·Special Topics·

Novel immunological approaches for the treatment of Alzheimer's disease

阿尔茨海默病新型免疫治疗方法

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Abstract

Alzheimer's disease (AD), the most prevalent form of dementia worldwide, can be deemed as the next global health epidemic. The biochemistry underlying deposition of amyloid beta (A β) and hyperphosphorylated tau aggregates in AD has been extensively studied. The oligomeric forms of Aβ that are derived from the normal soluble Aβ peptides are believed to be the most toxic. However, it is the fibrillar Aβ form that aggregates as amyloid plaques and cerebral amyloid angiopathy, which serve as pathological hallmarks of AD. Moreover, deposits of abnormally phosphorylated tau that form soluble toxic oligomers and then accumulate as neurofibrillary tangles are an essential part of AD pathology. Currently, many strategies are being tested that either inhibit, eradicate or prevent the development of plaques in AD. An exciting new approach on the horizon is the immunization approach. Dramatic results from AD animal models have shown promise for active and passive immune therapies targeting A β. However, there is very limited data in humans that suggests a clear benefit. Some hurdles faced with these studies arise from complications noted with therapy. Encephalitis has been reported in trials of active immunization and vasogenic edema or amyloid - related imaging abnormalities (ARIA) has been reported with passive immunization in a minority of patients. As yet, therapies targeting only tau are still limited to mouse models with few studies targeting both pathologies. As the majority of approaches tried so far are based on targeting a self - protein, though in an abnormal conformation, benefits of therapy need to be balanced against the possible risks of stimulating excessive toxic inflammation. For better efficacy, future strategies will need to focus on the toxic oligomers and targeting all aspects of AD pathology.

【摘要】 阿尔茨海默病为世界范围内的痴呆常见类型，是目前全球关注的健康热点问题。针对β-淀粉样蛋白（Aβ）沉积和过度磷酸化tau蛋白聚集的内在生物化学机制已有深入研究，来源于正常可溶性Aβ肽的Aβ寡聚体被认为最具毒性。然而，纤维状Aβ聚集形成淀粉样斑块和淀粉样脑血管病是阿尔茨海默病的主要病理改变；而异常磷酸化tau蛋白沉积并形成可溶性毒性寡聚体，进而聚集成为神经原纤维缠结，则是其另一重要病理特征。目前，已有许多措施用于抑制、清除或减缓阿尔茨海默病淀粉样斑块的病理进程，而免疫治疗是这一领域中的新的突破。针对Aβ沉积阿尔茨海默病动物模型进行的主动和被动免疫治疗，已取得重大研究成果。然而，临床试验仅有极少数据显示出明确的疗效，究其原因在于免疫治疗引起的并发症。主动免疫实验引起的脑炎，以及被动免疫治疗在少数人群中诱发的血管源性水肿或淀粉样蛋白相关显像异常已有相关报道。迄今为止，单纯针对tau蛋白聚集的治疗仍然仅局限于小鼠模型，鲜有

研究同时针对Aβ沉积和tau蛋白聚集两种病理特征。到目前为止,大部分免疫治疗均以自身蛋白为靶向,尽管其构造异常,在取得疗效的同时,需防止引起过度毒性炎症反应的可能。为取得更好的疗效,未来的免疫治疗应集中在毒性寡聚体,并以阿尔茨海默病的所有病理特征为靶向。

Introduction

Alzheimer's disease (AD) can epidemiologically be identified as the next global health epidemic, with more than 20 million people affected worldwide currently and about 135 million people expected to develop it by 2050[1]. The direct implication of this overwhelming disease burden translates into significant direct and indirect health care expenses, with costs for the USA alone estimated to be about $200 billion in 2013. Historically, AD has been characterized as a neurodegenerative disease chiefly defined by its pathological signature including β amyloid deposits in the form of extracellular amyloid β (Aβ) plaques and tau protein aggregates in the form of intracellular neurofibrillary tangles (NFTs)[2]. A central mechanism underlying the formation of both amyloid plaques and NFTs in AD is pathogenic cerebral protein aggregation. Though both amyloid plaques and aggregated tau have an essential role in AD pathology and clinical disease burden, recent work has shown that they are biologically relatively inert. However, their soluble oligomeric forms, which propagate via a "prion-like" mechanism, are the chief mediators of cytotoxicity in AD[3-5]. Both Aβ and tau oligomers have similar structural and biophysical properties, which include a high β-sheet content, resistance to proteolytic degradation and neuronal toxicity. Recent work has also revealed that Aβ and tau related pathology can, in certain scenarios, "seed" or transmit each other[5]. Current existing therapies have either no or minimal disease modifying benefit. To this end, a number of novel therapeutic strategies are currently under investigation.

