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Amyloid-β Immunotherapy for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive, degenerative disorder of the brain and the most common form of dementia among the elderly. As the population grows and lifespan is extended, the number of AD patients will continue to rise. Current clinical therapies for AD provide partial symptomatic benefits for some patients, however, none of them modify disease progression. Amyloid-β (Aβ) peptide, the major component of senile plaques in AD patients, is considered to play a crucial role in the pathogenesis of AD thereby leading to Aβ as a target for treatment. Aβ immunotherapy has been shown to induce a marked reduction in amyloid burden and an improvement in cognitive function in animal models. Although preclinical studies were successful, the initial human clinical trial of an active Aβ vaccine was halted due to the development of meningoencephalitis in ~ 6% of the vaccinated AD patients. Some encouraging outcomes, including signs of cognitive stabilization and apparent plaque clearance, were obtained in subset of patients who generated antibody titers. These promising preliminary data support further efforts to refine Aβ immunotherapy to produce highly effective and safer active and passive vaccines for AD. Furthermore, some new human clinical trials for both active and passive Aβ immunotherapy are underway. In this review, we will provide an update of Aβ immunotherapy in animal models and in human beings, as well as discuss the possible mechanisms underlying Aβ immunotherapy for AD.

Keywords

Amyloid-β; immunotherapy; Alzheimer's disease; transgenic mice; clinical trials

INTRODUCTION

Alzheimer's disease (AD) is a devastating neurodegenerative disease that affects more than 20 million elderly people worldwide. Its prevalence dramatically increases with aging, affecting 7–10% of individuals over age 65, and about 40% of persons over 80 years of age [1]. AD is characterized clinically by global cognitive dysfunction, especially memory loss, behavior and personality changes, and impairments in the activities of daily living that leave end-stage patients bedridden, incontinent and dependent on custodial care [2]. The neuropathological hallmarks of AD are extracellular neuritic plaques and cerebral amyloid angiopathy (CAA) formed by Aβ deposits, and intracellular neurofibrillary tangles (NFT) composed of filamentous aggregates called paired helical filaments of hyperphosphorylated protein tau, neuritic dystrophy, neuronal loss, gliosis, and inflammation [3–5]. While the exact causes of AD are unclear, accumulating evidence supports the "Aβ hypothesis", which hypothesizes that overproduction, insufficient clearance, and/or aggregation of Aβ peptide results in neuronal loss and dysfunction underlying dementia in AD [5].

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Aβ, a 39–42 residue peptide weighing ~ 4 KD, is formed through the "amyloidogenic pathway" in which amyloid precursor protein (APP) is sequentially cleaved by ß- and γ-secretase as opposed to the constituitive non-amyloidogenic pathway that involves processing APP by α-secretase [2]. Missense mutations in the APP or in the presenilin (PS) 1 and 2 (an important subunit of γ-secretase) genes can cause early-onset, familial forms of AD [4], providing genetic support for the role of Aβ in AD. Apolipoprotein E, especially its ε4 isoform, α1-antichymotrypsin, and C1q complement factor can greatly increase the aggregation of Aβ [6–9]. Once Aβ aggregates, its conformational change is thought to initiate a neurodegenerative cascade including impairment of long-term potentiation [10,11], changes in synaptic function [12–14], and accelerated formation of neurofibrillary tangles (NFT) that will ultimately lead to synaptic failure and neuronal death [15]. Thus, the Aβ cascade has become a central therapeutic target and reducing the Aβ burden in the brain by immunotherapy has developed as a promising strategy for the treatment of AD.

ACTIVE AND PASSIVE Aβ IMMUNOTHERAPY

Current AD treatments do little to modify the disease progression, although they do provide modest symptomatic benefit for some patients [16]. As a result of preclinical and early clinical trials, active and passive Aβ immunotherapies have become potentially useful disease-modifying strategies for combating AD. Aβ active immunization involves administration of synthetic Aβ peptide or Aβ fragments conjugated to a carrier protein and adjuvant to stimulate cellular and humoral immune responses in the host that, in turn, result in the generation of anti-Aβ antibodies. In passive immunotherapy, Aβ-specific antibodies (or conformational antibodies) are directly injected into the host, bypassing the need for engagement of the host's immune system. In both active and passive Aβ immunotherapies, anti-Aβ antibodies remove the Aβ from brain.

Active and passive Aβ immunization in mice

Schenk and colleagues were the first to report the beneficial effect of Aβ immunotherapy in a preclinical study of $A\beta_{1–42}$ active immunization in PDAPP transgenic mice [17]. Immunizing mice prior to the onset of pathology reduced levels of cerebral amyloid and produced high serum antibody titers. Also, amyloid deposition was reduced in mice that were immunized after they had developed significant amyloid pathology. This work was later confirmed by active intranasal immunization using a mixture of $A\beta_{1–40}$ and $A\beta_{1–42}$ peptides without adjuvant in PDAPP transgenic (tg) mice [18,19]. Two additional reports demonstrated that Aβ vaccination in Tg CRND8 [20] or APP/PS1[21] tg mice strongly improved behavioral performance in learning and memory tasks. Subsequently, numerous reports have confirmed the Aβ-lowering effect of Aβ vaccination in AD-like tg mouse models. The robust effect of Aβ immunotherapy on plaque deposition is illustrated in Fig. (1). We intranasally immunized 1 month-old J20 hAPP tg mice with full-length $A\beta_{1–}40/42$ and an adjuvant, *E. coli* heat labile enterotoxin LT (R192G), for 11 months. Abundant plaque deposition was seen in hippocampus and cortex of untreated, agematched control J20 mice however, Aβ-immunized J20 mice had almost no plaque deposition. Small punctate dots of Aβ immunoreactivity remained, often adjacent to blood vessels, possibly indicating clearance. It is clear from this and many other studies that immunizing APP tg mice prior to plaque deposition strongly prevents plaque deposition.

