

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

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**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  $\beta$  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  $\beta$  plaques. The amyloid  $\beta$  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  $\beta$  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 ( $A\beta$ ) 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  $A\beta$  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 favor 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  $A\beta$  plaques and intracellular hyperphosphorylated tau deposition, called neurofibrillary tangles, and unrelated or only indirectly related to the formation of  $A\beta$ , 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  $A\beta$  hypothesis (27-29).

However, the lack of a significant progress toward the mechanistic understanding of AD call for a reevaluation of the  $A\beta$  cascade hypothesis. The amyloid hypothesis states that the production of  $A\beta$  from its amyloid precursor protein (APP) in neurons and astrocytes by  $\beta$ -secretase (BACE) together with presenilin-containing complex called  $\gamma$ -secretase is the primary cause of AD (30-32). Thus, formation of  $A\beta$  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 *ApoEε4*, *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 A $\beta$ -containing plaques emerged almost a decade ago from the laboratory of Dr Tanzi, who had demonstrated the antimicrobial properties of A $\beta$  and first described it as an antimicrobial protein (AMP) (48). These crucial observations were later confirmed by other laboratories finding that A $\beta$  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 A $\beta$  hypothesis of AD origins from the failure, as already mentioned, of almost all trials which directly targeted A $\beta$  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 A $\beta$  generated in the brain, as a decrease in A $\beta$  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 A $\beta$  (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 A $\beta$  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 A $\beta$ -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 A $\beta$  making structure resembling to biofilm in the brain called senile or amyloid beta 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 A $\beta$  is produced resulting in its aggregates (plaques) (97). On the other hand, CRT production is upregulated by A $\beta$  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 A $\beta$  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 A $\beta$  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 *ApoE $\epsilon$ 4* carriers while the other alleles such as  $\epsilon$ 2 and  $\epsilon$ 3 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 APOE $\epsilon$ 4 heterozygosity (APOE $\epsilon$ 2/ $\epsilon$ 4 or  $\epsilon$ 3/ $\epsilon$ 4) 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 APOE $\epsilon$ 4 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 A $\beta$  is not the primary cause of AD, but itself the consequence of infection. A $\beta$  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 A $\beta$  in response to the virus (119,120). Interestingly, HIV suppresses production of A $\beta$  at early stages of the infection as a protection against the AMP role of A $\beta$  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 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 A $\beta$  (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-1 $\beta$ , TNF $\alpha$  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 immune innate 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 NF $\kappa$ B/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-1 $\alpha$ , 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 A $\beta$  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 A $\beta$  is an AMP gave a new impetus to the infectious hypothesis (48). They have tested A $\beta$  against bacteria and fungi and found it more powerful than even LL-37. More recently others and we have demonstrated that like LL-37, A $\beta$  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 A $\beta$  which inhibited HSV-1 infection of other neurons (155). This indicates that A $\beta$  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, A $\beta$  was more powerful than IFN type I. Recently, an interesting finding showed that A $\beta$  may also have anticancer properties (156) as well as BBB repair properties (157). The most important cells producing A $\beta$  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 A $\beta$  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 A $\beta$  could prevent infection in the brain (160,161). These authors hypothesized that the mechanism of action of A $\beta$  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 A $\beta$  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 ( $\beta$ - and  $\gamma$ -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 A $\beta$  has a clear pro-survival role.

The adaptive immune system also showed important changes in AD (163). Naïve T cells decreased and CD8<sup>+</sup> 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 NF $\kappa$ B 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

(181). 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 A $\beta$  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<sup>+</sup> 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). Gingipain 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 amyloid plaque deposition and IL-1 $\beta$  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.

Inflammaging 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 commensal) (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 A $\beta$  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 it manifests 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 out rate because of side effects. However, it seemed that the ADAS-Cog 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 3 months in prodromal and mild to moderate AD. The end point was Standardized Alzheimer's Disease Assessment Scale cognitive subscale (SADAS-cog) 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 A $\beta$  oligomers and neuroinflammation. However, by targeting  $\beta$ -amyloid oligomers as many other trials did its effect may 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 A $\beta$ -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 A $\beta$  (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 anti-microbial 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 A $\beta$  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 their 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 A $\beta$  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 A $\beta$  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 A $\beta$  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 A $\beta$ , 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. IC<sub>50</sub>), 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.

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### **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.

A $\beta$ : amyloid beta peptide; AD: Alzheimer's disease; BBB: blood brain barrier; PRR: Pattern recognition receptors; SASP: Senescence associated secretory phenotype.

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**Table 1**

**The most frequently involved microorganisms in AD**

<i>Viruses</i>	<i>HSV-1</i>
	<i>HIV</i>
	<i>HHV-6 and HHV-7</i>
<i>Bacteria</i>	<i>Borrelia burgdorferi</i>
	<i>Treponema denticola</i>
	<i>Chlamydia pneumoniae</i>
	<i>Porphyromonas gingivalis</i>
<i>Fungi</i>	<i>Candida albicans</i>
	<i>Malassezia furfur</i>

**Table 2****Potential interventions**

<i>Targeting directly microorganisms</i>	Antiviral agents
	Antibacterial agents (antibiotics)
	Antifungal agents
<i>Immune modulating treatment</i>	Vaccination
	Anti-inflammatory treatment
	Checkpoint inhibitors
<i>Cell biological treatment</i>	Senolytics
	Antimicrobial peptides
	Iron chelators and mito-modulators
<i>Supportive treatment</i>	Probiotics/prebiotics
	Ketone bodies
	Nutritional support
	Physical exercise