to constant neuronal destruction.

All these experimental results point to the fact that Aβ is deposited in the brain decades before the clinical manifestation of AD suggesting that AD is related to a chronic mutually sustaining inflammatory processes in the central nervous system and in the periphery as a result of a long-lasting antimicrobial response culminating in plaque deposition (20,80,255,256).

Whatever the pathway that microorganisms employ to cause AD, better understanding of these processes could suggest new innovative strategies to prevent or intervene in the progression of AD.

**What are the possible interventions targeting the prevention or cure of AD?**

The obvious treatments which come to mind are treatments by specific agents aiming at containing or direct elimination of the mentioned microorganism such as antivirals, antibacterial and antifungal products. In the case of viruses, the most relevant would seem to be the antiviral drugs penetrating the BBB which are very effective even in herpes viral encephalitis such as Valacyclovir (104,257,258). Unfortunately, we do not know which virus exactly, when and how may cause AD (and, as mentioned above, rather assume that the cause is prolonged and polymicrobial) it may be very difficult to determine when, how, and in what dose to use them (103). Nevertheless, each time that we have an infectious burst such as herpes labialis or herpes genitalis or zoster, we should treat the patients most vigorously whatever their age. If we consider data from the Taiwanese study mentioned above, each of these treatments should decrease the incidence of AD. Other viruses may also be involved and so we will have to discover antiviral agents to control them.

Are there any direct trials targeting any stages of AD with antiviral treatment? In fact, there is one ongoing, one which has been just finished and some may be actively planned (103). This is due to the uncertainty of the mechanisms causing AD by viruses. Another factor is knowing at what time to treat. Considering the long “incubation period” of AD it would be logical to treat any viral infection at any time when its manifest itself which would have a great advantage to decrease the deleterious effect not only on the immunobiography/inflammaging but also on the chronicity of such an accumulation of several infectious burden. Of course, one of the best periods would be when memory problems are starting in the subjective memory complaint and mild cognitive impairment (MCI) stages. In this way we could assess whether this treatment at least retard the progression towards AD. Logically, a pulse repeated intervention would be needed, but this will have to be demonstrated. The advantage of valacyclovir and related drugs is that they have very
few side effects even in elderly subjects. The epidemiological study from Taiwan seems to indicate that it could be a rewarding intervention.

Devanand in his paper of 2018 (103) mentions a phase II, proof of concept, randomized, double-blind, placebo-controlled, 18-month treatment trial of 130 patients (65 valacyclovir, 65 placebo) with mild AD (MMSE range 20–28) who test positive for antibodies to HSV1 or HSV2. Valacyclovir dose will be 2–4 g daily. The dose range was stated safe and is known to lead to CNS penetration with high CSF levels which should increase the chance of efficacy. The hypotheses were that, in comparison with patients treated with placebo, patients treated with valacyclovir will show a smaller decline on the Alzheimer’s Disease Assessment Scale-Cognition 11-item scale (ADAS-Cog11; cognitive measure; 0 to 78 weeks) and the Alzheimer’s Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL; function measure; 0 to 78 weeks). The authors state that if the trial will be successful, they will continue with a phase III trial. Indeed, there is a trial registered as ClinicalTrials.gov Identifier NCT03282916. This plans to use Valacyclovir in MCI/AD patients to establish whether this treatment will restore or decrease cognitive functions. We should wait for the results of these trials in the forthcoming years, more specifically in 2022. Another study the VALZ-Pilot study (NCT02997982) investigated the effects of Valaciclovir treatment in individuals with Alzheimer's disease or Mild Cognitive Impairment of Alzheimer's Disease Type. This study enrolled 36 persons for 4 weeks treatment then followed them for another 12 months. The study has been just finished in March 2020 and no results are still available. It will be interesting to have the results to plan larger phase III studies. A study (Apovir study) used Apovir (Apodemus AB in Solna), a combination of the experimental anti-enterovirus agent pleconaril, originally developed to treat the common cold, and the hepatitis C treatment ribavirin. This was reported at the CTAD conference in Barcelona (2018) as a 2a phase clinical trial including 69 people with mild AD with Apovir or placebo for nine months. There was a very drop our rate because of side effects. However, it seemed that the ADASCog improved by three points. Once the treatment finished both groups progressed with the same rate. These data were not yet published. There are no currently other ongoing clinical trials with antivirals for Alzheimer’s disease.

It is worthwhile to mention that several antibiotics were tried to treat or at least to slow down the progression in prodromal as well as in mild to moderate AD (266-). The most used antibiotics in these clinical trials were the doxycycline, minocycline and rifampin. In a clinical trial Loeb et al (2004) used oral doxycycline at 200 mg and rifampin 300 mg daily for 3months in prodromal and mild to moderate AD. The end point was Standardized Alzheimer's Disease Assessment Scale cognitive subscale (SADAScog) at 6 months. This trial concluded that there were no major adverse events and therapy with doxycycline and rifampin may have a therapeutic role in patients with mild to moderate AD however the mechanism could not be established as it seemed unlikely to be due to their effect on C. pneumoniae. A few years later Molloy et al (267) published the DARAD trial using the doxycycline and rifampin for treatment of AD. This was a multicenter, blinded, randomized, 2 × 2 factorial controlled trial, set at 14 geriatric outpatient clinics in Canada for 12 months. The results did not confirm the results of the study published by Loeb et al (266) instead there was a significant deterioration in SADAS-cog over time with both rifampin and doxycycline.
in comparison with placebo. Another recent clinical trial with minocycline reported by Howard et al (268) used an experimental device of 1:1:1 in a semifactorial design to receive minocycline (400 mg/d or 200 mg/d) or placebo for 24 months. This clinical trial also found that minocycline did not delay the progress of cognitive or functional impairment in people with mild AD during a 2-year period and also found that 400 mg of minocycline is poorly tolerated in this population. These contradictory results can be explained by the fact that antibiotics target directly the infectious agents which may not be present at the stage of the disease when they were used. Also, the differences in the patient selection as well as the period of administration, the various cognitive outcomes may also can explain the differences. Furthermore, as it was recently published by Balducci and Forloni (269) doxycycline which crosses the BBB has given compelling pre-clinical results in mouse models of AD against Aβ oligomers and neuroinflammation. However, by targeting β-amyloid oligomers as many other trials did its effect my be really not efficacious at these stages of the disease. Another interesting questioning is the relationship between microbiota, AD and dysbiosis. Recently a review discussed this relationship (270) raising the possibility that broad-spectrum antibiotics can greatly affect the composition of the gut microbiota, reduce its biodiversity, and delay colonization for a long period after administration which suggest that the action of antibiotics in AD could be wide and even opposite, depending on the type of antibiotic and on the specific role of the microbiome in AD pathogenesis. All these antibiotics modulate also the neuroinflammation however neuroinflammation may be somehow protective at some stages rather than the only cause for neurodegeneration (270). More studies at different stages of AD are warranted to assess the exact role of antibiotics in the treatment of AD. No tentative for fungi treatment has been initiated, but Aβ-like products could be envisioned.

It is well known that *P. gingivalis* is almost impossible to destroy by conventional antibiotics. Two other possibilities exist which would neutralize the virulence factors of these microorganisms. In animal studies recently developed COR286, Cor271 and COR388 have been shown to protect animals from neurodegeneration, decreased the *P. gingivalis* load and also decreased the burden of Aβ (61). One small molecule is under clinical trial by Cortexime to neutralize gingipain (61). The second strategy involves vaccination of individuals with virulence factors (266-269). Trials of vaccines to prevent or cure periodontitis are currently envisioned (270). We should wait to the conclusion of these studies to see whether by targeting the virulence factors we can prevent or decrease the progression of AD. Of course, there are other virulence factors which could be targeted from any of the microorganism. In the meantime, in the future another possibility would be the use of peptoids (short peptides) which were shown to be very effective anti-microbial substances in vitro and in mice (68,259,260). Furthermore, in this line other antimicrobial peptides like LL37 may be used (261,262). Recently it was demonstrated to be an effective agent against S. aureus biofilms (263), and so may also be useful against other biofilms such as those created by *P. gingivalis* besides their very short half-life. The cytotoxicity properties of LL37 may limit its effective use (264,265). Nevertheless, new engineered peptides may be developed.

However, it should also be noted that considering the polymicrobial nature of AD one antimicrobial agent might not be enough to treat this disease. A combined multi-target designed treatment should be envisaged.
There may be other possible treatments. The immune system may also be influenced by an anti-inflammatory treatment in a pulse form in later life or as soon as any chronic inflammatory disease manifests itself in the organism. The modulation by probiotics may also be imaginable to maintain the health of various microbiomes in the organism. Recently a large epidemiological study showed that *Bacteroides* species were less represented in AD patients suggesting that manipulation of the microbiota may be highly beneficial for AD (271). Recently, a bioengineered curli was used as a restorative therapy for the intestinal barrier (272). Curli patterned on bacterial models may promote tolerance against certain bacteria in the intestinal tract. They act by inhibiting instead of stimulating the TLRs (TLR2 and TLR4) (273).

Furthermore, immunotherapy as in the case of cancer may also be possible. Indeed, microbes have also been shown to pervert T cell co-receptors to decrease immune activation and evade detection (274). In this context it is worthwhile to mention that *P. gingivalis* is able to subvert PD-1, to further escape the host immune response (275).

Of course, other general supportive therapies which may reinvigorate the immune system, making the microbiome healthier through nutrition, exercise or the administration of ketone bodies may be envisaged. Modulation of dysbiosis by any means may alleviate the burden of neuroinflammation and microglial activation. In this line, a very recent study by Nagpal et al (276) used modified Mediterranean-ketogenic diet (MMKD) to modulate the gut microbiome in subjects with MCI. Their data suggested that in MCI patients, the gut microbiome has specific characteristics and MMKD can modulate the gut microbiome and metabolites in association with AD biomarkers such as Aβ in the CSF (276). However, these authors did not perform any cognitive tests so their observations remain to be validated at the clinical level. The group of Cunnane using a Medium chain triglyceride ketogenic diet showed an improvement in the executive functions of MCI patients, however its effect on the microbiome was not studied (277). In vitro studies showed that exposure of human macrophages to short chain fatty acid butyrate may increase macrophage antimicrobial activity through histone deacetylase 3 (HDAC3) inhibition (278). In small studies in China targeting gut dysbiosis, GV-971 (mixture of acidic linear oligosaccharides) reversed cognitive impairment by decreasing neuroinflammation (279). This could be related to its antiviral properties.

If we consider the role of senescent cells (SASP) in the pathogenesis of AD related to infection, inflammation, altered autophagy and mitophagy, one obvious treatment would be to eliminate these cells, as it has already been suggested as an anti-aging treatment (280,281). Indeed, in this context, ciprofloxacin has been shown to modulate the accumulation of senescent DNA in SASP and, as such, played a senolytic role (282). Further trials would be warranted to confirm this effect. Another molecule which may act as a senolytic is rapamycin which targets the inhibition of mTOR (283,284). Furthermore, recent studies have demonstrated that mTOR inhibition resulted in the restoration of the intestinal barrier damaged by *P. gingivalis* (285,286). Interestingly, lithium has been shown also to modulate mTOR and GSK3beta which protect the intestinal barrier by decreasing EC senescence as well as the integrity of the BBB (287). In this way, manipulation of mTOR may become a multi-effect treatment eliminating senescent cells, restoring integrity of the gut barrier and restoring altered gut microbiota occurring with aging (288).
Another molecule, azithromycin, an anti-*P. gingivalis* macrolide antibiotic has also mTOR modulating properties and has also senolytic effects and may be useful in AD treatment (289,290). Concomitantly, other known antibiotics, such as minocycline and rifampicin, aside from inhibiting the NLRP3 pathway may facilitate the removal of senescent cells (289,291). Thus, the use of antibiotics that double as senolytics links infection, inflammation and cell senescence which are accentuated by external and internal factors such as aging.

Thus, an obvious means to treat the infectious pathomechanism of AD would be the modulation of NLRP3 activation. This was shown in the case of fluoxetine, a selective serotonin reuptake inhibitor (292). Indeed, a recent trial showed that fluoxetine has been able to decrease the progression from MCI to AD (293). Along the same line of evidence, since defective mitochondria stimulate the NLRP3 pathway, the elimination of these defective mitochondria by increasing mitophagy may also be an effective therapy. Interestingly, some antibiotics such as tetracycline seemed to be able to increase mitophagy in AD (294). Obviously direct inflammasome inhibitory substances may also have a therapeutic role in AD. Among the most promising, as already mentioned, are short chain fatty acid (295).

Another interesting therapeutical approach may stem from observations showing that the glucagon-like peptide -1 (GLP-1) has been shown to facilitate immune tolerance (296,297) and may be upregulated by LPS stimulation. This generated the suggestion that GLP-1 may behave as an AMP (298). Moreover, GLP-1 seemed to inhibit the development of A1 inflammatory astrocytes (299). This has led to a new trial in AD using a well-known drug used in type 2 diabetes, liraglutide, which is a GLP-1 receptor agonist (300).

Yet other group of molecules which may be considered in AD therapy targeting the infection hypothesis at its origins are iron chelators (301). Iron is essential for bacterial growth; thus, its chelation may enhance body defenses and diminish the microbial load. Moreover, recently, iron has also been shown to contribute to cell senescence (302) via stimulation of the mTOR pathway and inhibition of mitophagy (303). Thus, iron chelators such as deferoxamine are mTOR inhibitors (304). A natural in vivo iron-chelator, lactoferrin, has been shown to bind LPS and thus to deactivate NLRP3 (305). It has also been demonstrated to be an AMP with anti-*P. gingivalis* activity (306,307). So lactoferrin could become a powerful treatment for AD (308,309-311).