Preclinical studies in transgenic (Tg) mouse models have shown great efficacy of immunotherapy in the prevention of both AD and prion diseases[6-8]. With a central role for Aβ in AD pathogenesis under the "amyloid cascade" model, several strategies directed towards eradication of Aβ and downstream targets through small molecules or immunotherapies are being explored[7, 9-13]. Though Aβ directed immunization via multiple approaches has shown promising results in AD Tg mouse models, the translation to safe and efficacious therapy for humans still remains a challenge. Insights from these studies have raised further issues that need to be addressed in current and future studies. Some questions that have come up from previous work and are critical for the development of successful immunotherapy include identification of the ideal target, the timing of therapy and the ideal blueprint for a vaccine. What is the best design for a vaccine that is both specific and safe? How could we avoid auto-immune toxicity? Would the ideal drug be monoclonal or polyclonal? Is it possible to develop a single vaccine targeting both Aβ and tau related pathology simultaneously? Here, we aim to review up-to-date preclinical and clinical data for Aβ and phosphorylated tau reduction immunotherapy.

Pathogenesis of Alzheimer's disease

AD is a complex neurodegenerative disease characterized by progressive deterioration of memory clinically and pathologically involves deposition of extracellular Aβ as senile neuritic plaques and congophilic angiopathy (CAA), and intracellular hyperphosphorylated tau as intracellular accumulation of abnormally phosphorylated tau in the form of NFTs. Genetic studies have shown that AD is a heterogeneous disorder that includes the more common late-onset sporadic form and the early onset, familial AD (FAD) that is seen in < 1% of AD patients. Studies of families with early onset inherited AD have identified missense mutations in amyloid precursor protein (*APP*) gene or in the presenilin (*PRES*) 1 and 2 genes that are implicated directly in the pathogenesis of FAD[13-14]. Several hypotheses have been postulated for the development of plaques and tangles, which lead to synaptic and neuronal loss and subsequent loss of memory and cognition in AD. The most favored theory currently in the field that has served as the platform for future therapeutic strategies is the amyloid cascade hypothesis[14-16]. The central idea proposed in the hypothesis is that Aβ aggregation, especially in its toxic oligomeric form, is the principal insult which produces neuronal toxicity and triggers downstream signaling events that in turn lead to hyperphosphorylation of tau and development of NFTs. A multitude of "chaperone" proteins have been described that stabilize pathological oligomers and mediate a conformational change of soluble Aβ (sAβ), including but not limited to apolipoprotein E (ApoE), especially its E4 isoform[17], alpha 1-antichymotrypsin (ACT)[18] or complement factor C1q[19-20]. Histological and biochemical evidence suggests that "pathological

chaperone" proteins co-localize with fibrillar Aβ deposits but not with pre-amyloid aggregates that are not linked to neuronal loss [21]. Functionally, "chaperone" proteins accelerate formation of Aβ fibrils from water-soluble oligomers [17-18]. From a biochemical perspective, a seminal event in the development of pathologic aggregates is the point at which a critical concentration of water-soluble Aβ oligomers and/or chaperone proteins is achieved. A critical concentration of oligomers would trigger conformational change, drive formation of Aβ aggregates and subsequent activation of the downstream signaling cascade. Mechanisms implicated for achieving this in sporadic AD could be a permutation of the impaired clearance of Aβ from the brain as a consequence of aging or inflow of serum Aβ into the CNS [14]. Several studies in FAD patients and in models of FAD have provided evidence in favor of the amyloid cascade hypothesis. The first line of evidence comes from functional analyses of *APP* gene or in the *PRES1* or *PRES2* genes that are associated with inherited forms of AD. Mutations in these genes show concomitant changes in APP processing biased towards over production of sAβ or generation of specific species of sAβ such as $Aβ_{1-42}$ that are more prone to aggregation [22]. The next line of evidence stems from the association of Down's syndrome with AD related pathology at a very young age. Here, an extra copy of the *APP* gene secondary to trisomy 21 provides excellent in vivo gain-of-function evidence supporting the amyloid hypothesis [23-24]. Further, animal models where Aβ and tau are co-expressed reveal that Aβ deposition predates formation of tau aggregates, supporting the concept that NFT formation is downstream from Aβ aggregation [25-28]. Lastly, enhancement of Aβ clearance in Tg mouse models with over-expression of mutant *APP*, but with no tau pathology, has been shown to improve cognitive function in mice [25, 29-30]. Subsequent work has also revealed that inhibition of Aβ in animal models with over-expression of mutant *APP* and tau not only prevents development of tau related aggregates but also improves cognitive deficits [31-33]. In contrast to the genetic forms of AD where the role of Aβ is well established, definitive evidence regarding Aβ's central function in late-onset sporadic AD is limited. Levels of biochemically extracted Aβ peptides from brains of people with sporadic AD correlate well with cognitive deficits [34]. Further, Aβ peptide dimer/oligomer extracts derived from sporadic AD brains have been shown to disrupt synaptic structure, function and plasticity that are key cellular correlates of memory [35]. Interestingly, exogenous injections of Aβ extracts from sporadic AD patients can induce amyloid aggregates in transgenic mice [5, 36]. One of the significant concerns with the amyloid cascade hypothesis comes from the post mortem analyses from the active vaccination trials in humans [37]. Individuals from the active immunization or the "test" arm revealed a significant decrease in plaque burden and strikingly reduced Aβ load relative to non-immunized controls. Regardless of these encouraging results, no improvement in long-term survival outcome, time to severe dementia and cognitive function was seen among the immunized groups. Cognitive function was assessed here by outcome measures such as Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Mini-Mental State Examination (MMSE) or Disability Assessment of Dementia (DAD). Two recent large phase Ⅲ trials of passive immunization for AD have also ended with no evidence of clinical benefit, although the following analysis suggested a positive trend in a subpopulation of patients in the Solanezumab trial [38-39]. One plausible explanation here is that immunization was conducted in the late stage of the disease process, possibly out of the window to translate into a meaningful clinical benefit [7, 10, 14]. Another theory that could be proposed would suggest that the amyloid hypothesis represents only part of the complete story. The existence of a currently unknown upstream factor (s) or insult that triggers both Aβ and tau pathways downstream of itself is also possible [40-42]. Regardless, immunotherapy still remains an attractive and effective strategy to target both of these mechanisms in clinically symptomatic AD. Here, we will review both active and passive immunotherapeutic approaches along with preclinical and clinical data that has been used to target both the Aβ and phosphorylated tau.