Passive immunization studies using Aβ antibodies against the N-terminus, mid-domain, and C-terminus of Aβ have been used in transgenic mice with AD-like pathology. Bard and colleagues performed passive immunization in PDAPP mice using several different monoclonal anti-Aβ antibodies that targeted various Aβ epitopes and represented different IgG isotypes [22]. The Aβ antibodies were able to enter the central nervous system (CNS), bind plaques and induce clearance of pre-existing amyloid. Later, the same authors showed that antibodies against the N-terminus of Aβ (3D6 against $A\beta_{1–5}$ or 10D5 against $A\beta_{3–7}$) were the

most effective at reducing brain amyloid [23]. Passive immunization of PDAPP tg mice with the 10D5 antibody led to reduced plaque burden, increased peripheral Aβ, improved hippocampal long-term potentiation (LTP), and improved cognitive performance [24]. Another monoclonal Aβ antibody, BAM-10 ($A\beta_{1–12}$), reversed memory impairment in Tg2576 APP tg mice, even in the absence of significant amyloid reduction [25].

Microhemorrhage has been reported following passive immunization with N-terminal Aβ antibodies in APP Tg mice [26–28]. In contrast, passive immunization with m266, a centraldomain Aβ monoclonal antibody, did not increase microhemorrhage in mouse brains [28], although it significantly decreased Aβ plaque pathology [29] and improved cognition [30]. In addition, passive immunization with C-terminal Aβ antibodies has been reported. Bard and colleagues first reported that the 16C11 antibody (against $A\beta_{33–42}$) failed to lower plaque burden or improve cognitive deficits [22]. In 2004, Wilcock and colleagues found that Tg2576 transgenic mice that were immunized with 2286, an IgG_1 C-terminal Aβ antibody against $A\beta_{28–40}$, for 3 months showed an improvement in alternation performance in the Y maze, a reduction in both diffuse and compact amyloid deposits, and transient but significant microglial activation [31]. However, this same C-terminal antibody led to a significant increase of CAA-associated microhemorrhage in immunized mice [27]. Subsequently, an IgG_{2b} C-terminal antibody (2H6) and its de-glycosylated version (de-2H6) were shown to reduce Aβ pathology and significantly improve performance in a radial arm water maze [32,33]. Vascular amyloid and microhemorrhages were reduced in de-2H6-vaccinated mice, possibly because deglycosylation of the antibody decreased its affinity for the Fcγ receptor.

Active Aβ vaccination in non-human primates

Using APP transgenic mouse models for the study of Aβ immunotherapy has the limitation that the immune response elicited is directed to transgene-expressed human Aβ but not endogenous mouse Aβ protein in brain. Therefore, a preclinical model that is genetically similar to humans, exhibits Aβ pathology with normal aging, and has a comparable immune response, would be of benefit for testing the safety and efficacy of an Aβ vaccine before transitioning to human clinical trials [34]. Several species of non-human primates, including rhesus monkeys (Macaca mulatta) and Caribbean vervets (*Chlorocebus aethiops*, SK) exhibit age-related Aβ deposition similar to AD in humans [35,36]. Our pilot study of Aβ vaccination in 5 aged vervets demonstrated that active immunization with aged $A\beta_{1–40/42}$ over ten months produced appreciable titers of plasma Aβ antibodies that recognized plaques in human, vervet, and APP tg mouse brains [36]. Anti-Aβ titers were approximately 1000-fold lower in cerebrospinal fluid (CSF) compared to titers in plasma. In addition, A Aβ protein levels in plasma were elevated while those in CSF and brain tissues were reduced in vaccinated vervets. Inflammation and T cells were absent in the brain tissues of immunized vervets.

Another study in rhesus monkeys using a similar active vaccine with aggregated $A\beta_{1–42}$ or aggregated islet amyloid polypeptide (IAPP) and CFA was investigated. Rhesus monkeys that received aggregated $A\beta_{1–42}$ generated moderate anti-Aβ titers as well as a 5–p10 fold increase of Aβ levels in plasma, as compared with the rhesus monkeys that were vaccinated with aggregated IAPP [35]. In contrast to previous vaccination studies in vervets [36], cerebral Aβ levels in these younger monkeys was not reduced even though plasma Aβ levels were elevated after vaccination possibly, because they had not reached a plaque-bearing age. Together, these two studies demonstrate that non-human primates display natural Aβ deposition with aging and generated anti-Aβ antibodies when actively vaccinated with an Aβ peptide.