New developments may include in the future mitochondria targeted small molecules such as MitoQ, Mdicvi-1, SS31 which have proved to be efficient in preventing mitochondrial dysfunction and restoring mitochondrial homeostasis in cell cultures and in experimental animals, however there use alone or in combination in humans awaits clinical trials (309). In addition to iron chelators, mito-modulators have also been proposed to counteract the dysfunction of mitochondria in AD that has possibly been induced by microbial by-products such as gingipains. The overproduction of ROS associated with infection and microglia stimulation may be targeted by endogenous antioxidants such as reduced glutathione (GSH) (310) as well as by exogenous antioxidants which are found in various nutrients as well as in diets such as the Mediterranean diet (311).

However, the most rewarding treatment would be prevention. In this way we can imagine that vaccines against the microorganisms that are involved may be developed. An agent capable of
destroying biofilms would also be a major breakthrough to treat the mouth microbiome and as such prevent AD.

Can we learn from “Why” to find “How” to prevent or treat?

While various interventions are possible, we still have not identified the reason(s) why a pathogen would migrate to the brain. Understanding the events leading to pathogenic migration and colonisation of the brain should help developing prophylactic strategies to reduce AD onset. The direct relationship between amyloid plaques and presence of pathogens in the brain has not been firmly established despite strong circumstantial evidences. We do know that amyloid plaques are also present in individuals with no Alzheimer’s disease. Similarly, individuals with atherosclerotic plaques are not all equal towards calcification and blood vessels disruption. This strongly suggests that pathogen migration to the brain may be independent of amyloid plaque formation per se. Is it then possible to prevent this migration? Would that be enough to prevent the onset of Alzheimer’s disease? The contribution of ApoE isoforms in the susceptibility to AD can also be due to the fact ApoE4 facilitates entry to the brain (312). Burgos et al. (313) have found that a humanized mice models expressing human ApoE4 have high levels of HSV1 in the brain compared to ApoE3 humanized mice, while no difference was observed in viral load in other organs. A systematic study of other pathogens would be necessary to understand the array of pathogens that ApoE4 carrier may be susceptible to. Other mechanisms such as crossing the blood brain barrier have been put forward. Lachenmaier et al (314) demonstrated T. gondii to modulate gene expression of brain endothelial cells to promote its own migration through the blood–brain barrier. This is likely to be happened via Trojan cells with a CD11b+CD11c+/− phenotype of antigen-presenting cells. The same applies to Toxoplasma gondii which was shown to develop a low metabolic activity (315) upon entry to the central nervous system. This fine balance that may also exist for a series of other pathogens located in the brain may be disrupted during an acute event. The current concepts and data would imply that brain from individuals with no Alzheimer’s disease are free of pathogens. However, it is very likely that research will lead and considering recent experimental data has already led (61) to the discovery of a brain symbiotic ecosystem where a restricted type of microorganisms can survive without inducing a pathology (neurobiome). Is this because of an efficient complex immune-pathogens interaction specific for the brain environment? Therefore, a trigger is needed to disrupt this fine equilibrium as it is occurring in the gut when the well-arranged balance between microbes is disrupted and results in dysbiosis. Which acute stress or repetitive acute stresses may be responsible for the activation of the metabolic switch leading to pathogen proliferation and subsequent sequelae is presently largely unknown. This will require intense research. Few possibilities exist (i) brain inflammation associated with microvasculature defects (ii) severe gut dysbiosis associated with leakage sensed in the brain (iii) acute infectious disease (iv) major organ failure leading to transfer of biological reserves from the brain to the corresponding organ/system. Independently of the cause, understanding the brain symbiotic ecosystem (neurobiome/neurodysbiosis) and its regulation will enable to better control the events associated with AD onset.

Searching for new directions in Drug Discovery
The National Alzheimer’s project act by world leaders mandates a plan, which articulates the ultimate goal of preventing or effectively treating AD by the year 2025 (316). To propose a possible pathway, it is important to put into perspective past failures, discuss novel opportunities and understand the feasibility of delivering a drug by 2025. Several decades of research on competing hypotheses for explaining the cause of AD (e.g. Cholinergic (317), Amyloid (318), tau (319), Glucose synthase kinase 3 (320), inflammation (321)) led to the development of drugs that reached clinical trials but failed. Despite billions of euros spent worldwide on drug development and clinical trials based largely on animal modelling, these have repeatedly failed to translate into effective interventions (322). Under these hard-to-accept empirical observations it is imperative to consider alternative hypotheses (e.g. infection hypothesis) but also to consider drug development and research strategies that shy away from transgenic animal models that do not recapitulate human AD.

Indeed, recent technological leaps in stem cell research have led to ground-breaking development of lab-grown human mini-brains, which reproduce the hallmarks of AD (323,324). This alternative model allows for testing of various in-vivo based hypotheses and extract correct and complex information. Combining these advances to the infection hypothesis of AD, as well as antimicrobial protection hypothesis of AD (161,325) provide clear targets and framework for novel AD drug designs. Indeed, since Aβ is a powerful antimicrobial peptide that targets and neutralises AD pathogens, then it is reasonable to consider the development of a cocktail of novel and more powerful antimicrobial peptides (AMPs) based on Aβ template. To achieve these ultimate goals, we envisage a multi-stage closed-loop framework between in-silico drug screening and drug testing in mini-brains as follows. First, data mining in existing databases (e.g. CAMP) and antimicrobial activity prediction via rational design (326) should generate analogues with improved activity. Second, state-of-the-art molecular simulations should be employed to determine the mechanism of action of Aβ against AD pathogens. Third, by combining information gained from step 1 and 2, and with further determination of physical-chemical descriptors of the generated analogues and Aβ, these can be used to train and screen potential AMP candidates via advanced machine-learning drug discovery softwares.

This final stage should involve testing against user-desired property (e.g. IC50), 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. Note that biofilm experiments in neural tissue based on multiomics data from patients and deceased frozen brains can be recreated in mini-brains and tested. Moreover, modern high-throughput technologies enable rapid and efficient simultaneous acquisition of multiomics data in the course of a single experiment (327). This is significant since 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. The observables of such modelling approach could in principle be integrated with drug discovery process and therefore lead to a systematic and holistic screening of AMPs with high-therapeutic efficacy against AD pathogens. Therefore, novel biological models and experimental approaches, as well as multiomics acquisition devices provide unique opportunities
to study and accelerate drug development in the context of novel hypotheses of AD by coupling it to advanced data analysis and state-of-the-art in-silico drug screening. Moreover, this proposed pathway has the potential of reducing the overall cost of drug development.

**Conclusion – perspectives**

It seems clear that it will be difficult to find one exquisite pathogen to explain the whole spectrum of AD in the spirit of infection hypothesis. From the experimental data already acquired it seems that we should think instead about a causative polymicrobial community which affects the immune/inflammatory reactions in the brain and in the periphery, and which interacts with various factors such as genetics, environment and age. Thus, more properly, AD may be considered a complex syndrome. Obviously, future treatments (and/or prevention) of AD will not be one simple molecule but a multimodal complex treatment. This will combine most probably anti-microbial, senolytic and anti-inflammatory agents with pro-mitophagy treatments. In this way, prevention and even treatment of AD will most probably become feasible. Many clinical investigations and trials will be necessary before we can arrive at this stage.

**Acknowledgment**

The works presented in the article were supported by grants from Canadian Institutes of Health Research (CIHR) (No. 106634) and No. PJT-162366) to AK and TF,, the Société des médecins de l’Université de Sherbrooke and the Research Center on Aging of the CIUSSS-CHUS, Sherbrooke and the FRQS Audace grant to TF and EF; by the Polish Ministry of Science and Higher Education statutory grant 02-0058/07/262 to JMW; by Agency for Science Technology and Research (A*STAR) to AL, by Ikerbasque (The Basque Foundation for Science), partially supported by the Basque Government under the grant “Artificial Intelligence in BCAM number EXP. 2019/00432”, by the Basque Government through the BERC 2018-2021 program and by the Ministry of Science, Innovation and Universities: BCAM Severo Ochoa accreditation SEV-2017-0718 and through project RTI2018-093860B-C21 funded by (AEI/FEDER, UE) with acronym “MathNEURO” to SR.

**Compliance with Ethical Standards**

**Funding**

No outside funding was received in support of this publication and the author did not receive funding for writing this paper.

**Conflict of interest**

The authors declare that they have no conflict of interest related to this article.

**Legend for figures**
Figure 1

**Possible intervention checkpoints according to the infection hypothesis.** This figure depicts the various putative players in the development of Alzheimer’s disease considering the infection hypothesis as well as the individual future target for intervention.

Aβ: amyloid beta peptide; AD: Alzheimer’s disease; BBB: blood brain barrier; PRR: Pattern recognition receptors; SASP: Senescence associated secretory phenotype.

References

1. Reiss AB, Arain HA, Stecker MM, Siegart NM, Kasselman LJ. Amyloid toxicity in Alzheimer's disease. Rev Neurosci. 2018 Aug 28;29(6):613-627.

2. Mayeux R, Stern Y. Epidemiology of Alzheimer disease. Cold Spring Harb Perspect Med. 2012 Aug 1;2(8). pii: a006239.
3. Hu H1, Tan CC1, Tan L2, Yu JT3. A Mitocentric View of Alzheimer's Disease. Mol Neurobiol. 2017 Oct;54(8):6046-6060.

4. Reddy PH, Manczak M, Yin X, Grady MC, Mitchell A, Tonk S, Kuruva CS, Bhatti JS, Kandimalla R, Vijayan M, Kumar S, Wang R, Pradeepkiran JA, Ogunmokun G, Thamarai K, Quesada K, Boles A, Reddy AP. Protective Effects of Indian Spice Curcumin Against Amyloid-β in Alzheimer's Disease. J Alzheimers Dis. 2018;61(3):843-866.

5. Fulop T, Witzkowski JM, Bourgade K, Khalil A, Zerif E, Larbi A, Hirokawa K, Pawelec G, Bocti C, Lacombe G, Dupuis G, Frost EH. Can an Infection Hypothesis Explain the Beta Amyloid Hypothesis of Alzheimer's Disease? Front Aging Neurosci. 2018 Jul 24;10:224.

6. Fulop T, Lacombe G, Cunnane S, Le Page A, Dupuis G, Frost EH, Bourgade-Navarro K, Goldeck D, Larbi A, Pawelec G. Elusive Alzheimer's disease: can immune signatures help our understanding of this challenging disease? Part 1: clinical and historical background. Discov Med. 2013 Jan;15(80):23-32.

7. Osorio C, Kanukuntla T, Diaz E, Jafri N, Cummings M, Sfera A. The Post-amyloid Era in Alzheimer's Disease: Trust Your Gut Feeling. Front Aging Neurosci. 2019 Jun 26;11:143.

8. Cummings JL, Morstorf T, Zhong K (2014) Alzheimer’s disease drug-development pipeline: Few candidates, frequent failures. Alzheimers Res Ther 6, 37-43.

9. Cummings J, Ritter A, Zhong K. Clinical Trials for Disease-Modifying Therapies in Alzheimer's Disease: A Primer, Lessons Learned, and a Blueprint for the Future. J Alzheimers Dis. 2018;64(s1):S3-S22.

10. Long JM, Holtzman DM. Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. Cell. 2019 Oct 3;179(2):312-339.

11. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science. 1992 Apr 10;256(5054):184-5.

12. Hardy J, Allsop D, (1991) Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol Sci 12:383-388.

13. McGeer PL, McGeer EG. (2013) The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy. Acta Neuropathol. 126:479-97.

14. Itzhaki RF, Lathe R, Balin BJ, Ball MJ, Bearer EL, Braak H, Bullido MJ, Carter C, Clerici M, Cosby SL, Del Tredici K, Field H, Fulop T, Grassi C, Griffith WS, Haas J, Hudson AP, Kamer AR, Kell DB, Licastro F, Letenneur L, Lövheim H, Mancuso R, Miklossy J, Otth C, Palamara AT, Perry G, Preston C, Pretorius E, Strandberg T, Tabet N, Taylor-Robinson SD, Whittum-Hudson JA. Microbes and Alzheimer's Disease. J Alzheimers Dis. 2016;51(4):979-84.

15. Castellani RJ, Rolston RK, Smith MA (2010) Alzheimer disease. Disease-a-Month 56:484-546.
16. Tam JH, Pasternak SH (2012) Amyloid and Alzheimer's disease: Inside and out. Can J Neurol Sci 39:286-298.

17. Kern A, Behl C. (2009) The unsolved relationship of brain aging and late-onset Alzheimer disease. Biochim Biophys Acta 10:1124–32.

18. Fülöp T, Larbi A, Witkowski JM. Human Inflammaging. Gerontology. 2019;65(5):495-504.

19. Fulop T, Witkowski JM, Olivieri F, Larbi A. The integration of inflammaging in age-related diseases. Semin Immunol. 2018 Dec;40:17-35.

20. Le Page A., Dupuis G., Frost E. H., Larbi A., Pawelec G., Witkowski J. M., et al. (2018). Role of the peripheral innate immune system in the development of Alzheimer’s disease. Exp. Gerontol. 107 59–66.

21. McManus R. M., Heneka M. T. (2017). Role of neuroinflammation in neurodegeneration: new insights. Alzheimers Res. Ther. 9:14.

22. Alzheimer A. (1907). Über eine eigenartige erkrankung der hirnrinde. Allg. Z. Psychiatr. Psychisch Gerichtl. Med. 64 146–148.

23. Lanoiselée HM, Nicolas G, Wallon D, Rovelet-Lecrux A, Lacour M, Rousseau S, Richard AC, Pasquier F, Rollin-Sillaire A, Martinaud O, Quillard-Muraine M, de la Sayette V, Boutoleau-Bretonniere C, Etcharry-Bouyx F, Chauviré V, Sarazin M, le Ber I, Epelbaum S, Jonveaux T, Rouaud O, Ceccaldi M, Félician O, Godefroy O, Formaglio M, Croisile B, Auriacombe S, Chamard L, Vincent JL, Sauvée M, Marelli-Tosi C, Gabelle A, Ozsancak C, Pariente J, Paquet C, Hannequin D, Campion D3; collaborators of the CNR-MAJ project. APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. PLoS Med. 2017 Mar 28;14(3):e1002270.