Active immune therapy targeting Aβ in humans

Preliminary work that suggested a strong role for immunotherapy for AD revealed that antibodies target anti-Aβ were capable of preventing Aβ peptide fibrillization, disrupting pre-formed fibrils and thus, thwarting neurotoxicity in *in vitro* cell culture based assays [43-44]. This initial work motivated further *in vivo* studies to test the role of Aβ first as an active immunogen and then to assess if it could prevent pathology in mouse models of AD. The first *in vivo* immunization trial, reported in a seminal paper by Schenk et al. demonstrated that full length, aggregated $Aβ_{1-42}$ in conjunction with Freund's adjuvant could reduce plaque load *in vivo* [45]. No obvious toxicity was reported in this trial. These results were confirmed and extended in later studies, where active immunization with $Aβ_{1-42}$ or Aβ homologous peptides along with Freund's or alum adjuvants not only prevented Aβ pathology, but also protected against development of cognitive deficits [25, 29, 46-50]. Biochemical assays have identified the first 15 amino acids of Aβ peptide as the principal epitope. Further, immunohistochemical assays have also revealed that antibodies generated towards Aβ can label amyloid

plaques on human AD brain sections. Interestingly, peripheral injections of anti-Aβ monoclonal antibodies into the systemic circulation could also reduce Aβ plaque burden and behavior, suggesting that the therapeutic effect of the vaccine was likely mediated by generating a humoral response [7, 25, 29, 51-52]. These pilot preclinical trials revealed no evidence of toxicity in the immunized mice. However, there was some debate about the type of immune response involved in mediating the beneficial effects by these peptides. One view speculated that the use of non-fibrillogenic, non-toxic Aβ homologous peptides together with strategies that activate primarily the humoral, Th-2 response rather than the Th-1 cell mediated response primarily might reduce potential toxicity [7, 53-55]. The design for the Aβ homologous peptide immunogens, albeit, with a few appropriate amino acid substitutions, was based on the fact that the major B cell epitopes were within the first 15 amino acids of Aβ form the principal B cell epitopes, while the mid and carboxyl terminus were the chief site for the T cell epitopes [49-50, 54].