Active and passive Aβ immunization: human clinical trials

Extensive preclinical studies of active immunization with pre-aggregated Aβ showed promising benefits such as stimulating high anti-Aβ antibody titers in plasma, and consequently reducing cerebral Aβ burden, as well as preventing or reversing cognitive decline in different mouse models. This approach was translated to clinical trials by ELAN/Wyeth in 2000 and 2001. After a single-dose Phase I study in 24 patients and a multiple-dose Phase I study in 80 patients with mild to moderate AD in the United Kingdom, the immunization of $A\beta_{1–42}$ peptide (AN1792) in combination with the adjuvant QS-21 showed good tolerability in patients and, 58% of the patients with multiple-dose vaccination developed an anti-Aβ humoral response. There were few adverse effects and some evidence of possible improvement in one of the clinical measurements [37]. Next, a Phase IIa study was initiated in which 372 mild to moderate AD patients were enrolled to receive either AN1792 (300 patients) or placebo (72 patients). The trial was stopped due to the development of meningoencephalitis in 18 of the 300 (6%) immunized AD patients [38,39]. Although the adverse events did not correspond to antibody response, it has been suggested that they may have been initiated by activation of cytotoxic T cells and/or autoimmune reactions [38,40–42]. Subsequent reports showed that even brief active immunization with AN1792 succeeded to some degree in generating an anti-Aβ antibody response, clearing Aβ from brain, and modestly stabilizing cognitive function [37,39,41–45]. However, Holmes and colleagues reported that small group of immunized AD patients who came to autopsy several years after the trial was stopped showed no significant differences between placebo and AN1792 vaccinated groups in survival outcomes or time to severe dementia, or in cognitive measures, even though large areas of cortex were devoid of amyloid plaques [46]. It is quite possible that the disease process, including synaptic and neuronal loss, was too far along when these AD patients entered the trial, suggesting that Aβ vaccination may have its best effects if given prior to or in the very early stages of AD. Active Aβ vaccine trials are current underway, sponsored by pharmaceutical companies such as ELAN/Wyeth, Novartis, Merck, Affiris, and United Biomedical.

Direct injection of anti-Aβ antibodies may be an easy and relatively safe method to provide Aβ antibodies without eliciting Th1-mediated autoimmunity. Intravenous immunoglobulin (IVIg) antibodies, a pooled mixture of human antibodies including anti-Aβ antibodies, were found to interfere with the oligomerization and fibrillization of Aβ peptide [47,48], protect neurons exposed to toxic concentrations of Aβ peptide [47], and promote the clearance of Aβ peptide from the brain [49], suggesting that IVIg treatment may be useful in humans as a type of passive immunotherapy to treat AD. In a small pilot study [50] IVIg reduced Aβ peptide levels in the CSF and significantly increased the Aβ levels in blood, suggesting that the antibody mixture induced efflux of Aβ from the brain to the periphery. Furthermore, some improvement in cognitive function was seen in immunized patients in the absence of adverse events. Anti-Aβ antibodies were detected in CSF of the patients subsequent to IVIg treatment, indicating that IVIg antibodies may cross the blood-brain barrier (BBB) and thereby affect Aβ levels in the brain [34]. Several other clinical trials have shown evidence of the potential of IVIg immunotherapy for AD but these trials were carried out only in only a small number of AD patients [34,51]. More recently, larger phase III clinical IVIg trial in AD patients was initiated by Baxter Biosciences and the Alzheimer's Disease Cooperative Study (ADCS). In addition, other passive Aβ vaccine clinical trials are underway, sponsored by pharmaceutical companies such as ELAN/Wyeth/Janssen, Eli Lilly, Pfizer, Hoffman-LaRoche, Genentech, and GlaxoSmithKline.

ONGOING DEVELOPMENT OF IMMUNOTHERAPEUTIC STRATEGIES

Second-generation active Aβ vaccines in murine models

Town and colleagues demonstrated that the original active $A\beta_{1–42}$ vaccine using CFA/IFA adjuvant as described by Schenk in 1999 [17] produced primarily a Th2 immune response in Tg APPsw (Tg2576) mice characterized by reduced IL-12 receptor beta chain and increased secretion of IL-4 and IL-10 by splenocytes cultured 3 months after the last immunization [52]. Interestingly, blocking the CD40-CD40L interaction, a key pathway that promotes Th1 immunity, actually increased Aβ vaccine efficacy in mice [53], suggesting that a Th2 response is more desirable. However, it seems that Aβ immunization in the presence of QS-21 adjuvant and polysorbate 80 resulted in a Th1 response that likely led to autoaggressive T cells and aseptic meningoencephalitis in a small subset (6%) of AD patients who received this form of the AN1792 vaccine. Current alternative immunotherapeutic strategies for boosting antibody generation as well as minimizing the Th1 immune response after active Aβ vaccination are focused on: (1) generating epitope-specific Aβ immunogens to avoid Aβ-specific T cell responses, (2) testing various adjuvants that favor a Th2 immune response to avoid adverse side effects, (3) producing Aβ DNA vaccines, and (4) using different routes of vaccine administration.