24. Hanger D. P., Lau D. H., Phillips E. C., Bondulich M. K., Guo T., Woodward B. W., et al. (2014). Intracellular and extracellular roles for tau in neurodegenerative disease. J. Alzheimers Dis. 40(Suppl. 1), S37–S45.

25. Sun X., Chen W. D., Wang Y. D. (2015). β-Amyloid: the key peptide in the pathogenesis of Alzheimer’s disease. Front. Pharmacol. 6:221

26. Terry RD, Davies P. Dementia of the Alzheimer type. Annu Rev Neurosci. 1980;3:77-95.

27. Roher AE, Maarouf CL, Kokjohn TA. Familial Presenilin Mutations and Sporadic Alzheimer's Disease Pathology: Is the Assumption of Biochemical Equivalence Justified? J Alzheimers Dis. 2016;50(3):645-58.

28. Hardy J., Allsop D. (1991). Amyloid deposition as the central event in the aetiology of Alzheimer’s disease. Trends Pharmacol. Sci. 12 383–388.

29. Karran E., De Strooper B. (2016). The amyloid cascade hypothesis: are we poised for success or failure? J. Neurochem. 139(Suppl. 2), 237–252.
30. Siegel G, Gerber H, Koch P, Bruestle O, Fraering PC, Rajendran L. The Alzheimer's Disease γ-Secretase Generates Higher 42:40 Ratios for β-Amyloid Than for p3 Peptides. Cell Rep. 2017 Jun 6; 19(10):1967-1976.

31. Chow V. W., Mattson M. P., Wong P. C., Gleichmann M. (2010). An overview of APP processing enzymes and products. Neuromol. Med. 12 1–12.

32. Galante D, Corsaro A, Florio T, Vella S, Pagano A, Sbrana F, Vassalli M, Perico A, D'Arrigo C. Differential toxicity, conformation and morphology of typical initial aggregation states of Aβ1–42 and Aβpy3–42 beta-amyloids. Int J Biochem Cell Biol. 2012 Nov; 44(11):2085-93.

33. Bolós M., Perea J. R., Avila J. (2017). Alzheimer’s disease as an inflammatory disease. Biomol. Concepts 8 37–43.

34. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JI, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May; 7(3):263-9.

35. Serrano-Pozo A, Mielke ML, Gómez-Isla T, Betensky RA, Growdon JH, Frosch MP, Hyman BT. Reactive glia not only associates with plaques but also parallels tangles in Alzheimer's disease. Am J Pathol. 2011 Sep; 179(3):1373-84.

36. Holtzman DM, Carrillo MC, Hendrix JA, Bain LJ, Catafau AM, Gault LM, Goedert M, Mandelkow E, Mandelkow EM, Miller DS, Ostrowitzki S, Polydoro M, Smith S, Wittmann M, Hutton M. Tau: From research to clinical development. Alzheimers Dement. 2016 Oct; 12(10):1033-1039.

37. Leyns CEG, Holtzman DM. Glial contributions to neurodegeneration in tauopathies. Mol Neurodegener. 2017 Jun 29; 12(1):50.

38. Rogers J, Cooper NR, Webster S, Schultz J, McGeer PL, Styren SD, Civin WH, Brachova L, Bradt B, Ward P. Complement activation by beta-amyloid in Alzheimer disease. Proc Natl Acad Sci U S A. 1992 Nov 1; 89(21):10016-20.

39. McGeer PL, McGeer EG. The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy. Acta Neuropathol. 2013 Oct; 126(4):479-97.

40. Kanatsu K, Tomita T. Molecular mechanisms of the genetic risk factors in pathogenesis of Alzheimer disease. Front Biosci (Landmark Ed). 2017 Jan 1;22:180-192.

41. Takatori S, Wang W, Iguchi A, Tomita T. Genetic Risk Factors for Alzheimer Disease: Emerging Roles of Microglia in Disease Pathomechanisms. Adv Exp Med Biol. 2019;1118:83-116.

42. Tao Q, Ang TFA, DeCarli C, Auerbach SH, Devine S, Stein TD, Zhang X, Massaro J, Au R, Qiu WQ. Association of Chronic Low-grade Inflammation With Risk of Alzheimer Disease in ApoE4 Carriers. JAMA Netw Open. 2018 Oct 5;1(6):e183597.
43. Yu L, Lutz MW, Wilson RS, Burns DK, Roses AD, Saunders AM, Yang J, Gaiteri C, De Jager PL, Barnes LL, Bennett DA. APOE ε4-TOMM40 ’523 haplotypes and the risk of Alzheimer's disease in older Caucasian and African Americans. PLoS One. 2017 Jul 3;12(7):e0180356.

44. Tasaki S, Gaiteri C, Mostafaví S, De Jager PL, Bennett DA. The Molecular and Neuropathological Consequences of Genetic Risk for Alzheimer's Dementia. Front Neurosci. 2018 Oct 8;12:699.

45. Lövheim H, Norman T, Weidung B, Olsson J, Josefsson M, Adolfsson R, Nyberg L, Elgh F. Herpes Simplex Virus, APOEε4, and Cognitive Decline in Old Age: Results from the Betula Cohort Study. J Alzheimers Dis. 2019;67(1):211-220.

46. Lopatko Lindman K, Weidung B, Olssonc J, Josefsson M, Kokf E, Johansson A, Eriksson S, Hallmanson G, Elgh F, Lovheim H. A genetic signature including apolipoprotein Eε4 potentiates the risk of herpes simplex–associated Alzheimer’s disease. Alzheimer’s & Dementia: Translational Research & Clinical Interventions 5 (2019) 697-704

47. Barroeta-Espar I, Weinstock LD, Perez-Nieves BG, Meltzer AC, Siao Tick Chong M, Amaral AC, Murray ME, Moulder KL, Morris JC, Cairns NJ, Parisi JE, Lowe VJ, Petersen RC, Kofler J, Ikonomovic MD, López O, Klunk WE, Mayeux RP, Frosch MP, Wood LB, Gomez-Isla T. Distinct cytokine profiles in human brains resilient to Alzheimer's pathology. Neurobiol Dis. 2019 Jan;121:327-337.

48. Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, Burton MA, Goldstein LE, Duong S, Tanzi RE, Moir RD. The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. PLoS One. 2010 Mar 3; 5(3):e9505.

49. Bourgade K, Garneau H, Giroux G, Le Page AY, Bocti C, Dupuis G, Frost EH, Fülöp T Jr. β-Amyloid peptides display protective activity against the human Alzheimer's disease-associated herpes simplex virus-1. Biogerontology. 2015 Feb; 16(1):85-98.

50. Bourgade K, Le Page A, Bocti C, Witkowski JM, Dupuis G, Frost EH, Fülöp T Jr Protective Effect of Amyloid-β Peptides Against Herpes Simplex Virus-1 Infection in a Neuronal Cell Culture Model. J Alzheimers Dis. 2016; 50(4):1227-41.

51. Wozniak MA, Itzhaki RF, Shipley SJ, Dobson CB. Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. Neurosci Lett. 2007 Dec 18; 429(2-3):95-100.

52. Itzhaki RF. Herpes and Alzheimer's Disease: Subversion in the Central Nervous System and How It Might Be Halted. J Alzheimers Dis. 2016 Oct 18; 54(4):1273-1281.

53. Lövheim H, Olsson J, Weidung B, Johansson A, Eriksson S, Hallmans G, Elgh F. Interaction between Cytomegalovirus and Herpes Simplex Virus Type 1 Associated with the Risk of Alzheimer's Disease Development. J Alzheimers Dis. 2018; 61(3):939-945.
54. Lövheim H, Gilthorpe J, Adolfsson R, Nilsson LG, Elgh F. Reactivated herpes simplex infection increases the risk of Alzheimer's disease. Alzheimers Dement. 2015 Jun; 11(6):593-9.

55. Carter C. J. (2017). Genetic, transcriptome, proteomic and epidemiological evidence for blood-brain barrier disruption and polymicrobial brain invasion as determinant factors in Alzheimer’s disease. J. Alzheimers Dis. Rep. 1 125–157. 10.3233/ADR-170017

56. Miklossy J. Alzheimer's disease - a neurospirochetosis. Analysis of the evidence following Koch's and Hill's criteria. J Neuroinflammation. 2011 Aug 4; 8():90.

57. Miklossy J. Bacterial Amyloid and DNA are Important Constituents of Senile Plaques: Further Evidence of the Spirochetal and Biofilm Nature of Senile Plaques. J Alzheimers Dis. 2016 Jun 13; 53(4):1459-73.

58. Miklossy J, McGeer PL. Common mechanisms involved in Alzheimer's disease and type 2 diabetes: a key role of chronic bacterial infection and inflammation. Aging (Albany NY). 2016 Apr; 8(4):575-88.

59. Balin BJ, Gérard HC, Arking EJ, Appelt DM, Branigan PJ, Abrams JT, Whittum-Hudson JA, Hudson AP. Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain. Med Microbiol Immunol. 1998 Jun; 187(1):23-42.

60. Balin BJ, Little CS, Hammond CJ, Appelt DM, Whittum-Hudson JA, Gérard HC, Hudson AP. Chlamydomphila pneumoniae and the etiology of late-onset Alzheimer's disease. J Alzheimers Dis. 2008 May; 13(4):371-80.

61. Dominy SS, Lynch C, Ermini F, Benedyk M, Marczyk A, Konradi A, Nguyen M, Haditsch U, Raha D, Griffin C, Holsinger LJ, Arastu-Kapur S, Kaba S, Lee A, Ryder MI, Potempa B, Mydel P, Hellvard A, Adamowicz K, Hasturk H, Walker GD, Reynolds EC, Faull RLM, Curtis MA, Dragunow M, Potempa J. Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. Sci Adv. 2019 Jan 23;5(1):eaau3333.

62. Itzhaki RF. Herpes simplex virus type 1 and Alzheimer's disease: possible mechanisms and signposts. FASEB J. 2017 Aug;31(8):3216-3226.

63. Sacks CA, Avorn J, Kesselheim AS. (2017) The Failure of Solanezumab - How the FDA Saved Taxpayers Billions. N Engl J Med. 376:1706-1708.

64. Mehta D, et al. (2017) Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010-2015. Expert Opin Investig Drugs. 26:735-739.

65. Ferrer I, Boada Rovira M, Sánchez Guerra ML, Rey MJ, Costa-Jussá F. Neuropathology and pathogenesis of encephalitis following amyloid-beta immunization in Alzheimer's disease. Brain Pathol. 2004 Jan;14(1):11-20.

66. de la Torre JC, Mussivand T. Can disturbed brain microcirculation cause Alzheimer's disease? Neurol Res. 1993 Jun;15(3):146-53.
67. Lanzillotta C, Di Domenico F, Perluigi M, Butterfield DA. Targeting Mitochondria in Alzheimer Disease: Rationale and Perspectives. CNS Drugs. 2019 Oct;33(10):957-969.

68. Oliver DMA, Reddy PH. Small molecules as therapeutic drugs for Alzheimer's disease. Mol Cell Neurosci. 2019 Apr;96:47-62.

69. de la Torre J. The Vascular Hypothesis of Alzheimer's Disease: A Key to Preclinical Prediction of Dementia Using Neuroimaging. J Alzheimers Dis. 2018;63(1):35-52.

70. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA. 1997 Mar 12;277(10):813-7.

71. Li L, Zhang X, Yang D, Luo G, Chen S, Le W. Hypoxia increases Abeta generation by altering beta- and gamma-cleavage of APP. Neurobiol Aging. 2009 Jul;30(7):1091-8.

72. Trumbore CN. Shear-induced amyloid formation of IDPs in the brain. Prog Mol Biol Transl Sci. 2019;166:225-309.

73. Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, Zhao QF, Li JQ, Wang J, Yu JT. Meta-analysis of modifiable risk factors for Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2015 Dec;86(12):1299-306.

74. de Heus RAA, Olde Rikkert MGM, Tully PJ, Lawlor BA, Claassen JAHR; NILVAD Study Group. Blood Pressure Variability and Progression of Clinical Alzheimer Disease. Hypertension. 2019 Nov;74(5):1172-1180.

75. Campbell LA, Rosenfeld ME. Infection and Atherosclerosis Development. Arch Med Res. 2015 Jul;46(5):339-50.

76. Swerdlow RH, Burns JM, Khan SM. The Alzheimer's disease mitochondrial cascade hypothesis: progress and perspectives. Biochim Biophys Acta. 2014 Aug;1842(8):1219-31.

77. Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. Lancet. 1997 Jan 25;349(9047):241-4.

78. Miklossy J. Alzheimer's disease—a spirochetosis? Neuroreport. 1993 Sep;4(9):1069.

79. Patrick KL, Bell SL, Weindel CG, Watson RO. Exploring the "Multiple-Hit Hypothesis" of Neurodegenerative Disease: Bacterial Infection Comes Up to Bat. Front Cell Infect Microbiol. 2019 May 28;9:138.

80. Moir RD, Lathe R, Tanzi RE. The antimicrobial protection hypothesis of Alzheimer's disease. Alzheimers Dement. 2018 Dec;14(12):1602-1614.

81. 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 Aug;47(2):425-32.
82. McGeer PL, McGeer E, Rogers J, Sibley J. Anti-inflammatory drugs and Alzheimer disease. Lancet. 1990 Apr 28;335(8696):1037.

83. Zhang C, Wang Y, Wang D, Zhang J, Zhang F. NSAID Exposure and Risk of Alzheimer's Disease: An Updated Meta-Analysis From Cohort Studies. Front Aging Neurosci. 2018 Mar 28;10:83.

83. de Smit M, Westra J, Vissink A, Doornbos-van der Meer B, Brouwer E, van Winkelhoff AJ. Periodontitis in established rheumatoid arthritis patients: a cross-sectional clinical, microbiological and serological study. Arthritis Res Ther. 2012 Oct 17;14(5):R222.

84. Lundberg K, Wegner N, Yucel-Lindberg T, Venables PJ. Periodontitis in RA-the citrullinated enolase connection. Nat Rev Rheumatol. 2010 Dec;6(12):727-30.