The striking results from these preclinical studies served as the launching pad for Elan/Wyeth's group to launch a randomized, multiple-dose, dose-escalation, double-blind Phase Ⅰ clinical trial. This trial, started in in April 2000 used the AN1792 vaccine, which was comprised of pre-aggregated $A\beta_{1-42}$ and QS21 as an adjuvant. The vaccine was designed to generate a strong cell mediated immune response. A strong inducer of Th-1 lymphocytes, QS21 produced an effect similar to that obtained in mice with the use of Freund's adjuvant (which is not approved for use in humans) [56]. The pilot study performed in the UK involved 80 patients with mild to moderate AD [57]. The primary aim here was to determine the efficacy and safety of full length $A\beta_{1-42}$ peptide with QS21. Multiple doses were tested and it was demonstrated that 53% of patients could mount an anti-Aβ humoral response. In the later segment of the phase Ⅰ trial, polysorbate 80, which acted as an emulsifier, was added to increase the solubility of $A\beta_{1-42}$. The increased emulsifier concentration caused a greater shift from a Th-2 humoral response to a proinflammatory Th-1 response [58]. A follow-up phase Ⅱa trial was conducted in October 2001 that involved 372 patients. Three hundred out of 372 enrolled patients were part of the arm that received a higher formulation of QS21 (aggregated $A\beta_{1-42}$ with QS21 in the polysorbate 80 formulation (AN1792 to placebo ratio of 4∶1). As 6% of immunized patients developed symptoms of aseptic meningoencephalitis (18 out of 298 subjects with no placebo patients developing this complication), the trial was concluded early in January 11, 2002 [56, 59-60]. The spectrum of onset of symptoms, which included confusion, lethargy and headache ranged from 5 to 168 days after the last immunization the patient had received. Neuroimaging revealed white matter lesions with or without evidence of brain edema, termed amyloid-related imaging abnormalities (ARIA). Consistent with data from animal models, post-mortem analyses in a sub-group of trial patients revealed dramatic clearance of plaques in the brain parenchyma, thus validating the efficacy of this approach for amyloid clearance in humans [60-65]. Histopatbology revealed that there were broad stretches of cerebral cortex devoid of plaques, interspersed with areas that had residual plaques. These persistent plaques had a "moth-eaten" appearance or seemed to have a "naked" dense core. Additionally, these plaques were seen along with microglia, that was immunoreactive for Aβ, suggesting that amyloid clearance here was in association with phagocytosis. Other notable features included the presence of unchanged tau reactive NFTs and the persistence of amyloid in cerebral vessels, as well as neuropil threads in apparent regions of plaque clearing, suggesting that this preliminary approach had not targeted amyloid or tau related pathology [63-65]. In some plaques, a T-cell reaction surrounding some cerebral vessels was observed, reminiscent of an overstimulated deleterious Th-1 immune response. These features suggested that the immune response seemed to be working as a two-edged sword and raised the concern that the beneficial effects of the vaccine were being counterbalanced by a deleterious T-cell response [60, 66]. Further support in favor of a toxic response came from *in vitro* studies, where peripheral blood mononuclear cells from patients in the trial were analyzed after stimulation with the Aβ peptide. Quantification of cytokines by enzyme-linked immunosorbent spot assays revealed that cells of responder patients could generate interleukin-2 (IL-2) and interferon-γ (IFN-γ) positive responses suggestive of a Class Ⅱ (CD_4^+) Th-1 type response [58]. Also, follow-up results from the Zurich cohort, a subgroup of the Elan/Wyeth trial [67-68], indicated that immunization as a strategy might be beneficial for some AD patients. In accordance with the date from the Zurich cohort, the results from a multi-center cohort demonstrated that people with high antibody titers or immune responders performed better in outcome measures that scored memory functions relative to low- and non-responders or to the placebo group of patients [58]. Though the pathology results with dramatic clearance of plaque burden have been striking, the benefits observed clinically in cognition have been very minimal [69]. No change in function was noted between the antibody responders and the placebo group when assessing via multiple neuropsychological rating scales. One possibility is that the timing of intervention was incorrect. Thus, there were no effects on tau related pathology with subsequent mild benefits in cognitive deficits. Another explanation is that this approach does not target the complete pathology of AD and some of the key players are still unidentified. Thus,

the amyloid hypothesis might be an over-simplification of the pathogenesis of sporadic AD.

A number of next generation Aβ vaccination trials in either Phase Ⅰ or Ⅱ (www.clinicaltrials.gov) are currently ongoing. Novartis Pharmaceuticals recently launched a Phase Ⅰ results with an active vaccine called CAD106 [10, 70]. The vaccine CAD106 is designed to target a B-cell epitope, the Aβ fragment ($A\beta_{1-6}$) in this case along with an adjuvant carrier that is derived from multiple copies of the coat protein of bacteriophage Qβ. Mild to moderate probable AD subjects with MMSE scores ranging from 16 – 26 were enrolled in the trial. They were randomized to two cohorts, the first which received 3 injections of 50 g CAD106 (24 test and 7 placebo subjects, cohort 1) or a second cohort which received 150 g CAD106 (22 test and 5 placebo subjects, cohort 2). With a treatment time span of 1 year and a 2-year follow-up period, the study revealed that 75% and 100% patients developed anti-Aβ immunoglobulin M (IgM) titers in cohort 1 and 2 respectively, while 67% and 82% developed anti-Aβ IgG titers respectively in cohort 1 and 2. Nine patients reported serious adverse reactions, but none were thought to be secondary to the immunogen. In support of this idea, no cases of meningitis, meningoencephalitis or vasogenic edema were identified clinically or by imaging during the initial trial or 2-year follow-up period. No significant change in CSF biomarkers was noted in the CAD106 subjects. However, some differences were seen in cohort 2 in treated subjects compared with controls for free plasma $A\beta_{1-40}$. A limitation of this trial was that it was not sufficiently powered to demonstrate a significant clinical difference between the treatment and control arms. The results from the Phase Ⅱ CAD106 trial, which was completed in February 2013, are yet to be reported.