Aβ epitope-specific vaccines

The use of N-terminal Aβ derivatives as immunogens was hypothesized to generate a strong humoral immune response while avoiding a deleterious Aβ-specific T cell response because the dominant B cell epitope for anti-Aβ antibodies generated by active immunization with full-length Aβ was found to reside within the first 15 amino acids of the Aβ N-terminus [18], which was later refined to $A\beta_{1–5}$, $_{1–7}$, $_{1–8}$, $_{1–9}$, $_{1–11}$, $_{1–16}$, $_{4–10}$, and $Ab_{3–7}$ in mice [23,40,54–56], $Ab_{1–7}$ in vervets [36], and $A\beta_{1–18}$ in humans [57]; while dominant Aβ T cell epitopes have been mapped to $A\beta_{6–28}$ [40] or beyond $A\beta_{1–15}$ [58] in mice and $A\beta_{16–33}$ in humans [59]. This hypothesis has been confirmed by several groups using short Aβ fragment active vaccines. AD tg mice immunized with $K6A\beta_{1–30}$-NH_2 vaccine containing 6 lysines linked to the first 30 residues of Aβ [60], $K6A\beta_{1–30}[E_{18}E_{19}]$ vaccine with mutations at positions 18 and 19 [61], PADRE-$A\beta_{1–15}$ epitope vaccine containing the $A\beta_{1–15}$ in tandem with the synthetic pan HLADR-binding peptide (PADRE) [62], or another epitope vaccine composed of two copies of $A\beta_{1–11}$ fused with PADRE [63], resulted in generation of anti-Aβ antibodies, reduction in plaque burden and/or cognitive impairment, and reduction or abolishment of autoreactive T cell responses.

We found that while $A\beta_{1–15}$ peptide was less immunogenic than $A\beta_{1–40/42}$ for antibody production in wild-type mice [64], intranasal boosting with dendrimeric $A\beta_{1–15}$ (16 copies of Aβ1–15 on a lysine tree; $dA\beta_{1–15}$) and a mucosal adjuvant after a single priming injection of $A\beta_{1–40/42}$ in J20 hAPP mice resulted in high anti-Aβ antibody titers and reduced cerebral amyloid plaque burden [65]. Later, we found that intranasal delivery of $dA\beta_{1–15}$ with LT (R192G) without a priming injection, also induced robust anti-Aβ titers and lowered cerebral Aβ levels and plaques in the brains of J20 APP tg mice without inducing an Aβ-specific cellular immune response [66]. Intranasal delivery of 2 short Aβ immunogens, $2xA\beta_{1–15}$ and $R2xA\beta_{1–15}$ (tandem repeat of $A\beta_{1–15}$ linked by 2 lysine residues, without or with an RGD motif at the N-terminus, respectively) resulted in high anti-Aβ antibody titers without an Aβ-specific T cell response, and reduced plaque load. In the case of the $2xA\beta_{1–15}$ vaccine, improved memory acquisition in the Morris water maze in J20 APP tg mice was observed [67]. Numerous other short Aβ fragment active vaccines are currently under investigation [68].

Modulating the immune response with adjuvants

QS21, a Th1 type adjuvant, used in the AN1792 clinical trial may have contributed to a possible Aβ-specific T-cell reaction, leading to the development of meningoencephalitis, the adverse event observed in this trial. Cribbs et al. compared the efficacy of CFA, alum, TiterMax Gold (TMG) and QS21 separately as adjuvants for $A\beta_{1–42}$ vaccination. Th1-type adjuvants, QS21 and CFA, induced the strongest humoral response to Aβ while the Th2-type adjuvant, alum, generated an intermediate humoral response. The Th1-type adjuvant TMG gave the weakest humoral response [40]. These researchers also compared the induction of humoral immune responses with another Th1-type adjuvant, Quil A, and Th2-type adjuvant Alum separately and in combination, using PADRE-$A\beta_{1–15}$ [69]. Switching adjuvants from Alum to Quil A increased antibody production compared to Alum alone and maintained Alum's Th2-type humoral response. Therefore, switching from Alum to Quil A after the priming dose might be beneficial for enhancing anti-Aβ antibody generation in AD patients without inducing a Th1-mediated immune response. Active Aβ vaccination using alum may be less effective in generating as robust a humoral immune response compared with some Th1 type adjuvants, but it avoided vascular microhemorrhages in AD tg mice [70]. An oral Aβ vaccine was proposed that involves loading Aβ peptides ($A\beta_{1–12}$, $A\beta_{29–40}$ and $A\beta_{1–42}$) onto poly(D,L-lactide co-glycolide) (PLG) microparticles using W/O/W double emulsion solvent evaporation method [71]. Oral immunization of Aβ peptide-loaded microparticles in wildtype mice induced a robust anti-Aβ antibody immune response that lasted for a prolonged time (24 weeks).

We have compared the humoral and cellular immune responses produced by two different adjuvants used for subcutaneous Aβ vaccination: monophosphoryl lipid A (MPL)/trehalose dicorynomycolate (TDM) and *E. coli* heat-labile enterotoxin LT(R192G). Subcutaneous injection of Aβ with MPL/TDM generated a stronger anti-Aβ antibody response than with LT (R192G) and was accompanied by moderate splenocyte proliferation and IFNγ production indicating a cellular response [72]. However, our previous studies showed that intranasal delivery of Aβ peptide with LT(R192G) induced robust Th2-type anti-Aβ titers. Thus, route of vaccine delivery can change the humoral and cellular immune responses to a vaccine.

Aβ DNA vaccines

DNA vaccination may have potential as a treatment for AD because it is simple, easily modified, and may not require the use of an adjuvant. Immune responses of the host can be easily manipulated to obtain a Th2-type reaction. Initially, Aβ DNA vaccines were produced using adeno-associated virus vectors or adenovirus vector. Recently, researchers have focused on developing non-viral plasmid vectors because such DNA vaccines can be mass-produced at a low cost and have no possibility of viral infection or transformation [73].