85. Wegner N, Wait R, Sroka A, Eick S, Nguyen KA, Lundberg K, Kinloch A, Culshaw S, Potempa J, Venables PJ. Peptidylarginine deiminase from Porphyromonas gingivalis citrullinates human fibrinogen and α-enolase: implications for autoimmunity in rheumatoid arthritis. Arthritis Rheum. 2010 Sep;62(9):2662-72

86. Mangat P, Wegner N, Venables PJ, Potempa J. Bacterial and human peptidylarginine deiminases: targets for inhibiting the autoimmune response in rheumatoid arthritis? Arthritis Res Ther. 2010;12(3):209.

87. Quirke AM, Lugli EB, Wegner N, Hamilton BC, Charles P, Chowdhury M, Ytterberg AJ, Zubarev RA, Potempa J, Culshaw S, Guo Y, Fisher BA, Thiele G, Mikuls TR, Venables PJ. Heightened immune response to autocitrullinated Porphyromonas gingivalis peptidylarginine deiminase: a potential mechanism for breaching immunologic tolerance in rheumatoid arthritis. Ann Rheum Dis. 2014 Jan;73(1):263-9.

88. Noble, J.M.; Scarmeas, N.; Celenti, R.S.; Elkind, M.S.; Wright, C.B.; Schupf, N.; Papapanou, P.N. Serum IgG antibody levels to periodontal microbiota are associated with incident Alzheimer disease. PLoS ONE 2014, 9,e114959.

89. Hashioka S, Inoue K, Miyaoka T, Hayashida M, Wake R, Oh-Nishi A, Inagaki M. The Possible Causal Link of Periodontitis to Neuropsychiatric Disorders: More Than Psychosocial Mechanisms. Int J Mol Sci. 2019 Jul 30;20(15). pii: E3723.

90. Stein PS, Desrosiers M, Donegan SJ, Yepes JF, Kryscio RJ. Tooth loss, dementia and neuropathology in the Nun study. J Am Dent Assoc. 2007 Oct;138(10):1314-22;

91. Konkel JE, O'Boyle C, Krishnan S. Distal Consequences of Oral Inflammation. Front Immunol. 2019 Jun 25;10:1403.

92. Singhrao, S.K.; Olsen, I. Assessing the role of Porphyromonas gingivalis in periodontitis to determine a causative relationship with Alzheimer’s disease. J. Oral Microbiol. 2019, 11, 1563405.
93. Poole S, Singhrao SK, Kesavalu L, Curtis MA, Crean S. Determining the presence of periodontopathogenic virulence factors in short-term postmortem Alzheimer’s disease brain tissue. J Alzheimers Dis. 2013, 36, 665–677.

94. Sadrameli M, Bathini P, Alberi L. Linking mechanisms of periodontitis to Alzheimer's disease. Curr Opin Neurol. 2020 Apr;33(2):230-238.

95. Leblhuber F, Huemer J, Steiner K, Gostner JM, Fuchs D. Knock-on effect of periodontitis to the pathogenesis of Alzheimer's disease? Wien Klin Wochenschr. 2020 Mar 25.

96. Dubar M, Delatre V, Moutier C, Sy K, Agossa K. Awareness and practices of general practitioners towards the oral-systemic disease relationship: A regionwide survey in France. J Eval Clin Pract. 2019 Dec 25.

97. Konkel JE, O'Boyle C, Krishnan S. Distal Consequences of Oral Inflammation. Front Immunol. 2019 Jun 25;10:1403.

98. Shaik MM, Ahmad S, Gan SH, Abuzenadah AM, Ahmad E, Tabrez S, Ahmed F, Kamal MA. How do periodontal infections affect the onset and progression of Alzheimer's disease? CNS Neurol Disord Drug Targets. 2014 Apr;13(3):460-6.

99. Sochocka M, Sobczyński M, Sender-Janeczek A, Zwolińska K, Błachowicz O, Tomczyk T, Ziętek M, Leszek J. Association between Periodontal Health Status and Cognitive Abilities. The Role of Cytokine Profile and Systemic Inflammation. Curr Alzheimer Res. 2017;14(9):978-990.

100. Sudhakara P, Gupta A, Bhardwaj A, Wilson A. Oral Dysbiotic Communities and Their Implications in Systemic Diseases. Dent J (Basel). 2018 Apr 16;6(2):10.

101. Hayashi K, Hasegawa Y, Takemoto Y, Cao C, Takeya H, Komohara Y, Mukasa A, Kim-Mitsuyama S. Continuous intracerebroventricular injection of Porphyromonas gingivalis lipopolysaccharide induces systemic organ dysfunction in a mouse model of Alzheimer's disease. Exp Gerontol. 2019 Jun;120:1-5.

102. Nie R, Wu Z, Ni J, Zeng F, Yu W, Zhang Y, Kadowaki T, Kashiwazaki H, Teeling JL, Zhou Y. Porphyromonas gingivalis Infection Induces Amyloid-β Accumulation in Monocytes/Macrophages. J Alzheimers Dis. 2019;72(2):479-494.

103. Han EC, Choi SY, Lee Y, Park JW, Hong SH, Lee HJ. Extracellular RNAs in periodontopathogenic outer membrane vesicles promote TNF-α production in human macrophages and cross the blood-brain barrier in mice. FASEB J. 2019 Dec;33(12):13412-13422.

104. Liu Y, Wu Z, Nakanishi Y, Ni J, Hayashi Y, Takayama F, Zhou Y, Kadowaki T, Nakanishi H. Infection of microglia with Porphyromonas gingivalis promotes cell migration and an inflammatory response through the gingipain-mediated activation of protease-activated receptor-2 in mice. Sci Rep. 2017 Sep 18;7(1):11759.
105. Gil Montoya JA, Barrios R, Sanchez-Lara I, Ramos P, Carnero C, Fornieles F, Montes J, Santana S, Luna JD, Gonzalez-Moles MA. Systemic inflammatory impact of periodontitis on cognitive impairment. Gerodontology. 2020 Mar;37(1):11-18.

94. Sakanaka A, Takeuchi H, Kuboniwa M, Amano A. Dual lifestyle of Porphyromonas gingivalis in biofilm and gingival cells. Microb Pathog. 2016 May;94:42-7.

95. Miklossy J. Bacterial Amyloid and DNA are Important Constituents of Senile Plaques: Further Evidence of the Spirochetal and Biofilm Nature of Senile Plaques. J Alzheimers Dis. 2016 Jun 13;53(4):1459-73.

96. Taguchi J, Fujii A, Fujino Y, Tsujioka Y, Takahashi M, Tsuboi Y, Wada I, Yamada T. Different expression of calreticulin and immunoglobulin binding protein in Alzheimer's disease brain. Acta Neuropathol. 2000 Aug;100(2):153-60.

97. Johnson RJ, Xiao G, Shanmugaratnam J, Fine RE. Calreticulin functions as a molecular chaperone for the beta-amyloid precursor protein. Neurobiol Aging. 2001 May-Jun;22(3):387-95.

98. Joerchel S, Raap M, Bigl M, Eschrich K, Schliebs R. Oligomeric beta-amyloid(1-42) induces the expression of Alzheimer disease-relevant proteins in cholinergic SN56.B5.G4 cells as revealed by proteomic analysis. Int J Dev Neurosci. 2008 May-Jun;26(3-4):301-8.

99. Lin Q, Cao Y, Gao J. Serum calreticulin is a negative biomarker in patients with Alzheimer's disease. Int J Mol Sci. 2014 Nov 25;15(12):21740-53.

100. Cockram TOJ, Puigdellívol M, Brown GC. Calreticulin and Galectin-3 Opsonise Bacteria for Phagocytosis by Microglia. Front. Immunol., 12 November 2019

101. Tzeng NS, Chung CH, Lin FH, et al. Anti-herpetic medications and reduced risk of dementia in patients with Herpes simplex virus infections—a nationwide, population-based cohort study in Taiwan. Neurotherapeutics. 2018;15(2):417-429.

102. Watson AM, Prasad KM, Klei L, Wood JA, Yolken RH, Gur RC, Bradford LD, Calkins ME, Richard J, Edwards N, Savage RM, Allen TB, Kwentus J, McEvoy JP, Santos AB, Wiener HW, Go RC, Perry RT, Nasrallah HA, Gur RE, Devlin B, Nimgaonkar VL. Persistent infection with neurotropic herpes viruses and cognitive impairment. Psychol Med. 2013 May;43(5):1023-31.

103. Devanand DP. Viral Hypothesis and Antiviral Treatment in Alzheimer's Disease. Curr Neurol Neurosci Rep. 2018 Jul 14;18(9):55.

104. Qin QS, Li Y. Herpes viral infections and antimicrobial protection for Alzheimer's disease: Implications for prevention and treatment. J Med Virol. 2019;91:1368–1377.

105. Fabisiak A, Murawska N, Fichna J. LL-37: Cathelicidin-related antimicrobial peptide with pleiotropic activity. Pharmacol Rep. 2016 Aug;68(4):802-8.

106. De Lorenzi E, Chiari M, Colombo R, Cretich M, Sola L, Vanna R, Gagni P, Bisciglia F, Morasso C, Lin JS, Lee M, McGeer PL, Barron AE. Evidence that the Human Innate Immune
Peptide LL-37 may be a Binding Partner of Amyloid-β and Inhibitor of Fibril Assembly. J Alzheimers Dis. 2017;59(4):1213-1226.

107. Linard M, Letenneur L, Garrigue I, Doize A, Dartigues JF, Helmer C. Interaction Between APOE4 and Herpes Simplex Virus Type 1 in Alzheimer's Disease. Alzheimers Dement, 2020 Jan;16(1):200-208

107. MacDonald AB, Miranda JM. Concurrent neocortical borreliosis and Alzheimer's disease. Hum Pathol. 1987 Jul;18(7):759-61.

108. Miklossy J, Khalili K, Gern L, Ericson RL, Darekar P, Bolle L, Hurlimann J, Paster BJ. Borrelia burgdorferi persists in the brain in chronic lyme neuroborreliosis and may be associated with Alzheimer disease. J Alzheimers Dis. 2004 Dec;6(6):639-49;

109. Feng J, Zhang S, Shi W, Zubcevik N, Miklossy J, Zhang Y. Selective Essential Oils from Spice or Culinary Herbs Have High Activity against Stationary Phase and Biofilm Borrelia burgdorferi. Front Med (Lausanne). 2017 Oct 11;4:169.

110. Fülöp T, Itzhaki RF, Balin BJ, Miklossy J, Barron AE. Role of Microbes in the Development of Alzheimer's Disease: State of the Art - An International Symposium Presented at the 2017 IAGG Congress in San Francisco. Front Genet. 2018 Sep 10;9:362.

111. Tuddenham S, Ghanem KG. Neurosyphilis: Knowledge Gaps and Controversies. Sex Transm Dis. 2018 Mar;45(3):147-151.

112. Marra CM. Neurosyphilis. Continuum. 2015;21:1714–1728.

113. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Chernier M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE (2007) Updated research nosology for HIV-associated neurocognitive disorders. Neurology 69:1789–1799

114. Robertson KR, Smurzynski M, Parsons TD, Wu K, Bosch RJ, Wu J, McArthur JC, Collier AC, Evans SR, Ellis RJ (2007) The prevalence and incidence of neurocognitive impairment in the HAART era. AIDS 21:1915–1921.

115. Nookala AR, Kumar A (2014) Molecular mechanisms involved in HIV-1 Tat-mediated induction of IL-6 and IL-8 in astrocytes. J Neuroinflammation 11:214.

116. Cole MA, Margolick JB, Cox C, Li X, Selnes OA, Martin EM, Becker JT, Aronow HA, Cohen B, Sacktor N, Miller EN (2007) Longitudinally preserved psychomotor performance in longterm asymptomatic HIV-infected individuals. Neurology. 69:2213–2220.

117. Milanini B, Valcour V. Differentiating HIV-Associated Neurocognitive Disorders From Alzheimer's Disease: an Emerging Issue in Geriatric NeuroHIV. Curr HIV/AIDS Rep. 2017, 14:123-132.
118. Ellis RJ, Badiee J, Vaida F, Letendre S, Heaton RK, Clifford D, Collier AC, Gelman B, McArthur J, Morgello S, McCutchan JA, Grant I. (2011) CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. AIDS. 25:1747–1751.

119. Clifford DB, Fagan AM, Holtzman DM, Morris JC, Teshome M, Shah AR, Kauwe JS (2009) CSF biomarkers of Alzheimer disease in HIV-associated neurologic disease. Neurology 73:1982

120. Everall I, Vaida F, Khanlou N, Lazzaretto D, Achim C, Letendre S, Moore D, Ellis R, Cherner M, Gelman B, Morgello S, Singer E, Grant I, Masliah E, National Neuro ATC (2009) Clinico neuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy. J Neurovirol 15:360–370

121. Fulop T, Witkowski JM, Larbi A, Khalil A, Herbein G, Frost EH. Does HIV infection contribute to increased beta-amyloid synthesis and plaque formation leading to neurodegeneration and Alzheimer's disease? J Neurovirol. 2019 Oct;25(5):634-647.

122. Alonso R, Pisa D, Fernández-Fernández AM, Rábano A, Carrasco L. Fungal infection in neural tissue of patients with amyotrophic lateral sclerosis. Neurobiol Dis. 2017 Dec;108:249-260.

123. Carter CJ. Genetic, Transcriptome, Proteomic, and Epidemiological Evidence for Blood-Brain Barrier Disruption and Polymicrobial Brain Invasion as Determinant Factors in Alzheimer's Disease. J Alzheimers Dis Rep. 2017 Sep 28;1(1):125-157.

124. Alonso R, Pisa D, Aguado B, Carrasco L. Identification of Fungal Species in Brain Tissue from Alzheimer's Disease by Next-Generation Sequencing. J Alzheimers Dis. 2017;58(1):55-67.

