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Alzheimer's disease: From immunotherapy to immunoprevention

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SUMMARY

Recent Aβ-immunotherapy trials have yielded the first clear evidence that removing aggregated Aβ from the brains of symptomatic patients can slow the progression of Alzheimer's disease. The clinical benefit achieved in these trials has been modest, however, highlighting the need for both a deeper understanding of disease mechanisms and the importance of intervening early in the pathogenic cascade. An immunoprevention strategy for Alzheimer's disease is required that will integrate the findings from clinical trials with mechanistic insights from preclinical disease models to select promising antibodies, optimize the timing of intervention, identify early biomarkers, and mitigate potential side effects.

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Recent Aβ-immunotherapy trials demonstrated that removing aggregated Aβ from the brains of symptomatic patients can slow progression of Alzheimer's disease. This Perspective analyzes different immunoprevention strategies by integrating findings from clinical trials with mechanistic insights from preclinical disease models.

INTRODUCTION

The recent reports that monoclonal antibodies (lecanemab [Leqembi™] and donanemab) stimulate the removal of abnormal β-amyloid (Aβ) from the brain and slow the progression of early Alzheimer's disease (AD)[1,2] have given the research community the first clear clinicopathological indication that a disease-modifying treatment for AD is feasible. Together with evidence that another monoclonal antibody (aducanumab [Aduhelm™])[3]

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DECLARATION OF INTERESTS

The authors declare no competing interests

also may be beneficial, the results provide clinical support for the importance of aberrant Aβ in the pathogenesis of AD. The findings also strengthen the 'amyloid (Aβ) cascade' hypothesis, which holds that the seminal event in the ontogeny of AD is the misfolding and aggregation of Aβ, followed by a host of sequelae that comprise the full clinical and pathological phenotype of the disease[4,5]

While there is now renewed hope for disease-modifying therapies, it is important to caution that the clinical benefit of the antibodies in the trials was limited and the disease still progressed in treated subjects, albeit at a slower pace. Removal of aberrant Aβ in symptomatic AD is unlikely to be a cure for the disease, which begins to germinate in the brain 20–30 years before the onset of obvious cognitive impairment[6–8]. By the time the signs and symptoms of AD first appear clinically, damage to the brain is considerable and at least partially beyond repair; hence a full return to baseline functionality is unlikely, in line with the limited efficacy of the antibody treatments. Hence, a prevention strategy is essential; chronic degenerative diseases such as AD are most effectively treated as early in their development as possible, preferably well before they become symptomatic[9,10]. Lessons learned from immunization treatment trials, combined with mechanistic insights from experimental and biomarker investigations, have now brought us a step closer to this goal.

THE PATHOBIOLOGY OF ALZHEIMER'S DISEASE

AD is defined histopathologically by the profusion of two proteinaceous lesions in the brain -Aβ plaques and neurofibrillary (tau) tangles. Burgeoning evidence indicates that the Aβ and tau proteins misfold, self-assemble, and propagate by an endogenous mechanism closely resembling the seeded aggregation and spread of the prion protein (PrP) in Creutzfeldt-Jakob disease and other prionopathies[11–14]. Aβ plaques disrupt circuits and neighboring brain cells[15–17], but Aβ also forms small, soluble, oligomeric assemblies that impair the function of neurons and glia[18,19]. In addition, Aβ often accumulates in the walls of small to medium sized cerebral blood vessels manifesting as cerebral β-amyloid angiopathy (CAA)[20] (Figure 1). Although the amount of CAA varies widely among AD patients, nearly half of end-stage AD patients exhibit moderate-to-severe CAA[21,22].

Aβ plaques and tau tangles both are abundant in advanced AD, but genetic, pathologic and biomarker findings show that Aβ-proteopathy is the crucial early impetus for the disease; widespread tauopathy and other sequelae are essential drivers of behavioral impairment that are downstream of Aβ[7,27,28]. AD thus is thought to progress in two stages; the first stage is characterized by the emergence and seeded propagation of aberrant Aβ and Aβ-associated pathologies, and the second stage includes a complex assortment of secondary changes that include tangles, inflammation, vascular abnormalities and neurodegeneration[29]. In the second stage, the disease appears to become at least partially independent of Aβ deposition[24–26] (Figure 1). This bi-phasic trajectory of AD pathogenesis has important implications for both treatment and prevention strategies. As a defining pathologic feature of AD, tauopathy also has been the object of immunization strategies[30,31], but the pathogenic primacy of Aβ makes it a particularly attractive target for early prevention.