$A\beta_{1–42}$ DNA vaccination with or without adjuvants has been shown to be efficient for breaking host $A\beta_{1–42}$ tolerance and inducing a Th2 immune response [74–77], significantly reducing the cerebral Aβ burden in different AD-like transgenic mouse models [74,76,77], and reducing CAA, high-molecular-weight oligomers, and Aβ trimers in TgCRND8 mice [77]. Movsesyan and colleagues recently developed and investigated a shorter DNA epitope vaccine containing three copies of $A\beta_{1–11}$ fused with a foreign T helper epitope (PADRE), and linked to macrophage-derived chemokine (MDC/CCL22) or three copies of Complement 3d (3C3d) for adjuvant activity. Vaccination of 3xTg-AD mice (encoding mutant human APP, PS1 and Tau) with the pMDC-$3A\beta_{1–11}$-PADRE construct led to high titers of Th2-biased anti-Aβ antibodies. Aβ pathology and glial activation were diminished in the absence of microhemorrhage and cognitive deficits were improved [78]. The $3A\beta_{1–11}$-PADRE-3C3d construct resulted in similar beneficial effects on antibody response and Aβ burden [79].

Okura and colleagues [73,80] immunized APP23 tg mice with non-viral Aβ DNA vaccines prior to Aβ deposition (prevention) or after the onset of Aβ deposition (therapy) in the brain. Cerebral Aβ burden was reduced in immunized mice following the prevention trial. Cerebral Aβ burden was reduced ~ 50% by the age of 18 months in the therapeutic trial. Neuroinflammation and T cell responses to Aβ peptide were absent in immunized APP23 and wildtype mice, even after long-term vaccination [80].

Novel routes for administration of active Aβ immunization

Another strategy to increase the generation of Aβ antibodies and the safety of active immunization is to optimize administration routes of the vaccine delivery. For example, we demonstrated that intranasal administration of Aβ peptides, in the absence of adjuvant, induced a modest anti-Aβ antibody response sufficient enough to significantly reduce cerebral Aβ levels in PDAPP mice [18,19]. Later, we found that adjuvant, *E. coli* heat labile enterotoxin LT (R192G), significantly enhanced anti-Aβ antibody generation in wildtype and APP tg mice when short Aβ peptide immunogens, $dA\beta_{1–15}$ [66] and $2xA\beta_{1–15}$ were delivered intranasally [67]. In both studies, intranasal Aβ immunization using LT(R192G) led to a predominantly Th2-biased immune response and a lowering of cerebral Aβ in the absence of any adverse effects.

Transcutaneous immunization utilizes antigen presentation by Langerhans cells in the skin. Previously, we reported that transcutaneous immunization with $dA\beta_{1–15}$, but not $A\beta_{1–40/42}$, and the adjuvant LT(R192G) resulted in moderate Th2-biased anti-Aβ antibody titers in wildtype mice [66]. Subsequently, Town and colleagues showed that transcutaneous immunization with $A\beta_{1–42}$ with cholera toxin adjuvant resulted in robust anti-Aβ antibody titers, reduced cerebral Aβ levels, and increased Aβ in blood, while avoiding T cell infiltration into brain and cerebral microhemorrhage [81].

An oral DNA vaccine consisting of an adeno-associated viral vector carrying Aβ cDNA (AAV/Aβ) without adjuvant induced the expression and secretion of $A\beta_{1–43}$ or $A\beta_{1–21}$ in Tg2576 mice, leading to the generation of long-lasting anti-Aβ antibodies [82]. A single oral administration of AAV/Aβ to 10 month-old Tg2576 mice protected against progressive cognitive impairment and decreased Aβ deposition, insoluble Aβ, soluble Aβ oligomers (Aβ56), microgliosis, and synaptic degeneration [83]. Oral immunization of Aβ peptide-loaded microparticles also induced long-term anti-Aβ antibody production in female BALB/c mice [71].

Second-generation active Aβ vaccines in non-human primates and canines

Second-generation Aβ vaccines have been tested in several non-human primate species. Non-human primates develop Aβ plaque deposition with aging, although the degree of deposition varies among species. Administration of site-specific UBITh Aβ vaccine ($A\beta_{1–14}$) in baboons and macaques showed that N-terminal-directed anti-Aβ antibodies were generated while bypassing any adverse Aβ cellular immune responses. The vaccine showed significant efficacy in both non-human primate species, suggesting a potential versatility of the vaccine. Furthermore, anti-Aβ antibodies generated by vaccinated monkeys sequestered toxic Aβ from the CNS into the periphery. In addition, repeat dosing with the UBITh vaccine did not appear to be detrimental or toxic in macaques, indicating it was a safe and well-tolerated vaccine in adult macaques [84]. Another recent active Aβ vaccination study in lemurs showed that moderate to robust anti-Aβ IgM and IgG titers were generated in those lemurs immunized with several Aβ derivatives described above, $K6A\beta_{1–30}$ and $K6A\beta_{1–30}[E_{18}E_{19}]$, with alum adjuvant. An increase of $A\beta_{1–40}$ in plasma suggested that resulting anti-Aβ antibodies may bind to Aβ in the brain and draw it to the periphery [85].