125. Pisa D, Alonso R, Fernández-Fernández AM, Rábano A, Carrasco L. Polymicrobial Infections In Brain Tissue From Alzheimer's Disease Patients. Sci Rep. 2017 Jul 17;7(1):5559.

126. Hill AB. The environment and disease: association or causation? Bull World Health Organ, 58 (1965), pp. 295-300

127. Monti D, Ostan R, Borelli V, Castellani G, Franceschi C. Inflammaging and human longevity in the omics era. Mech Ageing Dev. 2017 Jul;165(Pt B):129-138.

128. Müller L, Di Benedetto S, Pawelec G. The Immune System and Its Dysregulation with Aging. Subcell Biochem. 2019;91:21-43.

129. Fülöp T, Larbi A, Witkowski JM. Human Inflammaging. Gerontology. 2019;65(5):495-504.

130. Su F, Bai F, Zhou H, Zhang Z. Microglial toll-like receptors and Alzheimer’s disease. Brain Behav. Immun. 2016, 52 187–198.

131. Venegas C, Heneka MT. Danger-associated molecular patterns in Alzheimer’s disease. J. Leukoc. Biol. 2017, 101 87–98.
132. Yang SH. Cellular and Molecular Mediators of Neuroinflammation in Alzheimer Disease. Int Neurourol J. 2019 Nov;23(Suppl 2):S54-62.

133. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, Jacobs AH, Wyss-Coray T, Vitorica J, Ransohoff RM, Herrup K, Frautschy SA, Finsen B, Brown GC, Verkhratsky A, Yamanaka K, Koistinaho J, Latz E, Halle A, Petzold GC, Town T, Morgan D, Shinohara ML, Perry VH, Holmes C, Bazan NG, Brooks DJ, Hunot S, Joseph B, Deigendesch N, Garaschuk O, Boddeke E, Dinarello CA, Breitner JC, Cole GM, Golenbock DT, Kummer MP. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015 Apr;14(4):388-405.

134. Mosher KI, Wyss-Coray T. Microglial dysfunction in brain aging and Alzheimer's disease. Biochem Pharmacol. 2014 Apr 15;88(4):594-604.

135. Mawanda F, Wallace R. Can infections cause Alzheimer's disease? Epidemiol Rev. 2013;35:161-80.

136. Giridharan VV, Masud F, Petronilho F, Dal-Pizzol F, Barichello T. Infection-Induced Systemic Inflammation Is a Potential Driver of Alzheimer's Disease Progression. Front Aging Neurosci. 2019 May 28;11:122.

137. Gasparotto J, Ribeiro CT, da Rosa-Silva HT, Bortolin RC, Rabelo TK, Peixoto DO, Moreira JCF, Gelain DP. Systemic Inflammation Changes the Site of RAGE Expression from Endothelial Cells to Neurons in Different Brain Areas. Mol Neurobiol. 2019 May;56(5):3079-3089.

138. Gasparotto J, Girardi CS, Somensi N, Ribeiro CT, Moreira JCF, Michels M, Sonai B, Rocha M, Steckert AV, Barichello T, Quevedo J, Dal-Pizzol F, Gelain DP. Receptor for advanced glycation end products mediates sepsis-triggered amyloid-β accumulation, Tau phosphorylation, and cognitive impairment. J Biol Chem. 2018 Jan 5;293(1):226-244.

139. Wang LM, Wu Q, Kirk RA, Horn KP, Ebada Salem AH, Hoffman JM, Yap JT, Sonnen JA, Towner RA, Bozza FA, Rodrigues RS, Morton KA. Lipopolysaccharide endotoxemia induces amyloid-β and p-tau formation in the rat brain. Am J Nucl Med Mol Imaging. 2018 Apr 25;8(2):86-99.

140. Ehler J, Barrett LK, Taylor V, Groves M, Scaravilli F, Wittstock M, Kolbaske S, Grossmann A, Henschel J, Gloger M, Sharshar T, Chretien F, Gray F, Nöldge-Schomburg G, Singer M, Sauer M, Petzold A. Translational evidence for two distinct patterns of neuroaxonal injury in sepsis: a longitudinal, prospective translational study. Crit Care. 2017 Oct 23;21(1):262.

142. Bu XL, Yao XQ, Jiao SS, Zeng F, Liu YH, Xiang Y, Liang CR, Wang QH, Wang X, Cao HY, Yi X, Deng B, Liu CH, Xu J, Zhang LL, Gao CY, Xu ZQ, Zhang M, Wang L, Tan XL, Xu X, Zhou HD, Wang YJ. A study on the association between infectious burden and Alzheimer's disease. Eur J Neurol. 2015 Dec;22(12):1519-25.

143. Couturier J, Stancu IC, Schakman O, Pierrot N, Huaux F, Kienlen-Campard P, Dewachter I, Octave JN. Activation of phagocytic activity in astrocytes by reduced expression of the inflammasome component ASC and its implication in a mouse model of Alzheimer disease. J Neuroinflammation. 2016 Jan 27;13:20.
144. Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, Griep A, Axt D, Remus A, Tzeng TC, Gelpi E, Halle A, Korte M, Latz E, Golenbock DT. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature. 2013 Jan 31;493(7434):674-8.

145. Rea IM, Gibson DS, McGilligan V, Mc Nerlan SE, Alexander HD, Ross OA. Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. Front Immunol. 2018 Apr 9;9:586.

146. Abbayya K, Puthanakar NY, N aduwinmani S, Chidambar YS. Association between Periodontitis and Alzheimer's Disease. N Am J Med Sci. 2015 Jun;7(6):241-6.

147. Bergman P, Termén S, Johansson L, Nyström L, Arenas E, Jonsson AB, Hökfelt T, Gudmundsson GH, Agerberth B. The antimicrobial peptide rCRAMP is present in the central nervous system of the rat. J Neurochem. 2005 Jun;93(5):1132-40.

148. Lee M, Shi X, Barron AE, McGee R, McGeer PL. Human antimicrobial peptide LL-37 induces glial-mediated neuroinflammation. Biochem Pharmacol. 2015 Mar 15;94(2):130-41.

149. Brandenburg LO, Varoga D, Nicolaeva N, Leib SL, Podschun R, W ruck CJ, Schröder JM, Pufe T, Lucius R. Role of glial cells in the functional expression of LL-37/rat cathelin-related antimicrobial peptide in meningitis. J Neuropathol Exp Neurol. 2008 Nov;67(11):1041-54.

147. Jung YJ, Chung WS. Phagocytic Roles of Glial Cells in Healthy and Diseased Brains. Biomol Ther (Seoul). 2018 Jul 1;26(4):350-357.

148. Ashraf GM, Tarasov VV, Makhmutova A, Chubarev VN, Avila-Rodriguez M, Bachurin SO, Aliev G. The Possibility of an Infectious Etiology of Alzheimer Disease. Mol Neurobiol. 2019 Jun;56(6):4479-4491.

149. Linnartz B, Wang Y, Neumann H. Microglial immunoreceptor tyrosine-based activation and inhibition motif signaling in neuroinflammation. Int J Alzheimers Dis. 2010 Jun 22;2010.

150. Clarke LE, Liddelow SA, Chakraborty C, Münch AE, Heiman M, Barres BA. Normal aging induces A1-like astrocyte reactivity. Proc Natl Acad Sci U S A. 2018 Feb 20;115(8):E1896-E1905.

151. Vilalta A, Brown GC. Neurophagy, the phagocytosis of live neurons and synapses by glia, contributes to brain development and disease. FEBS J. 2018 Oct;285(19):3566-3575.

152. von Bernhardi R, Eugenín-von Bernhardi L, Eugenín J. Microglial cell dysregulation in brain aging and neurodegeneration. Front Aging Neurosci. 2015 Jul 20;7:124.

153. Lana D, Ugolini F, Nosi D, Wenk GL, Giovannini MG. Alterations in the Interplay between Neurons, Astrocytes and Microglia in the Rat Dentate Gyrus in Experimental Models of Neurodegeneration. Front Aging Neurosci. 2017 Sep 11;9:296.
154. White MR, Kandel R, Tripathi S, Condon D, Qi L, Taubenberger J, Hartshorn KL. Alzheimer's associated β-amyloid protein inhibits influenza A virus and modulates viral interactions with phagocytes. PLoS One. 2014 Jul 2;9(7):e101364.

155. Bourgade K., Dupuis G., Frost E. H., Fülöp T. Anti-viral properties of amyloid-β peptides. J. Alzheimers Dis. 2016, 54 859–878.

156. Maqbool M, Hoda N. GSK3 Inhibitors in the Therapeutic Development of Diabetes, Cancer and Neurodegeneration: Past, Present and Future. Curr Pharm Des. 2017 Nov 16;23(29):4332-4350.

157. Brothers HM, Gosztyla ML, Robinson SR. The Physiological Roles of Amyloid-β Peptide Hint at New Ways to Treat Alzheimer's Disease. Front Aging Neurosci. 2018 Apr 25;10:118.

158. Morizawa YM, Hirayama Y, Ohno N, Shibata S, Shigetomi E, Sui Y, NabeKura J, Sato K, Okajima F, Takebayashi H, Okano H, Koizumi S. Reactive astrocytes function as phagocytes after brain ischemia via ABCA1-mediated pathway. Nat Commun. 2017 Jun 22;8(1):28.

159. Ransohoff RM1, Brown MA. Innate immunity in the central nervous system. J Clin Invest. 2012 Apr;122(4):1164-71.

160. Kumar DK, Eimer WA, Tanzi RE, Moir RD. Alzheimer's disease: the potential therapeutic role of the natural antibiotic amyloid-β peptide. Neurodegener Dis Manag. 2016 Oct;6(5):345-8.

161. Kumar DK, Choi SH, Washicosky KJ, Eimer WA, Tucker S, Ghofrani J, Lefkowitz A, McColl G, Goldstein LE, Tanzi RE, Moir RD. Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Sci Transl Med. 2016 May 25;8(340):340ra72.

162. Golde TE. Alzheimer disease: Host immune defence, amyloid-β peptide and Alzheimer disease. Nat Rev Neurol. 2016 Aug;12(8):433-4.

163. Larbi A, Pawelec G, Witkowski JM, Schipper HM, Derhovanessian E, Goldeck D, Fulop T. Dramatic shifts in circulating CD4 but not CD8 T cell subsets in mild Alzheimer's disease. J Alzheimers Dis. 2009;17(1):91-103.

164. Derhovanessian E, Larbi A, Pawelec G. Biomarkers of human immunosenescence: impact of Cytomegalovirus infection. Curr Opin Immunol. 2009 Aug;21(4):440-5.

165. Pawelec G, Derhovanessian E, Larbi A, Strindhall J, Wikby A. Cytomegalovirus and human immunosenescence. Rev Med Virol. 2009 Jan;19(1):47-56.

166. Shen-Orr SS, Furman D, Kidd BA, Hadad F, Lovelace P, Huang YW, Rosenberg-Hasson Y, Mackey S, Grisar FA, Pickman Y, Maecker HT, Chien YH, Dekler CL, Wu JC, Butte AJ, Davis MM. Defective Signaling in the JAK-STAT Pathway Tracks with Chronic Inflammation and Cardiovascular Risk in Aging Humans. Cell Syst. 2016 Oct 26;3(4):374-384.e4.
167. Kritsilis M1, V Rizou S2, Koutsoudaki PN3, Evangelou K4, Gorgoulis VG5, Papadopoulos D6. Ageing, Cellular Senescence and Neurodegenerative Disease. Int J Mol Sci. 2018 Sep 27;19(10). pii: E2937.

168. Tsai CY, Shen CY, Liao HT, Li KJ, Lee HT, Lu CS, Wu CH, Kuo YM, Hsieh SC, Yu CL. Molecular and Cellular Bases of Immunosenescence, Inflammation, and Cardiovascular Complications Mimicking "Inflammaging" in Patients with Systemic Lupus Erythematosus. Int J Mol Sci. 2019 Aug 9;20(16). pii: E3878.

169. Chen Y, Liu S, Leng SX. Chronic Low-grade Inflammatory Phenotype (CLIP) and Senescent Immune Dysregulation. Clin Ther. 2019 Mar;41(3):400-409.

170. Olivieri F, Prattichizzo F, Grillari J, Balistreri CR. Cellular Senescence and Inflammaging in Age-Related Diseases. Mediators Inflamm. 2018 Apr 17;2018:9076485.

171. Sanada F, Taniyama Y, Muratsu J, Otsu R, Shimizu H, Rakugi H, Morishita R. Source of Chronic Inflammation in Aging. Front Cardiovasc Med. 2018 Feb 22;5:12.

172. Yamazaki Y, Baker DJ, Tachibana M, Liu CC, van Deursen JM, Brott TG, Bu G, Kanekiyo T. Vascular Cell Senescence Contributes to Blood-Brain Barrier Breakdown. Stroke. 2016 Apr;47(4):1068-77.

173. Burton DGA1, Stolzing A2. Cellular senescence: Immunosurveillance and future immunotherapy. Ageing Res Rev. 2018 May;43:17-25.

174. Bossù P, Ciaramella A, Salani F, Vanni D, Palladino I, Caltagirone C, Scapigliati G. Interleukin-18, from neuroinflammation to Alzheimer's disease. Curr Pharm Des. 2010;16(38):4213-24.

175. Wang Y, Jin S, Sonobe Y, Cheng Y, Horiuchi H, Parajuli B, Kawanokuchi J, Mizuno T, Takeuchi H, Suzumura A. Interleukin-1β induces blood-brain barrier disruption by downregulating Sonic hedgehog in astrocytes. PLoS One. 2014 Oct 14;9(10):e110024.

176. Bester J, Soma P, Kell DB, Pretorius E. Viscoelastic and ultrastructural characteristics of whole blood and plasma in Alzheimer-type dementia, and the possible role of bacterial lipopolysaccharides (LPS). Oncotarget. 2015 Nov 3;6(34):35284-303.

177. Man SM, Karki R, Kanneganti TD. Molecular mechanisms and functions of pyroptosis, inflammatory caspases and inflammasomes in infectious diseases. Immunol Rev. 2017 May;277(1):61-75.