Aβ-IMMUNOTHERAPY FOR AD

Immunization therapy for AD was launched in earnest in 1999, when active immunization of Aβ-precursor protein- (APP) transgenic mice with synthetic polymers of Aβ was shown to dramatically reduce cerebral plaque burden[32]. This report prompted a flurry of research on the potential of immune mechanisms to treat or prevent AD[33]. The initial clinical trial of active Aβ immunotherapy in humans (AN1792) was halted when a subset of the recipients developed aseptic meningoencephalitis[34]. A follow-up study of a small number of patients showed hints of slowed cognitive decline[35] along with fairly compelling evidence in postmortem tissue for the clearance of Aβ plaques[36,37]. However, the meningoencephalitic side-effects, coupled with the inability to fully reverse the errant immune response, was a setback for active immunization. As a result, much research was steered toward passive immunotherapy with humanized monoclonal antibodies as a potentially safer alternative.

The antibodies that have advanced the farthest in clinical development include bapineuzumab, solanezumab, crenezumab, gantenerumab, aducanumab, lecanemab, and donanemab (Figure 2). These antibodies recognize partly different antigenic sites on Aβ, and they differ in their apparent clinical efficacy and in their ability to lower plaque load. All of them have been tested in phase 3 studies of patient cohorts with mild cognitive impairment or mild AD dementia[2,38]. Except for solanezumab and crenezumab, the antibodies reduced cerebral Aβ content as measured by positron-emission tomography (Aβ-PET)[2,28]. Although postmortem confirmation is largely lacking, based on previous comparisons of the Aβ-PET signal and postmortem Aβ load, a corresponding reduction of Aβ deposits is likely[37,39]. Thus far, the antibodies that yielded the greatest removal of Aβ deposition (>60% after 18 months of treatment) - lecanemab, donanemab and aducanumab - have shown evidence of slowed clinical decline[1–3], though it is important to stress that direct comparison of clinical efficacy is hindered by differences in the trials such as dosage, treatment schedule, and the patient populations evaluated.

Notably, reduction of Aβ burden was accompanied by decreased phosphorylated Tau (pTau) species and glial fibrillary acidic protein (GFAP) in the CSF or blood[1,2,45–48]. Thus, immunotherapy not only decreased β-amyloid load, but (based on fluid biomarkers) may also have decreased cerebral Aβ-associated tauopathy and astrocytic activation. In contrast, neurofilament light chain (NfL; a marker of neuronal abnormalities[49–51] continued to rise in treated subjects, albeit somewhat more slowly than in controls, thereby mirroring the slowed (but not stopped) decline of cognitive changes[1,2,45,46,48] (Figure 1).

Unfortunately, in some immunotherapy patients, the removal of aggregated Aβ has been associated with troublesome and sometimes serious side-effects known as amyloidrelated imaging abnormalities (ARIAs)[1–3,45], which appear to be linked to the abundance of pre-existing Aβ deposition, especially as CAA. Aβ removal has been associated with an expansion of ventricular volume and an increased reduction of brain volume[2,52,53], the functional significance of which remain uncertain. Overall, both the limited clinical benefit of antibody therapy and the risk of serious side-effects that are associated with the presence of a high amyloid burden underscore the importance of starting treatment much earlier in the pathogenic process.

FROM IMMUNOTHERAPY TO IMMUNOPREVENTION: WHAT DO WE NEED?

Below we consider four key research objectives that are needed to extend the results of past and ongoing clinical trials of anti-Aβ antibodies to the effective immunoprevention of AD: Define the best molecular target for Aβ-immunotherapy (epitopes), optimize the schedule of treatment (timing), establish early biological indicators of preventive efficacy (biomarkers), and identify and mitigate potential adverse reactions to antibody administration (side-effects).