Similar to non-human primates, the Aβ gene in dogs is similar to human Aβ and aged canines, in particular, beagles, accumulate Aβ plaques in the brain with normal aging. Head and colleagues immunized aged beagles presumed to have cerebral Aβ deposition, with fibrillar $A\beta_{1–42}$ and alum [86]. Aβ-vaccinated beagles generated strong anti-Aβ antibody responses and had reduced Aβ plaque load in several brain regions. However, Aβ vaccination in aged beagles did not ameliorate cognitive impairments, suggesting that early vaccination (i.e., prior to pathogenesis) may be needed to see cognitive benefits.

Second-generation passive immunotherapy in murine models

Passive Aβ immunization has been shown to have some beneficial effects on synaptic plasticity and neuronal function. Chauhan et al. reported that intracerebroventricular (i.c.v.) infusion of Aβ antibodies protected APP transgenic mice from synaptic loss and gliosis [87,88]. Klyubin and co-workers reported that i.c.v. infusion of 4G8, a monoclonal antibody directed to the mid-region of Aβ ($A\beta_{17–24}$), prevented synaptic plasticity disruption induced by naturallyoccurring, cell-derived Aβ oligomers [89], and by human CSF containing Aβ dimers [90]. A study by Spires-Jones et al. found that immunization with the Aβ monoclonal antibody 3D6 that recognizes the free N-terminus enhanced structural plasticity in PDAPP mouse brain [91].

Recent evidence suggests that Aβ oligomers (dimers, trimers, tetramers, etc.) rather than monomers or fibrils may be the major toxic agents that specifically inhibit LTP and synaptic plasticity in AD [92]. As a result, there is a surge of passive Aβ immunotherapies focusing on inhibiting or reversing Aβ oligomerization using specific anti-oligomer antibodies. One example of an oligomer conformation-specific antibody, NAB61, was used to immunize aged Tg2576 mice and it showed significant improvement in spatial learning and memory, without altering brain amyloid deposition or APP processing [93]. This result supports the hypothesis that cognitive deficits in APP tg mice are at least partially caused by toxic soluble Aβ oligomers.

Interestingly, Britschgi et al. recently reported that abundant natural, endogenous anti-Aβ antibodies (IgGs), especially those reactive against high molecular mass assemblies of oligomeric Aβ and pyroglutamate or oxidized residues of Aβ, can be found in plasma and CSF of both AD patients and healthy controls [94]. Once isolated from human blood, these natural antibodies protected primary neurons from oligomeric Aβ toxicity *in vitro*. Plasma IgG reactivities against several Aβ forms, including oligomeric $A\beta_{1–42}$ in particular, as well as amyloidogenic non-Aβ peptides were reduced with aging and AD in humans. In addition, natural Aβ IgGs observed in plasma samples from our aged vervets were similar to those in human AD patients [94]. Active immunization with $A\beta_{1–40/42}$ in aged vervets led to high titers not only against conformation-specific Aβ assemblies, but also against non-amyloidogenic peptides. Thus, it appears that enhancing the generation of neuroprotective natural anti-Aβ antibodies or passive applying them to the elderly might be beneficial for the prevention and treatment of AD.

Arbel and colleagues reported a novel approach to inhibit Aβ production via antibodies against the beta-secretase cleavage site of the APP[95]. Long-term systemic administration of this anti-beta-site antibody in Tg2576 mice improved cognitive deficits, reduced inflammation, and decreased the incidence of microhemorrhage without inducing any peripheral autoimmunity responses. However, cerebral Aβ levels were unchanged by the antibody treatment [96].

Alternative strategies to improve the efficacy of passive immunization and reduce its side effects have been reported. Compared with systemic immunization of Aβ Mab 6E10, prolonged i.c.v. infusions by osmotic mini-pump dose-dependently reduced the parenchymal plaque burden, astrogliosis, and dystrophic neurites at much lower doses [97]. In addition, side effects observed after administration of some N-terminal Aβ antibodies such as microhemorrhage were reduced by modulating antibody dose [98], deglycosylating whole IgG Aβ antibody

[33], removing the Fc portion by proteolysis to produce Fab'2 [99], or designing recombinant Fab or single-chain variable fragment [100].

POTENTIAL MECHANISMS UNDERLYING Aβ IMMUNOTHERAPY

The mechanisms by which Aβ is cleared from the brain via active or passive vaccination are not clear yet, however, several major hypotheses have been proposed including microglia-mediated phagocytosis, antibody-mediated alterations of Aβ aggregation and neutralization of Aβ toxicity, peripheral sink, and intracerebral sequestration of Aβ in a monomeric state.

Microglia-mediated phagocytosis

Intracellular Aβ immunoreactivity within microglia and macrophage in PDAPP tg mice immunized with Aβ monoclonal antibodies indicated that peripherally administered Aβ antibodies can cross the BBB, bind to Aβ in plaques and trigger the Fc receptors (FcR)-mediated microglial phagocytosis [22,23]. The mechanism of microglial FcR-dependent Aβ clearance was further proven in an *ex vivo* assay with sections of PDAPP tg or AD brain tissue. The data showed that antibodies against Aβ peptide activated microglial cells and subsequently removed plaques via Fc receptor (FcR)-mediated phagocytosis [22]. Active vaccination with $A\beta_{1-42}$ in PDAPP tg mice [17] and in AD patients [41,42] also showed evidence that the reduction of compact and densely stained Aβ deposits were associated with microglial Fc-receptor phagocytosis. Additionally, the activation of microglial phagocytosis and removal of Aβ deposits were also observed in mice treated with Aβ nonviral DNA vaccines [73,101]. The combined results of numerous active and passive Aβ immunotherapy studies indicate that FcR-mediated activation of microglia could be a central mechanism of reducing Aβ load in brain.