178. O'Neill LA1, Kishton RJ2, Rathmell J2. A guide to immunometabolism for immunologists. Nat Rev Immunol. 2016 Sep;16(9):553-65.

179. Yellen G. Fueling thought: Management of glycolysis and oxidative phosphorylation in neuronal metabolism. J Cell Biol. 2018 Jul 2;217(7):2235-2246.

180. Potter M, Newport E, Morten KJ. The Warburg effect: 80 years on. Biochem Soc Trans. 2016 Oct 15;44(5):1499-1505.
181. Salmond RJ. mTOR Regulation of Glycolytic Metabolism in T Cells. Front Cell Dev Biol. 2018 Sep 25;6:122.

182. Díaz-García CM, Mongeon R, Lahmann C, Koveal D, Zucker H, Yellen G. Neuronal Stimulation Triggers Neuronal Glycolysis and Not Lactate Uptake. Cell Metab. 2017 Aug 1;26(2):361-374.e4.

183. Fang EF, Hou Y, Lautrup S, Jensen MB, Yang B, SenGupta T, Caponio D, Khezri R, Demarest TG, Aman Y, Figueroa D, Morevati M, Lee HJ, Kato H, Kassahun H, Lee JH, Filippelli D, Okur MN, Mangerich A, Croteau DL, Maezawa Y, Lyssiotis CA, Tao J, Yokote K, Rusten TE, Mattson MP, Jasper H, Nilsen H, Bohr VA. NAD+ augmentation restores mitophagy and limits accelerated aging in Werner syndrome. Nat Commun. 2019 Nov 21;10(1):5284.

184. Fang EF, Hou Y, Palikaras K, Adriaanse BA, Kerr JS, Yang B, Lautrup S, Hasan-Olive MM, Caponio D, Dan X, Rocktäschel P, Croteau DL, Akbari M, Greig NH, Fladby T, Nilsen H, Cader MZ, Mattson MP, Tavernarakis N, Bohr VA. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. Nat Neurosci. 2019 Mar;22(3):401-412.

185. Kerr JS, Adriaanse BA, Greig NH, Mattson MP, Cader MZ, Bohr VA, Fang EF. Mitophagy and Alzheimer's Disease: Cellular and Molecular Mechanisms. Trends Neurosci. 2017 Mar;40(3):151-166.

186. Sweeney MD1, Zhao Z1, Montagne A1, Nelson AR1, Zlokovic BV1. Blood-Brain Barrier: From Physiology to Disease and Back. Physiol Rev. 2019 Jan 1;99(1):21-78.

187. Villabona-Rueda A, Erice C, Pardo CA, Stins MF. The Evolving Concept of the Blood Brain Barrier (BBB): From a Single Static Barrier to a Heterogeneous and Dynamic Relay Center. Front Cell Neurosci. 2019 Sep 20;13:405.

188. Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicanono M, Sepehrband F, Nelson AR, Buennagel DP, Harrington MG, Benzinger TLS, Fagan AM, Ringman JM, Schneider LS, Morris JC, Chui HC, Law M, Toga AW, Zlokovic BV. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. Nat Med. 2019 Feb;25(2):270-276.

189. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, Toga AW, Jacobs RE, Liu CY, Amezcua L, Harrington MG, Chui HC, Law M, Zlokovic BV. Blood-brain barrier breakdown in the aging human hippocampus. Neuron. 2015 Jan 21;85(2):296-302.

190. Nwafor DC, Brichacek AL, Mohammad AS, Griffith J, Lucke-Wold BP, Benkovic SA, Targeting the Blood-Brain Barrier to Prevent Sepsis-Associated Cognitive Impairment. Geldenhuys WJ, Lockman PR, Brown CM. J Cent Nerv Syst Dis. 2019 Apr 9;11:1179573519840652.

191. Cain MD1, Salimi H1, Gong Y1, Yang L1, Hamilton SL1, Heffernan JR1, Hou J1, Miller MJ2, Klein RS3. Virus entry and replication in the brain precedes blood-brain barrier disruption during intranasal alphavirus infection. J Neuroimmunol. 2017 Jul 15;308:118-130.
192. Al-Obaidi MMJ, Desa MNM. Mechanisms of Blood Brain Barrier Disruption by Different Types of Bacteria, and Bacterial-Host Interactions Facilitate the Bacterial Pathogen Invading the Brain Cell Mol Neurobiol. 2018 Oct;38(7):1349-1368.

193. Miner JJ, Diamond MS. Mechanisms of restriction of viral neuroinvasion at the blood-brain barrier. Curr Opin Immunol. 2016 Feb;38:18-23.

194. Shi Q, Chowdhury S, Ma R, Le KX, Hong S, Caldarone BJ, Stevens B, Lemere CA. Complement C3 deficiency protects against neurodegeneration in aged plaque-rich APP/PS1 Sci Transl Med. 2017 May 31;9(392). pii: eaaf6295.

195. Ju F, Ran Y, Zhu L, Cheng X, Gao H, Xi X, Yang Z, Zhang S. Increased BBB Permeability Enhances Activation of Microglia and Exacerbates Loss of Dendritic Spines After Transient Global Cerebral Ischemia. Front Cell Neurosci. 2018 Aug 3;12:236.

196. Siegel JL. Acute bacterial meningitis and stroke. Neurol Neurochir Pol. 2019;53(4):242-250.

197. Williams WM, Castellani RJ, Weinberg A, Perry G, Smith MA. Do β-defensins and other antimicrobial peptides play a role in neuroimmune function and neurodegeneration? ScientificWorldJournal. 2012;2012:905785.

198. Frost GR, Li YM. The role of astrocytes in amyloid production and Alzheimer's disease. Open Biol. 2017 Dec;7(12). pii: 170228.

199. Orsini F, De Blasio D, Zangari R, Zanier ER, De Simoni MG. Versatility of the complement system in neuroinflammation, neurodegeneration and brain homeostasis. Front Cell Neurosci. 2014 Nov 7;8:380.

200. Miller KD, Matullo CM, Milora KA, Williams RM, O'Regan KJ, Rall GF. Immune-Mediated Control of a Dormant Neurotropic RNA Virus Infection. J Virol. 2019 Aug 28;93(18). pii: e00241-19.

201. Zhao Y, Jaber V, Lukiw WJ. Secretory Products of the Human GI Tract Microbiome and Their Potential Impact on Alzheimer's Disease (AD): Detection of Lipopolysaccharide (LPS) in AD Hippocampus. Front Cell Infect Microbiol. 2017 Jul 11;7:318.

202. Louw C, Gordon A, Johnston N, Mollatt C, Bradley G, Whiteley CG. Arginine deiminases: therapeutic tools in the etiology and pathogenesis of Alzheimer's disease. J Enzyme Inhib Med Chem. 2007 Feb;22(1):121-6.

203. Odamaki T, Kato K, Sugahara H, Hashikura N, Takahashi S, Xiao JZ, Abe F, Osawa R. Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. BMC Microbiol. 2016 May 25;16:90.

204. Riccio P, Rossano R. Undigested Food and Gut Microbiota May Cooperate in the Pathogenesis of Neuroinflammatory Diseases: A Matter of Barriers and a Proposal on the Origin of Organ Specificity. Nutrients. 2019 Nov 9;11(11). pii: E2714.
205. Sochocka M, Donskow-Łysoniewska K, Diniz BS, Kurpas D, Brzozowska E, Leszek J. The Gut Microbiome Alterations and Inflammation-Driven Pathogenesis of Alzheimer's Disease-a Critical Review. Mol Neurobiol. 2019 Mar;56(3):1841-1851.

206. Maurer K, Rahming S, Prvulovic D. Dental health in advanced age and Alzheimer's Disease: A possible link with bacterial toxins entering the brain? Psychiatry Res Neuroimaging. 2018 Dec 30;282:132-133.

207. Sato S1, Kiyono H, Fujihashi K. Mucosal Immunosenescence in the Gastrointestinal Tract: A Mini-Review. Gerontology. 2015;61(4):336-42.

208. Rodrigues M1, Fan J1, Lyon C1, Wan M3, Hu Y1,2. Role of Extracellular Vesicles in Viral and Bacterial Infections: Pathogenesis, Diagnostics, and Therapeutics. Theranostics. 2018 Apr 9;8(10):2709-2721.

209. Mantri CK, Chen CH, Dong X, Goodwin JS, Pratap S, Paromov V, Xie H. Fimbriae-mediated outer membrane vesicle production and invasion of Porphyromonas gingivalis. Microbiologyopen. 2015 Feb;4(1):53-65.

210. Singhrao SK, Olsen I. Are Porphyromonas gingivalis Outer Membrane Vesicles Microbullets for Sporadic Alzheimer's Disease Manifestation? J Alzheimers Dis Rep. 2018 Dec 20;2(1):219-228

211. Liu Y, Wu Z, Nakanishi Y, Ni J, Hayashi Y, Takayama F, Zhou Y, Kadowaki T, Nakanishi H. Infection of microglia with Porphyromonas gingivalis promotes cell migration and an inflammatory response through the gingipain-mediated activation of protease-activated receptor-2 in mice. Sci Rep. 2017 Sep 18;7(1):11759.

212. Ilievski V, Zuchowska PK, Green SJ, Toth PT, Ragozzino ME, Le K, Aljewari HW, O'Brien-Simpson NM, Reynolds EC, Watanabe K. Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice. PLoS One. 2018 Oct 3;13(10):e0204941.

210. Junges VM, Closs VE, Nogueira GM, Gottlieb MGV. Crosstalk between Gut Microbiota and Central Nervous System: A Focus on Alzheimer's Disease. Curr Alzheimer Res. 2018;15(13):1179-1190.

211. Abdel-Haq R. Schlachetzki J.C.M. Glass C.K. Mazmanian S.K. Microbiome-microglia connections via the gut-brain axis. J. Exp. Med. 2019; 216: 41-59

212. Bell JS, Spencer JI, Yates RL, Yee SA, Jacobs BM, DeLuca GC. Invited Review: From nose to gut - the role of the microbiome in neurological disease. Neuropathol Appl Neurobiol. 2019 Apr;45(3):195-215.

213. Heiss CN, Olofsson LE. The role of the gut microbiota in development, function and disorders of the central nervous system and the enteric nervous system. J Neuroendocrinol. 2019 May;31(5):e12684.
214. Salazar N, Valdés-Varela L, González S, Gueimonde M, de Los Reyes-Gavilán CG. Nutrition and the gut microbiome in the elderly. Gut Microbes. 2017 Mar 4;8(2):82-97.

215. Li B, He Y, Ma J, Huang P, Du J, Cao L, Wang Y, Xiao Q, Tang H, Chen S. Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota. Alzheimers Dement. 2019 Oct;15(10):1357-1366.

216. Zhuang ZQ, Shen LL, Li WW, Fu X, Zeng F, Gui L, Lü Y, Cai M, Zhu C, Tan YL, Zheng P, Li HY, Zhu J, Zhou HD, Bu XL, Wang YJ. Gut Microbiota is Altered in Patients with Alzheimer's Disease. J Alzheimers Dis. 2018;63(4):1337-1346.

217. Lin L, Zheng LJ, Zhang LJ. Neuroinflammation, Gut Microbiome, and Alzheimer's Disease. Mol Neurobiol. 2018 Nov;55(11):8243-8250.

218. Giau VV, Wu SY, Jamerlan A, An SSA, Kim SY, Hulme J. Gut Microbiota and Their Neuroinflammatory Implications in Alzheimer's Disease. Nutrients. 2018 Nov 14;10(11). pii: E1765.

219. Hwang JS, Im CR, Im SH, Immune disorders and its correlation with gut microbiome. Immune Netw 12, 129-138

220. Cerovic M, Forloni G, Balducci C. Neuroinflammation and the Gut Microbiota: Possible Alternative Therapeutic Targets to Counteract Alzheimer's Disease? Front Aging Neurosci. 2019 Oct 18;11:284.

221. Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, Ferrari C, Guerra UP, Paghera B, Muscio C, Bianchetti A, Volta GD, Turla M, Cotelli MS, Gennuso M, Prelle A, Zanetti O, Lussignoli G, Mirabile D, Bellandi D, Gentile S, Belotti G, Villani D, Harach T, Bolmont T, Padovani A, Boccardi M, Frisoni GB; INDIA-FBP Group. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging. 2017 Jan;49:60-68.

222. Vogt NM, Kerby RL, Dill-McFarland KA, Harding S, Merluzzi AP, Johnson SC, Carlsson CM, Asthana S, Zetterberg H, Blennow K, Bendlin BB, Rey FE. Gut microbiome alterations in Alzheimer's disease. Sci Rep. 2017 Oct 19;7(1):13537.

223. Zhuang ZQ, Shen LL, Li WW, Fu X, Zeng F, Gui L, Lü Y, Cai M, Zhu C, Tan YL, Zheng P, Li HY, Zhu J, Zhou HD, Bu XL, Wang YJ. Gut Microbiota is Altered in Patients with Alzheimer's Disease. J Alzheimers Dis. 2018;63(4):1337-1346.

224. Pritchard AB, Crean S, Olsen I, Singhrao SK. Periodontitis, Microbiomes and their Role in Alzheimer's Disease. Front Aging Neurosci. 2017 Oct 24;9:336.

225. Konkel JE, O'Boyle C, Krishnan S. Distal Consequences of Oral Inflammation. Front Immunol. 2019 Jun 25;10:1403.

226. Xie H. Biogenesis and function of Porphyromonas gingivalis outer membrane vesicles. Future Microbiol. 2015;10(9):1517-27.
227. Henneberger C1,2,3, Steinhäuser C4. Astrocytic TLR4 at the crossroads of inflammation and seizure susceptibility. J Cell Biol. 2016 Dec 5;215(5):607-609.

228. Gui MJ, Dashper SG, Slakeski N, Chen Y-Y, Reynolds EC. Spheres of influence: Porphyromonas gingivalis outer membrane vesicles. Mol. Oral Microbiol. 2016, 31, 365–378.