Another ongoing active Phase Ⅱ immunization trial being conducted by Janssen and Pfizer is ACC-001, that uses the $A\beta_{1-6}$ fragment coupled to a carrier protein, and surface-active saponin adjuvant QS21 [71]. Further, Affiris AG together with GlaxoSmithKline (GSK) has utilized AFFITOME® technology to generate synthetic antigenic peptides called mimotopes to target the unmodified Aβ N-terminus in their AD02 trials [72]. Affiris AG has also started another Phase Ⅰ trial with the same technology to target a pyroglutamic-3 modified Aβ N-terminus, a post-translational modified version of Aβ. This post-translational modification for Aβ that renders it more prone to aggregation is believed to happen after its deposition in plaques or vascular amyloid [73-74]. Interestingly, pyroglutamic-3 modified Aβ, which is normally present in plaques and vascular amyloid deposits but is not detectable in the CSF or plasma, is only found in these biological fluids during therapeutic interventions where deposited Aβ has been mobilized [75]. AC Immune has initiated Phase Ⅰ/Ⅱa trials with their product, ACI-24, which works by generating a humoral immune response to Aβ in a primarily β-sheet conformation. The design is based on previous work by this group in an AD Tg model, where a tetra-palmitoylated amyloid 1 – 15 peptide that exists chiefly in a β-sheet conformation was used as an immunogen [76-77]. The preliminary results from these ongoing active immunization trials have yet to be reported. These second generation active immunization strategies specifically target pathological conformers of Aβ that hopefully makes them more specific with less cross reactivity and decreased chances of autoimmune toxicity. However, as the immunogens are still derived from the Aβ sequence, some element of cross reactivity to normal Aβ peptides is to be expected, with the plausible risk of inflammatory toxicity. Moreover, none of the approaches so far have even begun to directly address tau related pathology.

Past passive immunization experience for AD

The process of injecting pre-made antibodies to provide host immunity is known as passive immunization. This is in contrast to the process of stimulating the immune system of host by agents like pre-formed antigen, a process that is called as active immunization. One of the easiest ways to provide anti-Aβ antibodies without increasing chances of uncontrolled Th-1 mediated antibody is passive transfer of exogenous monoclonal anti-Aβ antibodies. Importantly, studies have shown that AD Tg model mice treated by this method, developed significantly reduced Aβ level and showed cognitive benefit [51-52]. Passive immunization has been associated with problems like difficulty in selection of appropriate antigen targets, expensive costs, needing to repeated injections in chronic diseases, blood-brain barrier (BBB) penetration, hemorrhagic risk and the triggering of immune response to the antibodies that are injected.

Interestingly, studies have shown a number of possible congruent mechanisms of action, which can benefit AD pathology [29, 78-80]. Anti-Aβ antibodies can lead to direct Aβ disassembly by targeting Aβ deposits in the brain. Microglial activation by antibodies in the brain can also target plaques and clear them. In addition, blockage of Aβ toxicity or sequestration of Aβ monomers by antibodies prevents their aggregation in the CNS. "Peripheral sink effect" has been proposed as an important mechanism via which anti-Aβ antibodies can block Aβ deposition, namely by binding sAβ circulating in the blood stream and reducing free sAβ levels, leading to sAβ being drawn out for the brain. Additional studies are needed in this area for understanding, as to which of these mechanisms is (are) the most important in the transgenic AD mouse model, or in the more limited human trials. At present, several passive immunization trials are under

study. Recently reported trials of both Bapineuzumab and Solunezumab are the two most advanced phase Ⅲ trials in this field, unfortunately both failed to show overall clinical improvement or any clear disease modifying results [38-39]. Bapineuzumab is a humanized version of the mouse monoclonal antibody 3D6, which has an epitope of residues 1-5 of Aβ. 3D6 is known to cross the BBB, and in Tg mouse studies, it was shown to bind plaques in the brain and elicit Fc receptor mediated, microglial phagocytosis of Aβ plaques [51, 81]. The Phase Ⅱ trials of Bapineuzumab (study 201 with 234 patients and study 202 with 28 patients) involved 6 infusions that were done every 13 weeks over 8 months at 4 different dosages (0.15 mg/kg, 0.50 mg/kg, 1 mg/kg and 2 mg/kg) [80, 82]. Even though these trials have not shown statistically significant results overall, there was a trend towards efficacy on DAD and ADAS-Cog and in non-*ApoE4* carrier patients significant (but small) benefits was documented on the ADAS-Cog, Neuropsychological Test Battery (NTB), MMSE and Clinical Dementia Rating (CDR) scales. Some of the noteworthy complications in these trials were related to amyloid related imaging abnormalities [83]. The abnormalities included FLAIR MRI signal abnormalities due to parenchymal vasogenic edema and sulcal effusions (ARIA-E) and MRI abnormalities due to microhemorrhages and hemosiderosis as seen on the T2*-weighted gradient echo (ARIA-H). Though 36 patients (17% of total patients) developed ARIA-E during treatment, it was symptomatic only in 8 of these 36 patients (22% of patients with ARIA-E). Adverse events included headache, confusion, neuropsychiatric and gastrointestinal symptoms. ARIA-H occurred in 17 patients with ARIA-E and in 7 of 177 patients without ARIA-E [83]. An association was seen of these side effects with both the increased dose and presence of *ApoE4* allele. Out of 8 symptomatic patients 7 were *ApoE4* carriers and 6 were treated with the two highest doses of Bapineuzumab. A possible mechanism for these adverse events is increase in BBB permeability and microhemorrhages, due to removal of cerebral vessel Aβ [80, 83]. A higher CAA burden has previously been characterized in *ApoE4* carriers [21]. On the basis of these Phase Ⅱ results, the Phase Ⅲ trials were created, with aim of giving a lower dose (0.50 mg/kg limit) to *ApoE4* carriers and to restrict the maximum dose in *ApoE4* non-carriers to 1 mg/kg. A total of 1121 patients were involved in this phase Ⅲ trial, and infusions were given every 13 weeks for total of 6 infusions in one and a half years. No clinical improvement was noted in the either the *ApoE4* carrier or non-carrier groups. In 15% of *ApoE4* group ARIA occurred, while in *ApoE4* non-carrier groups, occurrences were 9% and 4%, of the 1 mg/kg and 0.50 mg/kg categories, respectively. In light of these observations, the clinical development of Bapineuzumab has been halted. However, AAB-003 a humanized version of Bapineuzumab (3D6), which has mutations in the Fc domain to reduce effector function and reduce ARIA, is in two Phase Ⅰ clinical trials (www.clinicaltrials.gov).