However, effective clearance of Aβ deposits were also observed in $A\beta_{1-42}$ immunized FcRγ −/− Tg2576 mice [102] or in APP transgenic mice treated with F(ab')2 fragments of 3D6 antibody (antibody without Fc portion) [99,103], implying that the FcR-mediated phagocytosis is not the only mechanism involved in microglia-induced plaque removal. These findings demonstrate that Fc-independent mechanisms, in addition to Fc-dependent mechanisms, are capable of mediating the effects of active and passive Aβ immunization.

Antibody-mediated alterations of Aβ aggregation and neutralization of Aβ toxicity

Certain anti-Aβ antibodies have been reported to directly bind to Aβ and either prevent oligomerization and fibril formation of Aβ [55,104,105] or dissolve Aβ aggregates [106,107] *in vitro*. Specific conformational Aβ antibodies target existing plaques in the brain and lead to direct disassembly *in vivo* [108]. These findings suggest that direct interaction of anti-Aβ antibodies with Aβ could potentially affect Aβ aggregation both *in vitro* and *in vivo*. In addition, Aβ antibodies that recognize an oligomeric conformation have been shown to reverse or ameliorate the cognitive deficits in vivo [89,93,109–111], indicating that another possible mechanism of Aβ immunotherapy may be the blockade of neurotoxicity induced by Aβ oligomers.

Aβ clearance via peripheral sink

The peripheral sink mechanism was first proposed by DeMattos and colleagues [29] in the study using m226, an Aβ mid-region antibody with a high affinity for soluble Aβ, in PDAPP tg mice. Later, this mechanism was confirmed by active [60,61,112,113] and passive [30, 114–116] Aβ immunization studies. These studies suggest that Aβ antibody in plasma can reduce circulating Aβ level by directly binding to plasma Aβ, which in turn disrupts the brain-blood equilibrium of Aβ and drives the removal of soluble Aβ from the brain. Furthermore, the studies performed by Deane and colleagues indicate that net clearance can involve a peripheral sink effect and an active FcR-mediated process at the BBB as well [115,116].

Intracerebral sequestration of monomeric Aβ

Another mechanism, intracerebral sequestration of monomeric Aβ, has been proposed recently by Yamada and colleagues [117], who found that peripheral injection of anti-Aβ monoclonal antibody, m266, with high affinity to soluble Aβ, followed by intracerebral microinjection of radiolabeled $A\beta_{1–40}$ in wildtype mice slowed Aβ clearance from mouse brains. In addition, peripheral administration of m266 antibody in young, pre-plaque APP transgenic mice led to increased levels of monomeric, antibody-bound Aβ in brain without affecting total soluble Aβ levels in brain. Their results indicate that certain Aβ antibodies may sequester soluble, monomeric Aβ in the brain thereby preventing the formation of multimeric Aβ and related neurotoxicity.

Other possible mechanisms

In addition, antibody-independent immune cell-mediated plaque clearance, effects on Aβ-mediated vasoconstriction, and modulation of CNS cytokine production as well as IgM-mediated hydrolysis of Aβ may be other possible mechanisms underlying Aβ immunotherapy [111,118]. Overall, as illustrated in Fig. (2), there may be many mechanisms involved in Aβ clearance and cognitive improvement resulting from active and passive immunization. These mechanisms may act independently, concomitantly or sequentially for Aβ immunotherapy depending on the severity of the disease, antibody specificity and Ig isotype, and specific animal model used.

CONCLUSIONS

Aβ immunotherapy in animal models and human AD patients has been shown to induce anti-Aβ antibody generation, reduce cerebral Aβ levels, and in some studies, stabilize or improve cognition. Building upon lessons learned from the AN1792 trial, many groups, both academic and commercial, have generated novel active and passive Aβ vaccines. The goals of active Aβ immunization are to induce long-lasting, safe, and cost-effective vaccines to lower cerebral Aβ and/or prevent Aβ aggregation. The goals of passive Aβ immunization are to lower safely cerebral Aβ via monthly injections of antibodies. The ultimate goal for both types of vaccines is to prevent or diminish the downstream effects of Aβ on synapses and neurons, thereby providing cognitive benefits. Multiple active and passive Aβ immunotherapy clinical trials are currently underway. In addition, tau-related vaccines are also being studied in tangle-bearing tau tg mouse models [119]. As the average lifespan increases worldwide, the number of AD patients who suffer from this devastating neurodegenerative disease grows as well. Therefore, it is necessary to find a safe and effective way to prevent or cure the disease as soon as possible. Although there is much work to be done, we remain hopeful that Aβ immunotherapy, either alone or in combination with other therapies, will succeed in preventing or treating AD.