229. Grenier D, Roy S, Chandad F, Plamondon P, Yoshioka M, Nakayama K, Mayrand D. Effect of inactivation of the Arg- and/or Lys- gingipain gene on selected virulence and physiological properties of Porphyromonas gingivalis. Infect. Immun. 2003, 71, 4742–4748.

230. Jay TR, von Sauken VE, Landreth GE, TREM2 in neurodegenerative diseases. Mol Nuerodegener 2017, 12:56

231. Minoretti P, Gazzaruso C, Vito CD, Emanuele E, Bianchi MP, Coen E, Reino M, Geroldi D. Effect of the functional toll-like receptor 4 Asp299Gly polymorphism on susceptibility to late-onset Alzheimer’s disease. Neurosci. Lett. 2006, 391, 147–149.

232. Brouwers N, Van Cauwenberghe C, Engelborghs S, Lambert J-C, Bettens K, Le Bastard N, Pasquier F, Montoya AG, Peeters K, Mattheijssens M, Vandenbergher R, Deyn PP, Cruts M, Amouyel P, Sleegers K, Van Broeckhoven C. Alzheimer risk associated with a copy number variation in the complement receptor 1 increasing C3b/C4b binding sites. Mol. Psychiatry 2012, 17, 223–233.

233. Tan M-S, Yu J-T, Jiang T, Zhu X-C, Wang H-F, Zhang W, Wang Y-L, Jiang W, Tan L. NLRP3 polymorphisms are associated with late-onset Alzheimer’s disease in Han Chinese. J. Neuroimmunol. 2013, 265, 91–95.

234. Olsen L, Yilmaz O. Modulation in inflammasome activity by Porphyromonas gingivalis in periodontitis and associated systemic diseases, J Oral Microbiol. 2016,8:30385.

235. Venegas C, Kumar S, Franklin BS, Dierkes T, Brinkschulte T, Tejera D, Vieira-Saecker A, Schwartz S, Santarelli F, Kummer MP, Griep A, Gelpi E, Beilharz D, Riedel D, Golenbock DT, Geyer M, Walter J, Latz E, Heneka M, Microglia-derived ASC specks cross-seed amyloid-β in Alzheimer’s disease. Nature 2017, 552, 355–361.

236. Franklin BS, Latz E, Schmidt Fl. The intra- and extracellular functions of ASC specks. Immunol Rev. 2018 Jan;281(1):74-87.

237. Mariathasan S, Weiss DS, Dixit VM, Monack DM, Innate immunity against Francisella tularensis is dependent on the ASC/caspase-1 axis. J. Exp. Med. 2005, 202, 1043–1049.

238 Cecil JD, O’Brien-Simpson NM, Lenzo JC, Holden JA, Singleton W, Perez-Gonzalez A, Mansell A, Reynolds EC. Outer membrane vesicles prime and activate macrophage inflammasomes and cytokine secretion in vitro and in vivo. Front. Immunol. 2017, 8, 1017.

239. Fleetwood AJ, Lee MKS, Singleton W, Achuthan A, Lee M-C, O’Brien-Simpson NM, Cook AD, Murphy AJ, Dashper SG, Reynolds EC, Hamilton JA. Metabolic remodeling, inflammasome activation, and pyroptosis in macrophages stimulated by Porphyromonas gingivalis and its outer membrane vesicles. Front. Cell. Infect. Microbiol. 2017, 7, 351.
240. Vincents B, Guentsch A, Kostolowska DA, von Pawel-Rammingen U, Eick S, Jan Potempa J, Abrahamson M. Cleavage of IgG1 and IgG3 by gingipain K from Porphyromonas gingivalis may compromise host defense in progressive periodontitis. FASEB J. 2011, 25, 3741–3750.

241. Arndt Guentsch, Christiane Hirsch, Wolfgang Pfister, Bjarne Vincents, Magnus Abrahamson, Aneta Sroka, Jan Potempa, and Sigrun Eick. Cleavage of IgG1 in GCF is associated with presence of Porphyromonas gingivalis. J Periodontal Res. 2013 August ; 48(4): 458–465.

242. Stobernack T, du Teil Espina M, Mulder LM, Palma Medina LM, Piebenga DR, Gabarrini G, Zhao X, Janssen KMJ, Hulzebos J, Brouwer E, Sura T, Becher D, van Winkelhoff AJ, Götz F, Otto A, Westra J, van Dijl JM. 2018. A secreted bacterial peptidylarginine deiminase can neutralize human innate immune defenses. mBio 9:e01704-18.

243. Gabarrini G, Palma Medina LM, Stobernack T, Prins RC, du Teil Espina M, Kuipers J, Chlebowicz MA, Rossen JWA, van Winkelhoff AJ, van Dijl JM. There's no place like OM: Vesicular sorting and secretion of the peptidylarginine deiminase of Porphyromonas gingivalis. Virulence. 2018 Jan 1;9(1):456-464.

244. Gutner M, Chaushu S, Balter D, Bachrach G. Saliva enables the antimicrobial activity of LL-37 in the presence of proteases of Porphyromonas gingivalis. Infect Immun. 2009 Dec;77(12):5558-63.

245. Maisetta G, Petruzzelli R, Brancatisano FL, Esin S, Vitali A, Campa M, Batoni G. Antimicrobial activity of human hepcidin 20 and 25 against clinically relevant bacterial strains: effect of copper and acidic pH. Peptides. 2010 Nov;31(11):1995-2002.

246. Wang YX, Kang XN, Cao Y, Zheng DX, Lu YM, Pang CF, Wang Z, Cheng B, Peng Y. Porphyromonas gingivalis induces depression via downregulating p75NTR-mediated BDNF maturation in astrocytes. Brain Behav Immun 2019,

247. Mougeot J.-LC, Stevens CB, Paster BJ, Brennan MT, Lockhart PB, Mougeot FKB, Porphyromonas gingivalis is the most abundant species detected in coronary and femoral arteries. J. Oral Microbiol. 9, 1281562 (2017).

248. Kim S, Goel R, Kumar A, Qi Y, Lobaton G, Hosaka K, Mohammed M, Handberg EM, Richards EM, Pepine CJ, Raizada MK. Imbalance of gut microbiome and intestinal epithelial barrier dysfunction in patients with high blood pressure. Clin Sci (Lond). 2018 Mar 30;132(6):701-718.

249. Nakamura K, Kawakami T, Yamamoto M, Tomizawa M Fujiwara T, Ishii T. Activtion of the NLRP3 inflammasome by cellular labile iron. Exp Hematol 2016, 44:116-124

250. Calvani R, Picca A, Lo Monaco MR, Landi F, Bernabei L, Marzetti E. Of microbes and mind: a narrative review on the second brain aging. FrontMed 2018, 5:53

251. Seo DO, Holtzman DM. Gut microbiota: from the forgotten organ to a potential key player in the pathology of Alzheimer disease. J Gerontol A Biol Sci Med Sci. 2019 Nov 18. pii: glz262.
252. Friedland RP, Chapman MR. The role of microbial amyloid in neurodegeneration. PLOS Pathog 2017, 13:e1006654.

253. Netea MG, van der Meer JW. Trained immunity: an ancient way of remembering. Cell Host Microb 2017, 21:297-300.

254. Baëhl S, Garneau H, Lorrain D, Viens I, Svetelis A, Lord JM, Cabana F, Larbi A, Dupuis G, Fülöp T. Alterations in Monocyte Phenotypes and Functions after a Hip Fracture in Elderly Individuals: A 6-Month Longitudinal Study. Gerontology. 2016;62(5):477-90.

255. Penke B, Bogar F, Fulop L. Beta-amyloid and the Pathomechanisms of Alzheimer's disease: a comprehensive view. Molecules (Basel, Switzerland) 2017;22:10.

256. Kagan BL, Jang H, Capone R, Teran Arce F, Ramachandran S, Lal R, et al. Antimicrobial properties of amyloid peptides. Mol Pharm 2011;9(4):708–17.

257. Wu JJ, Brentjens MH, Torres G, Yeung-Yue K, Lee P, Tying SK. Valacyclovir in the treatment of herpes simplex, herpes zoster, and other viral infections. J Cutan Med Surg. 2003 Sep-Oct;7(5):372-81.

258. Itzhaki RF. Herpes simplex virus type 1 and Alzheimer's disease: increasing evidence for a major role of the virus. Front Aging Neurosci.

259. Kadowaki T, Baba N, Abe R, Takki M, Hashimoto T, Tsukuba S, Okazaki Y, Suda T, Akao K, Yamamoto Y. Suppression of pathogenicity of Porphyromonas gingivalis by newly developed gingipain inhibitors Mol Pharmacol. 2004, 66:1599-1606.

260. Czyzewski AM, Jenssen H, Fjell CD, Waldbrook M, Chongsiriwatana NP, Yuen E, Hancock RE, Barron AE. In Vivo, In Vitro, and In Silico Characterization of Peptoids as Antimicrobial Agents. PLoS One. 2016 Feb 5;11(2):e0135961.

261. Overhage J, Campisano A, Bains M, Torfs ECW, Rehm BHA, Hancock REW. Human host defense peptide LL-37 prevents bacterial biofilm formation. Infect Immun 2008(9):4176-4182.

262. Singh PK, Parseck MR, Greenberg EP, Welsh MJ. A component of innate immunity prevents bacterial biofilm development Nature 2002, 417:552-555.

263. Kang J, Dietz MJ, Li B. Antimicrobial peptide LL-37 is bactericidal against Staphylococcus aureus biofilms. POS One 2019, 14(6) e:0216676.

264. Svenson D, Wilk L, Mørgelin M, Herwald H, Nilsson B-O. LL-37 induced host cell cytotoxicity depends on cellular expression of the globular C1q receptor (CD33). Biochem J. 2016, 473, 87-98.

265. Johansson J, Gudmudsson GH, Rottenberg ME, Agerberth B. Conformation dependent antibacterial activity of the naturally occurring human peptide LL-37. J Biol. Chem. 1998, 273, 3716-3724.

266. Loeb MB, Molloy DW, Smieja M, Standish T, Goldsmith CH, Mahony J, Smith S, Borrie M, Decoteau E, Davidson W, McDougall A, Gnarpe J, O'DONNell M, Chernesky M. A
randomized, controlled trial of doxycycline and rifampin for patients with Alzheimer's disease. J Am Geriatr Soc. 2004 Mar;52(3):381-7.

267. Molloy DW, Standish TI, Zhou Q, Guyatt G; DARAD Study Group. A multicenter, blinded, randomized, factorial controlled trial of doxycycline and rifampin for treatment of Alzheimer's disease: the DARAD trial. Int J Geriatr Psychiatry. 2013 May;28(5):463-70.

268. Howard R, Zubko O, Bradley R, Harper E, Pank L, O'Brien J, Fox C, Tabet N, Livingston G, Bentham P, McShane R, Burns A, Ritchie C, Reeves S, Lovestone S, Ballard C, Noble W, Nilforooshan R, Wilcock G, Gray R; Minocycline in Alzheimer Disease Efficacy (MADE) Trialist Group. Minocycline at 2 Different Dosages vs Placebo for Patients With Mild Alzheimer Disease: A Randomized Clinical Trial. JAMA Neurol. 2019 Nov 18;77(2):164-74.

269. Balducci C, Forloni G. Doxycycline for Alzheimer's Disease: Fighting β-Amyloid Oligomers and Neuroinflammation. Front Pharmacol. 2019 Jul 3;10:738.

270. Angelucci F, Cechova K, Amlerova J, Hort J. Antibiotics, gut microbiota, and Alzheimer's disease. J Neuroinflammation. 2019 May 22;16(1):108.

266. O'Brien-Simpson NM, Holden JA, Lenzo JC, Tan Y, Brammar GC, Walsh KA, Singleton W, Orth RKH, Slakeski N, Cross KJ, Darby IB, Becher D, Rowe T, Morelli AB, Hammet A, Nash A, Brown A, Ma B, Vingadassalom D, McCluskey J, Kleanthous H, Reynolds EC. A therapeutic Porphyromonas gingivalis gingipain vaccine induces neutralising IgG1 antibodies that protect against experimental periodontitis. NPJ Vaccines. 2016 Dec 1;1:16022.

267. Puth S, Hong SH, Park MJ, Lee HH, Lee YS, Jeong K, Kang IC, Koh JT, Moon B, Park SC, Rhee JH, Lee SE. Mucosal immunization with a flagellin-adjuvanted Hgp44 vaccine enhances protective immune responses in a murine Porphyromonas gingivalis infection model. Hum Vaccin Immunother. 2017 Dec 2;13(12):2794-2803

268. Wilensky A, Potempa J, Houri-Haddad Y, Shapira L. Vaccination with recombinant RgpA peptide protects against Porphyromonas gingivalis-induced bone loss. J Periodontal Res. 2017 Apr;52(2):285-291.

269. Reynolds EC, O'Brien-Simpson N, Rowe T, Nash A, McCluskey J, Vingadassalom D, Kleanthous H. Prospects for treatment of Porphyromonas gingivalis-mediated disease - immune-based therapy. J Oral Microbiol. 2015 Sep 18;7:29125.

270. Choi JI, Seymour GJ. Vaccines against periodontitis: a forward-looking review. J Periodontal Implant Sci. 2010 Aug;40(4):153-63.

271. Saji N, Niida S, Murotani K, Hisada T, Tsuduki T, Sugimoto T, Analysis of the relationship between the gut microbiome and dementia a cross-sectional study conducted in Japan. Sci Rep 2019, 9:1008.

272. Duraj-Thatte AM, Pravschotinunt P, Nash TR, Ward FR, Joshi N, Modulating bacterila and gut mucosal interactions with engineered biofilm matrix protein. 2018, Sci Rep 8:3475
273. d’Hennezel E, Abubucker S, Murphy LO, Cullen TW. Total polysaccharide from the human gut microbiome silences toll like receptor signaling. mSystems 2017, 2:00046-e00017.