Identify the optimal Aβ epitopes

Based on the results of the recent clinical trials, the most coherent (but still provisional) conclusion is that lowering cerebral Aβ load can slow the progression of AD. Solanezumab selectively binds Aβ monomers; although a meta-analysis suggests that it may have had some clinical efficacy[54], solanezumab failed to reach primary endpoints in clinical trials[55]. Monomeric Aβ is abundant in brain, and its complete neutralization would require stoichiometric amounts of high-affinity antibodies able to compete with the binding of monomers to existing Aβ aggregates. Preclinical evidence indicates that the toxicity of Aβ is linked to its aggregated state[26,27], and the antibodies that have shown the best evidence of clinical efficacy also achieved the largest reduction of aggregated Aβ[1–3]. For these reasons, an antibody that generally recognizes monomeric Aβ is unlikely to be the most favorable immunotherapeutic tool.

The multiple manifestations of aberrant Aβ could present challenges for immunoprevention. Aβ multimers range in size from small oligomers to protofibrils and long amyloid fibrils, and they differ in their cytotoxicity and ability to seed further aggregation (Figure 2). Moreover, the predominant species of Aβ can vary among patients, between the vasculature and parenchyma, and over the course of the disease[12,20,42,56,57]. Given the biochemical and structural complexity of Aβ aggregates, the best epitopic targets for the prevention or removal of Aβ multimers remain uncertain. As one example, the positive clinical outcome of the lecanemab trial might imply that Aβ-protofibrils are a particularly promising target[58]. Lecanemab was raised against recombinant ‘arctic’ mutant (E22G) Aβ, a form of the protein that is linked to a rare familial form of AD characterized by marked accumulation of protofibrils[59]. However, the protofibrillar nature of arctic Aβ in patients’ brains is incompletely understood[60], and there is evidence that recombinant Aβ folds into a conformation that differs from that of Aβ that folds within the brain[57,42,60]. Hence, the clinical efficacy of lecanemab[1] could result from the overall reduction of β-amyloid (at which the antibody is quite effective), and not from the neutralization of a specific type of multimer (i.e., protofibrils).

Similarly, *in vitro* studies suggest that aducanumab decreases Aβ oligomer generation from secondary nucleation[61], but the general reduction of β-amyloid load in the aducanumab clinical trial[3] precludes linking the clinical outcome to certain oligomeric species. To complicate things further, smaller, ‘soluble’ assemblies might be in a state of dynamic equilibrium with Aβ plaques[18] such that eliminating plaques would indirectly reduce the population of oligomers and protofibrils, and *vice versa* (Figure 2). Imaging and fluid

biomarkers for oligomeric Aβ are needed to meaningfully connect pathogenic molecular species to clinical efficacy (see ‘Optimize biomarker use’, below).

Pyroglutamate-modification of Aβ (e.g., $Aβ_{N3pE}$) enhances the propensity of the protein to aggregate; $Aβ_{N3pE}$ emerges predominantly in later stages of cerebral β-amyloidosis[62,63] and thus exemplifies how abnormal Aβ can change over the course of AD. Donanemab is directed at $Aβ_{N3pE}$, and it has been shown to be highly effective at removing amyloid in symptomatic patients[2]. However, it is conceivable that donanemab’s specificity for a relatively late-arising epitope could diminish its ability to impede Aβ deposition at a much earlier stage of disease. Another molecular modification that occurs late in the maturation of Aβ plaques is phosphorylation at position 8 ($Aβ_{pS8}$)[64]. Accordingly, Aβ-immunotherapy might need to be tailored to the characteristics of Aβ at different stages of AD in order to achieve optimal therapeutic and preventive efficacy (see ‘Establish the best timing for immunoprevention’, below).

To identify the most promising immunotherapeutic or immunopreventive Aβ epitope, clinical studies directly comparing several different antibodies would be informative. Moreover, postmortem biochemical analyses of the brain after treatment will then help to pinpoint changes induced by the antibodies that are most pertinent to effective prevention. In parallel, comparison of antibodies and the multimers they engage in preclinical models[65], along with structural studies of the epitopes recognized by the various antibodies, are needed. Together with such properties of the antibodies as affinity, immunoglobulin subtype, posttranslational modifications, and half-life in blood (as well as the inherent immunogenicity of the antibodies themselves[66]), these data should help to facilitate the design of next-generation antibodies and define the most suitable molecular target for immunoprevention.