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Abbreviations

Aβ	amyloid-β
AD	Alzheimer's disease
ADCS	Alzheimer's disease cooperative study
APP	amyloid precursor protein
BBB	blood-brain barrier

CAA	cerebral amyloid angiopathy
CFA	Complete Freund's Adjuvant
CNS	central nervous system
CSF	cerebrospinal fluid
FcR	Fc receptor
IAPP	islet amyloid polypeptide
i.c.v	intracerebroventricular
IVIg	intravenous immunoglobulin
LTP	long-term potentiation
MPL	monophosphoryl lipid A
NFT	neurofibrillary tangles
PADRE	pan human leukocyte antigen DR-binding peptide
PLG	poly (D,L-lactide co-glycolide)
PS	presenilin
TDM	trehalose dicorynomycolate
Tg	transgenic
3xTg	triple transgenic
TMG	TiterMax Gold

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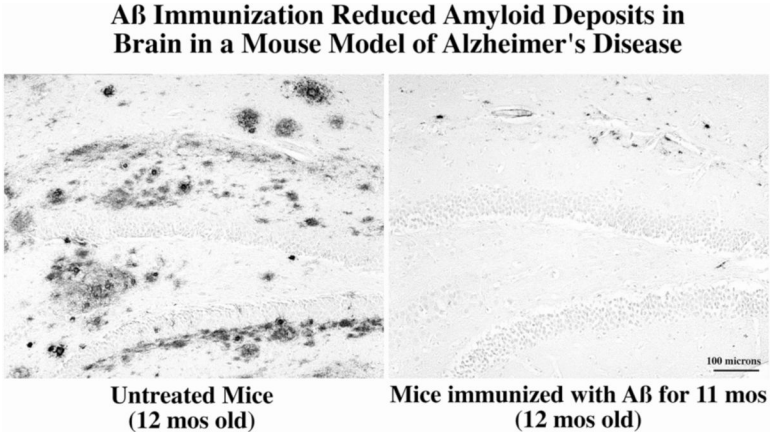

Fig (1). Immunization with full-length Aβ dramatically reduced cerebral Aβ plaque burden in J20 hAPP transgenic mice, a mouse model of Alzheimer's disease

In this study, 1 mo-old mice were primed by giving an intraperitoneal injection of 100 μg $Aβ_{1–40/42}$ synthetic peptide plus 50 μg Complete Freund's adjuvant. The mice were then boosted weekly by intranasal application of 100 μg $Aβ_{1–40/42}$ plus 5 μg adjuvant LT(R192G) for a total of 11 months and euthanized at 12 months, an age in which these mice typically accumulate many plaques in cortex and hippocampus (left panel). Immunohistochemical analysis with an Aβ-specific polyclonal antibody, R1282 (gift of Dennis Selkoe, CND, Boston, MA), revealed a significant reduction in plaque burden in cortex and hippocampus (shown in right panel). Scale bar: 100 μm. [Reprinted with permission from Lemere, C.A., Maier, M., Jiang, L., Peng, Y., Seabrook, T.J. Amyloid-beta immunotherapy for the prevention and treatment of Alzheimer's disease: Lessons from mice, monkeys and men. Rejuvenation Research 9:77–84, 2006.]

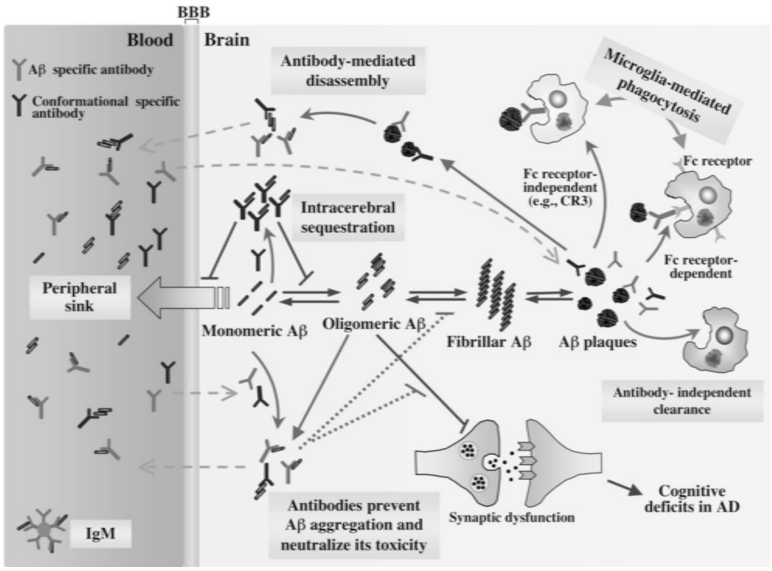

Fig (2). Potential mechanisms underlying Aβ immunotherapy in AD models

Antibody-mediated microglial FcR-dependent and FcR-independent clearance of plaques by phagocytosis; antibody-mediated direct disassembly of plaques; prevention of A**β** aggregation and neutralization of oligomer toxicity; peripheral sink effect by clearance of circulating A**β**; intracerebral sequestration of A**β** in a monomeric state; hydrolysis of A**β** by IgM; and antibody-independent, cell mediated plaque clearance have all proposed to play roles in the removal of A**β** from the brain by A**β** immunotherapy in AD models. These potential mechanisms may act concomitantly or sequentially and play independent roles depending on the stage of AD pathogenesis and type of antibody, as well as the specific animal model used.