274. Attanasio J, Wherry EJ. Costimulatory and coinhibitory receptor pathways in infectious disease. Immunity 2016, 44:1052-1068

275. Groeger S, Jarzina F, Mamat U, Meyle J. Induction of B7-H1 receptor by bacterial cells fractions of Porphyromonas gingivalis on human oral epithelial cells: B7-H1 induction by Porphyromonas gingivalis fractions. Immunobiology 2017, 222, 137-147

276. Nagpal R, Neth BJ, Wang S, Craft S, Yadav H, Modified Mediterranean-ketogenic diet modulates gut microbiome and short-chain fatty acids in association with Alzheimer's disease markers in subjects with mild cognitive impairment. EBioMedicine 47 (2019) 529–542

277. Fortier M, Castellano CA, Croteau E, Langlois F, Bocti C, St-Pierre V, Vandenbergh C, Bernier M, Roy M, Descoteaux M, Whittingstall K, Lepage M, Turcotte ÉE, Fulop T, Cunnane SC. A ketogenic drink improves brain energy and some measures of cognition in mild cognitive impairment. Alzheimers Dement. 2019 May;15(5):625-634.

278. Schulthess J, Pandey S, Capitani M, Rue-Albrecht KC, Arnold I, Franchini F, Chomka A, Ilott NE, Johnston DGW, Pires E, McCullagh J, Sansom SN, Arancibia-Cárccamo VC, Uhlig HH, Powrie F. The Short Chain Fatty Acid Butyrate Imprints an Antimicrobial Program in Macrophages Immunity 50, 432–445, February 19, 2019

279. Wang X, Sun G, Feng T, Zhang J, Huang X, Wang T, Xie Z, Chu X, Yang J, Wang H, Chang S, Gong Y, Ruan L, Zhang G, Yan S, Lian W, Du C, Yang D, Zhang Q, Lin F, Liu J, Zhang H, Ge C, Xiao S, Ding J, Geng M. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. Cell Res. 2019 Oct;29(10):787-803.

280. Baar MP, Brandt RMC, Putavet DA, Klein JDD, Derks KWJ, Bourgeaósis BRM. Targeted apoptosis of senescent cells restores tissue homeostasis in response to chemotoxicity and aging. Cell 2017, 132-147.

281. Kirkland JL, Tchokonia T, Zhu Y, Niedernofer LJ, Robbins PD. The clinical potential of senolytic drugs. J Am Geriatr Soc 2017, 65 2297-2301.

282. Németh A, Orgovan N, Sodar BW, Osteikoetxea X, Paloczi K, Szabo-Taylor KE. Antibiotic induced release release of small extracellular vesicles (exosomes) with surface associated DNA. Sci Rep 2017, 7:8202

283. Wang R, Yu Z, Sunchub B, Shoaf J, Dang I, Zhao S. Rapamycin inhibits the secretory phenotype of senescent cells by Nfr2-independent mechanism. Aging Cell. 2017, 16:565-574

284. Wang S, Xie X, Lei T, Zhang K, Lai B, Zhang Z. Statins attenuate activation of the NLRP23 inflammasome by oxidized LDL or TNFalpha in vascular endothelial cells through a PXR dependent mechanism. Mol Pharmacol 2017, 92:256264.
285. Xu G, Li Z, Ding L, Tang H, Guo S, Liang H. Intestinal mTOR regulates GLP-1 production in mouse L-cells. Diabetologia 2015, 58 1887-1897.

286. Ji Y, Luo X, Yang Y, Dai Z, Wu G, Wu Z. Endoplasmic reticulum stress-induced apoptosis in intestinal epithelial cells: a feed back regulation by mechanistical target of rapamycin complex 1 (mTORC1) J Anim Sci Biotechno. 2018, 9:38

287. Martin SA, Souder DC, Miller KN, Clark JP, Sugar AK, Eliceiri KW. GSK3beta regulates brain energy metabolism. Cell Rep. 2018, 23 :1922-1931.

288. Salem I, Ramser A, Isham N, Ghannoum M. The gut microbiome as a major regulator of the gut skin axis. Front Microbiol 2018, 9:1459.

289. Ozsvari B, Nuttal JR, Sotgia F, Lisanti MP. Azythromycin and roxithromycin define a new family of senolytic drugs that target senescent human fibroblasts. Aging 2018, 10:3294-3307.

290. Weng D, Wu Q, Chen XQ, Du YK, Chen T, Li H, Azythromycin treats diffuse panbronchiolitis by targeting T cells via inhibition of mTOR pathway. Biomed. Pharmacother 2019, 110:440-448.

291. Lee GJ, Lim JJ, Hyun S. Minocycline treatment increases resistance to oxidative stress and extends lifespan of Drosophyla melanogastertia FOXO. Oncotarget 2017, 8:87879-87890.

292. Du RH, Tan J, Sun XY, LU M, Ding JH, Hu G. Fluoxetine inhibits NLRP3 inflammasome activation: implication in depression. Int J. Neuropsychopharmacol 2016, 19 :pyw037.

293. Bartels C, Wagner M, Wolfsgruber S, Ehrenreich H, Schneider A. Impact of SSRI therapy on risk of conversion from mild cognitive impairment to Alzheimer’s dementia in individuals with previous depression. Am J Psychiatry 2018, 175:232-241.

294. Xing Y, Liqi Z, Jian L, Quinghua Y, Qian Y. Doxicyclin inuces mitophagy and suppresses production of interferon beta IPEC J2 cells. Front Cel Infect Microbiol 2017, 7 :21.

295. Feng Y, Wang Y, Wang P, Huang Y, Wang F. Short chain fatty acids manifest stimulative and protective effects on intestinal barrier functions through the inhibition of the NLRP3 inflammasome and autophagy. Cell Physiol Biochem. 2018, 49:190-205.

296. Bendlin BB. Antidiabetic therapies and Alzheimer disease. Dialogues Clin Neurosci. 2019 Mar;21(1):83-91.

297. Yusta B, Baggio LL, Koehler J, Holland D, Cao X, Pinnell LJ. GLP-1R agonists modulate enteric immune responses through the intestinal intraepithelial lymphocyte (IEL) GLP1R. Diabetes 2015, 64, 2537-2549.

298. Lebrun LJ, Lenaertz K, Kiers D, Pais de Barros JP, Le Guern N, Plesnik J. Enteroendocrine L cells sens LPS after gut barrier injury to enhance GLP-1 secretion. Cell Rep 2017, 21 :1160-1168.

299. Yun SP, Kam TL, Panicker N, Kim S, Oh Y, Parl JS. Block of A1 astrocuiyte conversion by microgllia is neuroprotective in models of Parkinosn’s disease. Nature Med 2018, 24:931-938
300. Kim DS, Choi HI’, Wang Y, Luo Y, Hoffer BJ, Greig NH. A new treatment strategy for Parkinson’s disease through the gut brain axis the glucagon like peptide-1 receptor pathway. Cell transplant 2017, 26:1560-1571.

301. Wang T, Xu SF, Fan YG, Li LB, Guo C. Iron Pathophysiology in Alzheimer's Diseases. Adv Exp Med Biol. 2019;1173:67-104.

302. Killilea DW, Atamna H, Liao C, Ames BN. Iron accumulation during cellular senescence in human fibroblasts in vitro. Antioxyd Redox Sign 2003, 5:507-516.

303. Bayeva M, Kechaduri A, Puig S, Chang HC, Patial S, Blackshear J. mTOR regulates cellular iron homeostasis through tristetrapolin. Cell Metab. 2012, 16, 645-657.

304. Inoue H, Hanawa N, Katsumata-Tsuboi R, Katsumata SI, Takahashi N, Uehara M. Down regulation of senescence marker protein 30 bu iron specific chelator deferoxamine drives cell senescence. Biosci Biotechnol Biochem 2018, 82, 900-903.

305. Sfera A, Bullock K, Price A, Inderias L, Osorio C. Ferrosenescence of iron age of neurodegeneration? Mech Age Dev 2018, 174, 63-75.

306. Drago-Serrano ME, de la Graza-Amaya M, Luna JS, Campos-Rodrigues R. Lactoferrin-lipopolysaccharide (LPS) binding as key to antibacterial and antiendotoxin effects. Int Immunopharmacol 2012, 12, 1-9.

307. Kruzel ML, Zimecki M, Acor JK. Lactoferrin in a context of inflammation-induced pathology. Front Immunol 2017, 8:1438.

308. van Splunter M, Perdijk O, Fick-Brinkhof H, Feitsma AL, Floris-Vollenbroek EG, Meijer B, Brugman S, Savelkoul HFJ, van Hoffen E, van Neerven RJJ. Bovine Lactoferrin Enhances TLR7-Mediated Responses in Plasmacytoid Dendritic Cells in Elderly Women: Results From a Nutritional Intervention Study With Bovine Lactoferrin, GOS and Vitamin D. Front Immunol. 2018 Nov 20;9:2677.

309. Bramanti TE, Holt SC. Roles of porphyrins and host iron transport proteins in regulation of growth of Porphyromonas gingivalis W50. J Bacteriol. 1991 Nov;173(22):7330-9.

310. Grenier D, Chen H, Ben Lagha A, Fournier-Larente J, Morin MP. Dual Action of Myricetin on Porphyromonas gingivalis and the Inflammatory Response of Host Cells: A Promising Therapeutic Molecule for Periodontal Diseases. PLoS One. 2015 Jun 29;10(6):e0131758.

311. Moon JH, Herr Y, Kim SW, Lee JY. In vitro activity of deferoxamine against Porphyromonas gingivalis. FEMS Microbiol Lett. 2011 Oct;323(1):61-7309.

309. Reddy PH, Manczak M, Yin X, Reddy AP. Synergistic Protective Effects of Mitochondrial Division Inhibitor 1 and Mitochondria-Targeted Small Peptide SS31 in Alzheimer's Disease. J Alzheimers Dis. 2018;62(4):1549-1565.

310. Reddy, P.H., 2008. Mitochondrial medicine for aging and neurodegenerative diseases. NeuroMolecular Med. 10 (4), 291–315.
311. Reddy, P.H., 2006. Mitochondrial oxidative damage in aging and Alzheimer's disease: implications for Mitochondrially targeted antioxidant therapeutics. J. Biomed. Biotechnol. 2006 (3), 31372.

312. Burgos JS, Ramirez C, Sastre I, Valdivieso F. Effect of apolipoprotein E on the cerebral load of latent herpes simplex virus type 1 DNA. J Virol. 2006 Jun;80(11):5383-7.

313. Burgos JS1, Ramirez C, Sastre I, Bullido MJ, Valdivieso F. ApoE4 is more efficient than E3 in brain access by herpes simplex virus type 1. Neuroreport. 2003 Oct 6;14(14):1825-7.

314. Lachenmaier SM, Deli MA, Meissner M, Liesenfeld O. Intracellular transport of Toxoplasma gondii through the blood-brain barrier. Journal of Neuroimmunology. 2011;232(1-2):119–130.

315. Kamerkar S, Davis PH. Toxoplasma on the Brain: Understanding Host-Pathogen Interactions in Chronic CNS Infection. J Parasitol Res. 2012; 2012: 589295.

316. WHO. First WHO ministerial conference on global action against dementia: meeting report. Geneva: World Health Organization, 2015.

317. P T Francis et al. The cholinergic hypothesis of Alzheimer’s disease: a review of progress. Journal of Neurology, Neurosurgery, and Psychiatry, 66(2):137–147, 1999.

318. John Hardy and Dennis J. Selkoe. The amyloid hypothesis of alzheimer’s disease: Progress and problems on the road to therapeutics. Science, 297(5580):353, 2002.

319. Allal Boutajangout and Thomas Wisniewski. Tau-based therapeutic approaches for alzheimer’s disease - a mini-review. Gerontology, 60(5):381–385, 2014.

320 Claudie Hooper, Richard Killick, and Simon Lovestone. The gsk3 hypothesis of alzheimer’s disease. Journal of Neurochemistry, 104(6):1433–1439, 2008.

321. Elizabeth E Spangenberg and Kim N Green. Inflammation in Alzheimer’s disease: Lessons learned from microglia-depletion models. Brain, Behavior, and Immunity, 61:1–11, 2017.

322. Todd E. Golde, Steven T. DeKosky, and Douglas Galasko. Alzheimer’s disease: The right drug, the right time. Science, 362(6420):1250, 2018.

323. Se Hoon Choi et al. A three-dimensional human neural cell culture model of Alzheimer’s disease. Nature, 515:274, 2014.

324. Rebecca M. Marton et al. Differentiation and maturation of oligodendrocytes in human three-dimensional neural cultures. Nature Neuroscience, 2019.

325. Deepak Kumar Vijaya Kumar et al. Amyloid-β peptide protects against microbial infection in mouse and worm models of alzheimer’s disease. Science Translational Medicine, 8(340):340ra72, 2016.

326. Christopher Loose et al. A linguistic model for the rational design of antimicrobial peptides. Nature, 443:867–869, 2006.
Table 1

The most frequently involved microorganisms in AD

| Microorganisms | Viruses | Bacteria                          | Fungi    |
|----------------|---------|-----------------------------------|----------|
|                | HSV-1   | Treponema denticola               | Candida albicans   |
|                | HIV     | Chlamydia pneumoniae             | Malassezia furfur |
| Potential interventions                      | Example interventions                                      |
|---------------------------------------------|------------------------------------------------------------|
| **Targeting directly microorganisms**       | Antiviral agents                                           |
|                                             | Antibacterial agents (antibiotics)                         |
|                                             | Antifungal agents                                          |
| **Immune modulating treatment**             | Vaccination                                                |
|                                             | Anti-inflammatory treatment                                |
|                                             | Checkpoint inhibitors                                       |
| **Cell biological treatment**               | Senolytics                                                 |
|                                             | Antimicrobial peptides                                      |
|                                             | Iron chelators and mito-modulators                          |
| **Supportive treatment**                    | Probiotics/prebiotics                                      |
|                                             | Ketone bodies                                              |
|                                             | Nutritional support                                         |
|                                             | Physical exercise                                           |