A humanized version of mAb266, known as Solanezumab, which has an epitope at residues 16-24 of Aβ is also under study. In Tg mouse models, 266 was shown to bind specifically with monomeric sAβ, thereby lowering amyloid pathology, while increasing total sAβ levels in the plasma [51, 81]. A reduction of free circulating sAβ and Aβ sequestration in the CNS are proposed as the major mechanisms of action. A total of roughly 800 AD patients with mild to moderate disease, in both control and treated groups have been followed in two Phase Ⅲ trials. The treatment group was given 400 mg of Solanezumab (about 5.70 mg/kg) every 4 weeks. Cognition was studied at 80 weeks and no differences were noted compared to controls. Of note when patients with mild AD were studies separately, a small but statistically significant benefit was noted in the cognitive scores [39, 80]. Importantly, even though a high dose of Solanezumab was used (compared to Bapineuzumab), ARIAs were not found as a complication and an increase in plasma Aβ was found [84]. Inspired by these results, Solanezumab will be used in two preventive or very early treatment trials. The Dominantly Inherited Alzheimer Network (DIAN) trial will target adult children in families with known mutations and a diagnosis of familial AD; as well as utilizing Gantenerumab, a mAb that selectively binds fibrillar Aβ and is in an ongoing Phase Ⅲ prevention trial, involving about 770 patients that lack clinical AD symptoms but on PET scan have appreciable amyloid disease [30, 85-86]. Another significant prevention trial, aiming to test Solanezumab is the A4 Trail (Anti-Amyloid Treatment for Asymptomatic Alzheimer's Disease Trail), which includes about 1000 patients that lack symptoms of AD but are positive for amyloid on PET scan.

The Alzheimer's Prevention Initiative (API) is a further prevention trial, to be performed in about 300 people, from a Colombian kindred with PS1 mutation (E280A). A very severe AD phenotype is seen in this mutation, characterized by Aβ deposition from about 25 years. The study aims to test patients 30 years and older, using Genetech's Crenezumab mAb. This antibody interacts with multiple species of Aβ [87]. The effector function of Crenezumab is reduced by using an IgG4 backbone.

Another avenue of active research in passive immunization trials is role of intravenous immunoglobulin (IVIg) in AD. The basis for its use is that IVIg obtained from a large cohort of donors contains a small but significant amount of naturally acting anti-Aβ antibodies. In a number of autoimmune neurological disorders, IVIg is used as an immunosuppressant and even with multiple successive

doses, showing no major side effects. Remarkably, a decreased risk of developing dementia is seen in patients who receive regular IVIg infusions [88]. In a phase Ⅰ open label study, IVIg was infused in 8 mild AD patients for 6 months, followed by an interruption and then resumed for another 9 months [89]. Following each infusion the plasma Aβ levels increased transiently, with CSF Aβ being decreased after 6 months. Moreover the MMSE increased after 6 months by an average of 2.50, and returned to baseline level after washout. A total of 23 AD biomarkers were studied in these patients by collecting CSF from spinal taps before initiation of therapy, 6 months afterward and after 3-month washout. Out of 8 study subjects, significant improvement in biomarkers was seen in 6 subjects after 6-month therapy, which gradually returned to baseline levels after IVIg washout [90]. Nonetheless, in two recent trials, no significant slowing of AD progression could be documented [29, 91]. In the Octapharma, IVIg trial with about 60 mild to moderate AD patients, infusions were done over 6 months at 3 different doses. Study methodologies such as MRI volume measurement, ^{18}F-FDG PET or cognitive measures did not show any significant improvement. Of the 43 IVIg treated patients, 6 patients had new asymptomatic microhemorrhages. Studies by Baxter Healthcare Corporation included an 18-month phase Ⅲ trial of Gammagrad 10% IVIg in about 400 AD patients with mild to moderate disease. The results from this trial have not been fully released but so far no significant improvement in cognitive measures has been detected [29].