Establish the best timing for immunoprevention

Abnormal Aβ begins to accumulate in the brain two to three decades before the clinical signs and symptoms of AD become manifest[6–8]. True primary prevention - stopping Aβ aggregation before it begins - is a particularly attractive objective, but establishing an acceptable risk:benefit ratio for long-term administration of a preventive agent is a formidable task. From a practical standpoint, secondary prevention is a more likely scenario, i.e., initiating preventive measures in response to biomarker evidence that aberrant Aβ has begun to accumulate, but before the onset of the cognitive and behavioral changes of AD[67] (Figure 1).

In the two-stage model of AD[24–26], Aβ proteopathy initially drives the disease, but its relative influence diminishes concomitant with the emergence of myriad subsequent changes that include neurofibrillary tangle formation, inflammation, neurodegeneration and, eventually, behavioral impairments[5]. The transition from the first to the second stage is heralded by a steep rise in the CSF levels of NfL, and this has been estimated to occur around 10 years before the onset of symptoms[26]. At least in mouse models, the increase in NfL (and thus presumed neurodegeneration) coincides with saturated Aβ seeding activity of brain tissue[26]. Once the second stage is underway, it is not clear how much clinical benefit can be expected from Aβ-removing therapies alone (Figure 1); rather, treatments directed at

both Aβ-proteopathy and its sequelae may be required. A clinical trial targeting Aβ in the first disease stage is being planned in carriers of dominant AD mutations 10 years or more prior to the estimated onset of symptoms (https://clinicaltrials.gov/ct2/show/NCT05552157). In addition, a clinical trial targeting both Aβ (lecanemab) and tau (antibody E2814) in the second disease stage (i.e., less than 10 years from the estimated disease onset) was recently launched (https://clinicaltrials.gov/ct2/show/NCT05269394).

For future investigations aiming to optimize the timing of immunoprevention, we need to determine whether the antibodies must be given continuously, or whether intermittent administration will suffice, and what the frequency and duration of treatment should be. When, and how often, treatment should be repeated for maximal efficacy in humans is not yet known, but insights into such mechanistic questions can be gleaned from studies in animal models. For example, experiments with mouse models suggest that acute removal of Aβ seeds at a very early stage of Aβ deposition delays both the accumulation of Aβ and the onset of downstream pathologies later in life[68,44]. Thus, it might not be necessary to continuously administer anti-Aβ antibodies to delay or prevent Aβ deposition (and, by extension, AD). Finally, we need to determine if methods to augment antibody entry into the brain, such as brain shuttle antibody constructs[69] or ultrasound[70], are necessary (or even desirable) to reduce the number of treatments required for immunoprevention.

Optimize biomarker use

Advances in Aβ-PET imaging and in the measurement of Aβ in biofluids have substantiated the decades-long presymptomatic development of AD[6,71,72], and these technologies have been foundational for the implementation of recent clinical trials[71 72]. As sensitive and informative as these methods have become, they do not detect aberrant Aβ that might be revealed even earlier if the brains were to be analyzed with sensitive biochemical or immunohistological techniques[44,73–75]. Similarly, when Aβ-PET scans signal that immunotherapy has reduced the Aβ-load below detection levels, it is likely that a pathologically significant amount of aberrant Aβ remains. Moreover, current Aβ-PET imaging and biofluid Aβ measurements do not provide detailed information about the biochemical and structural characteristics of cerebral Aβ before and after immunotherapy, nor can they satisfactorily discriminate vascular from parenchymal amyloid to gauge the risk of side-effects (see ‘Mitigate the side-effects’, below). Thus, further improvements in assay sensitivity and specificity for early and different forms of aberrant brain Aβ are needed.

Multiple biomarkers in fluids now can track many of the sequelae of Aβ proteopathy. Major progress has been achieved in measuring Aβ-associated phosphorylated Tau (pTau 181, pTau217, pTau231) in CSF and blood[76,77]. More recently, tests have been developed to detect activated astrocytes and microglia (glial fibrillary acidic protein [GFAP] and soluble triggering receptor expressed on myeloid cells 2 [Trem2], respectively)[72,78,79]. In presymptomatic AD, the trajectories of these biomarkers closely parallel that of Aβ-deposition. In contrast, NfL in the CSF increases robustly only after half-maximal Aβ-deposition is reached, and this appears to mark the transition from the first to the second stage of AD progression[26] (Figure 1).

Despite the considerable clinical utility of fluid biomarkers, the interpretation of clinical trial outcomes would be enriched by a better understanding of the molecular and cellular alterations that these biomarkers represent. For example, the paradoxical finding that pTau fluid biomarkers are strongly associated with the trajectories of Aβ-deposition but poorly with aberrant Tau as measured by PET currently lacks a persuasive explanation. In addition, the pathophysiologic basis of increased GFAP and Trem2 levels in biofluids is still uncertain, as is the means by which proteinaceous biomarkers, in particular intracellular structural proteins such as Tau, GFAP and NfL, make their way into the CSF and blood.

Many mechanistic questions about biomarkers now can be addressed in disease models (mainly genetically modified mice) that enable a direct and timely comparison of brain pathology to protein changes in biofluids. Animal models also can help to clarify issues that confound investigations of humans, including diagnostic uncertainty, comorbidities, perimortem irregularities (such as agonal state and postmortem interval), and lifestyle variability. For example, in APP-transgenic mouse models, Aβ deposition *per se* (i.e., in the absence of neurofibrillary tangles and neuron loss) is sufficient to induce increases in CSF pTau[80]. Moreover, transgenic mouse models manifesting distinct proteopathies enable the separation of Aβ-dependent secondary biomarker changes from those associated with possible co-morbid pathologies such as α-synucleinopathy[81].

Finally, to optimize immunopreventive strategies, biomarkers of early pathogenesis with a robust effect size are needed to define both the inception and initial trajectory of the disease process. For instance, in both prion diseases[14] and AD[26], the respective seeding activities of PrP and Aβ in brain tissue rise steeply in the initial stage of protein aggregation before reaching a plateau around the time that neurodegeneration becomes apparent. Seeds of misfolded PrP have been amplified from the CSF of patients with Creutzfeldt-Jakob disease[82], and α-synuclein seeds have been detected in CSF and blood from patients with α-synucleinopathies[83,84]). Similar novel biomarkers would help to characterize the earliest stages of AD, and could serve as informative readouts in immunoprevention trials.

Mitigate the side-effects

Amyloid-related imaging abnormalities (ARIAs) can be a serious side-effect of Aβ immunotherapy[1,2,85]. ARIAs include focal cerebral edema/effusion (ARIA-E) and hemosiderin accumulation (ARIA-H; a marker of previous microbleeds)[20,86]. Although ARIAs often are asymptomatic and can be managed in treated subjects by titration of the antibody dose[1,85,87], in some instances severe reactions to treatment have occurred, raising concerns about the risk:benefit ratio of immunotherapy for AD[38,88,89].

The mechanisms underlying ARIAs are incompletely understood, but the abnormalities are strongly associated with the presence of CAA[20,90]. CAA appears to be increased – at least temporarily – in response to Aβ immunotherapies that reduce parenchymal β-amyloid both in mouse models[91] and in humans[36,37,92,93]. This increase may result from the translocation of Aβ from the parenchyma to the vascular wall[94,95], although the precise mechanism is uncertain. As the immune system (e.g., perivascular macrophages) engages with Aβ in the vascular wall, the blood vessel is compromised and becomes prone to leakage and rupture[20]. In rare cases, Aβ-immunotherapy combined with blood thinners has caused fatal cerebral

hemorrhage in subjects with CAA[88], an adverse event that could have been predicted from preclinical studies in mouse models[91,96].