The passive immunization approaches which have been described above, lack an essential element and that is their inability to specifically target Aβ oligomers, which are the most deleterious components of Aβ. The prior approaches target either both the normal and pathological conformers of Aβ or only the sAβ (i.e. Solanezumab) [92]. The lack of specificity is a major setback in these therapeutic approaches as targeting normal sAβ can interfere with its crucial physiological functions like neuroprotection, modulation of long term potentitation and innate immunity. This may also increase the risk of autoimmune complications [7-8, 93-95]. Another crucial aspect is that these therapies may have to be started very early in AD pathology build up, for them to be therapeutically beneficial. Prior studies have demonstrated that the appearance of earliest clinical signs of AD corresponds to peak Aβ deposition, along with substantial NFTs formation and neuronal loss, which have still not yet reached peak levels [2, 96]. It is postulated that in order to have a significant effect, amyloid directed therapy targeting sAβ alone, or both the sAβ and deposited Aβ, should be started early, preferably even before cognitive impairment starts. It can be safely said that as of now, these therapeutic approaches have limited utility in symptomatic AD.

Tau related pathology as an immune target

NFTs, a pathognomonic feature of AD, are intracellular inclusion bodies that consist of deposits of paired helical filaments (PHFs), which are primarily composed of hyperphosphorylated tau. Recently, there is considerable interest on targeting phosphorylated tau for immunomodulation in AD [8, 96-100]. Though most evidence suggests that tau pathology develops the downstream of Aβ deposition in signaling cascade [2], there is some data to suggest that this might not be the case. Some recent work has shown that in the locus ceruleus, tau pathology precedes formation of amyloid plaques and then spreads to other brainstem nuclei and the entorhinal cortex [101-102]. However, the role of this early tau pathology in the pathogenesis of AD is not clearly understood. Further studies are needed that address whether this early tau pathology plays a fundamental role in development of AD related pathology or is part of the normal aging process [96]. Regardlessly, work by multiple groups has shown that the degree of tau related pathology is better correlated with the degree of dementia when compared to the amyloid plaque burden, hence making tau as a desirable target in symptomatic AD patients [103-105]. Further support for this idea is provided by the results from the human immunization trials (as reviewed above), where the reduction in amyolid plaque load did not produce a cognitive benefits in symptomatic AD subjects.

In animal models, treatment with a phospho-tau peptide (containing the phosphorylated PHF-1 epitopes Ser 396, Ser 404) for two to five months that was given prior to the onset of pathology was able to prevent development of tau aggregates in the Tg P301L mice related pathology [106]. Phosphorylation at these specific epitopes has been shown to increase the fibrillogenic character of tau and enhances PHFs formation [107-108]. Analyses of the mice by histochemical and biochemical techniques revealed a decrease in aggregated tau plaques in the brain and improved performance on motor tasks [106], thus providing strong support in favor of the idea that it is possible to also reduce tau related pathology with active immunization. These results were also confirmed in a similar study done in an htau/PS1 tau pathology model [109]. As the transgenic mice used in these studies had severe locomotor deficits, a major limitation of this work was that cognition could not be assessed as a therapeutic endpoint.

How an antibody response to a protein that has intracellular inclusions could have beneficial effects can initially be difficult to understand. However, support for this idea is lent from immunization studies done in transgenic mouse model of Parkinson's disease where a reduction in intracellular α-synuclein aggregates was

demonstrated [110]. Studies done recently by multiple groups have suggested that anti-tau antibodies can cross the BBB and are translocated inside neurons via low-affinity Fc receptors where they can bind to pathological tau within the endosomal/lysosomal system [111]. Additionally, injection of fibrillar tau brain extract into the brains of transgenic wild - type tau expressing mice can push the induction of tau into filaments, along with the spread of pathology from the injection site into adjacent brain regions [112]. Such an "infectivity" of abnormal protein conformation from outside the cell has also been established for polyglutamine aggregates [113] and is well described in prion disease [6, 114]. Hence, one can reason that if certain pathological forms of tau can spread and lead to PHF pathology in AD via a "prion like" mechanism, anti - phosphorylated tau antibodies might not necessarily need to enter cells in order to be effective.

With active immunization using tau epitopes, there exists a risk of inducing encephalitis or neuronal apoptosis. This line of thought is backed by an early study, where immunization of female C57BL/6 mice with full length recombinant tau produced neurological deficits, NFTs - like changes, gliosis and an inflammatory infiltrate [115]. Even with phosphorylated tau as an epitope, the possibility of deleterious effects still persists. Data from a study, done recently, revealed that E257T/P301S - tau transgenic mice and wild type mice repetitively immunized with a mixture of three phospho - tau peptides produced neuroinflammation in conjunction with significant neurological disability in the tau Tg mice [116]. Hence, one might speculate that a passive immunization approach with anti-phospho-tau directed mAbs might be safer. Two trials have been conducted where passive immunization was chosen as the targeting strategy, and revealed that tau related pathology and motor deficits were reduced if the timing of the antibody administration was prior to the onset of tau pathology [117 - 118]. Another study, with serial intracerebroventricular administration of anti-tau antibodies (starting at 6 months of age over a 3-month period), demonstrated a decrease in pathology and contextual fear conditioning deficits in P301S tau Tg mice [119]. Even though this study demonstrated that administration of anti-tau antibodies at a point when pathology is already present could improve, the intraventricular route used in this case was a major disadvantage. Further, the only study to date to show improvement in pathology after its onset has been unable to show any benefits on animal survival as compared to controls [120]. In this report, the authors compared DA31 (a pan - tau antibody), PHF1 (detects pSer396/404) and MCI (detects a pathological tau conformation) in P301L Tg tau mice, (which have an onset of pathology at about 3 months of age). Mice injected with MCI revealed a reduction of tau related pathology immunohistochemically and biochemically from 7 to 10 months. However, there was no change in survival between mice injected with either PHF1 or MCI from 6 to 14 months of age versus control trangenic mice [120]. Previously, it has been shown that PHF1 is able to decrease in tau related pathology when treatment is started prior to the onset of disease [117]. Together, these results suggest that though immunotherapy directed towards tau holds promise, there is some risk of toxicity. For best results, more work needs to be done to clearly define the optimal timing of tau directed immunotherapy.

Targeting abnormal protein conformation rather than Aβ or tau related pathology individually

The most pathological conformers of Aβ and aggregated tau have been proposed to be oligomeric. Both of these entities have been demonstrated to spread by extracellular soluble oligomers in a prion like mechanisms. Notably, recent studies have shown that in the presence of Aβ amyloid pathology, therapeutic interventions that impede Aβ oligomer toxicity can reverse cognitive deficits within a remarkably short treatment duration [121 - 122]. It can be safely concluded that these molecular targets have great potential even when significant pathology is present. A number of structural and biophysical properties are shared between Aβ and tau oligomers, like a high β-sheet content, neuronal toxicity and imperviousness to proteolytic degradation. A limited number of studies targeting Aβ oligomers reflect the potentially powerful role of this approach and warrant further attention [123 - 127]. Another benefit of targeting only the oligomeric form of Aβ or tau is that the normal physiological function of these proteins remains intact. A more recent proposed approach uses conformationally specific antibodies or active immunization aiming to target the abnormal β - sheet conformation of amyloid proteins [123 - 124, 128]. This approach has the benefit of simultaneously targeting both the Aβ and tau related pathologies. In order to accomplish this goal, we developed a therapeutic immunomodulation, specific for pathological β - sheet conformation, shared by Aβ and tau disease associated species. In our studies, we employed a polymerized British amyloidosis (pBri) related peptide which is in a mostly β-sheet oligomeric form and is prepared by the use of glutaraldehyde as a cross linker. One of the rare forms of familial human amyloidosis is British amyloidosis (ABri), and this is associated with a missense mutation in a stop codon, which leads to transcription of an intronic sequence, thereby causing production of a highly amyloidogenic protein, with a carboxy terminus that lacks sequence homology to Aβ,

tau or any other native human proteins [129 - 131]. We proposed that via conformational mimicry, the pBri peptide can initiate a conformation selective immune response that is specific to pathological aggregated/oligomeric conformers of phosphorylated tau and Aβ. An immunomodulatory approach of such design will have a decreased risk of causing autoimmune complications, as it is specific to pathological conformers and the immunogen does not have sequence homology to any mammalian peptide. Our studies in past have shown that this immunomodulation targeting of pathological conformation of Aβ is highly effective in reducing amyloid plaques and produces cognitive rescue [131]. Our recent studies have demonstrated that our approach of targeting abnormal protein conformation is effective in both the TgSwDI mice, which have a high burden of vascular pathology, and 3xTg mice which have both Aβ and tau related pathology, decreasing the disease pathology, oligomer levels and leading to improvement in cognitive deficits [132].

Summary

It is an exciting time, with many different active and passive immunization therapeutic approaches currently either under development or in trials. Strategies that target Aβ peptides could be effective if used very early in disease onset before the development of any clinical dysfunction and are currently in ongoing prevention trials. Though immunotherapy targeted towards tau pathology has shown some promise, it bears the risk of toxicity. With the current knowledge, it remains undefined if it can be used effectively in symptomatic AD where there is preexisting pathology. Many studies have shown that even at the mild cognitive impairment stage of AD, extensive amyloid and tau pathology is already present [2]. In addition, it has been proposed that in sporadic late-onset AD, tau pathology is not simply downstream of Aβ related pathology but that these pathologies could be generated by dual independent pathways [40, 96]. If this holds true, it would be essential to devise an approach that could simultaneously and effectively target both pathologies.

We postulate that such a strategy that can harness the immune system to clear both Aβ and tau toxic oligomers concurrently might be most efficacious in symptomatic AD. This might be possible by seeking similarities in the tau and Aβ toxic conformers to actively induce a humoral immune response via conformational mimicry. An active immunization approach can also be used for the development of monoclonal antibodies, to be used alone or together with other agents in different stages of AD. This "β-sheet buster" approach, where pathological protein conformation is being targeted, offers potential and promise for multiple conformational neurodegenerative diseases.

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Disclosure

No authors report any conflict of interest.

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