ARIAs are most frequent in immunotherapy recipients bearing the *ε4* allele of the gene for apolipoprotein E (*APOEε4*)[20,38], consistent with *APOEε4* being a prominent risk factor for CAA[97]. (CAA can be significant also in non-carriers of *APOEε4*[98], albeit less commonly than in carriers). Because CAA is moderate-to-severe in approximately 45% of AD cases[21,22], Aβ-immunotherapy could put nearly half of symptomatic AD patients at greater risk of ARIAs. Experimental work with mouse models has found that Aβ-immunotherapy-related hemorrhages are evident only when substantial CAA is present[91,99]. It is therefore possible that the risk of ARIAs would be diminished or even eliminated if Aβ antibodies are administered before CAA becomes widespread in the brain, i.e., as a preventive measure.

The incidence of treatment-related ARIAs differed among past therapeutic trials of anti-Aβ-monoclonal antibodies[38,86]. It is uncertain whether this variation is related to characteristics of the antibodies (such as their antigen-recognition profiles), to differences in the trial participants (such as their disease stage or CAA load), or to methodological issues such as sensitivity in ARIA detection. CAA can be suspected based on certain clinical and biomarker signs[20,100], but a definitive biomarker for CAA would enhance the prognostic precision for ARIAs in potential recipients of immunotherapeutics. CAA-specific PET ligands could emerge from recent findings that the 3-D architecture of β-amyloid fibrils in CAA differs from that in plaques[57,42]. The discovery that the protein medin co-deposits exclusively with Aβ in the vasculature[101] also could enable the development of a biomarker specific for CAA.

Additional research is needed to delineate the fundamental mechanisms underlying the CAA-associated side effects of Aβ-immunotherapy. Recent insights into the clearance of Aβ by the vasculature-associated brain fluid drainage system[102,103], the role of perivascular macrophages[104], and neuro-immune interactions along CAA-prone meningeal and parenchymal blood vessels[105] have set the stage for further research in preclinical models to understand and mitigate the side-effects of Aβ-immunotherapy. This work also is important for gauging any possible risks posed by immunopreventive measures initiated before CAA becomes widespread in the brain.

CONCLUDING REMARKS

Evidence of disease modification by monoclonal antibodies is a small but encouraging step forward in the campaign to subdue AD. We now need to extend the lessons learned from treatment trials to a new framework for the prevention of the disorder. A salient challenge for implementing early prevention is the need for robust prognostic indicators of incipient disease, whereas later preventive measures will be hindered by the relative complexity of advanced disease, which may necessitate combination therapy for multiple targets[10,106].

To learn as much as possible from current and past treatment trials, an increasingly refined analysis is essential, not only of the behavioral and biomarker findings during the first 18 months of treatment, but more importantly the biomarker trajectories beyond this point.

This applies to participants who continue antibody treatment past 18 months and those who discontinue treatment at any point in the trial. Ideally, such an analysis should be combined with a careful investigation of the biochemical and pathological status of the brain postmortem (similar to the long-term follow-up examination of actively immunized subjects[37]).

More research with experimental disease models is needed to address fundamental questions that have emerged from the immunotherapy trials[65]. For example, the interpretation of biomarker trajectories and treatment responses in humans is hampered by the incomplete mechanistic understanding of what these changes represent in the brain. Advances in analytic technologies now enable the measurement of low-abundance proteins in very small volumes of biofluids, making it feasible to measure the same analytes in the CSF and blood of mice and humans; such comparative analyses can inform the design and interpretation of therapeutic and prevention trials[26,49,80,107]. More broadly, the development of advanced disease models that more completely represent the complexity of later-stage AD would improve the translatability of basic research[65].

Although passive immunization with anti-Aβ antibodies is especially promising as a preventive approach to AD, it is useful to consider alternative strategies. For instance, Aβ-proteopathy might be prevented indirectly by targeting proteins that co-deposit with Aβ (e.g., ApoE[108] or β_2-microglobulin[109]), or by delivering antibodies against Trem2, which stimulate microglial phagocytosis of Aβ assemblies[110,111].

There are also good reasons to keep active immunization in play; current practical impediments to passive antibody treatment, such as cost and the mode and frequency of delivery, are likely to limit the widespread deployment of passive immunoprevention. The chief drawbacks of active immunization (vaccination) are the risks associated with an immune reaction to a ‘self’ antigen and the difficulty moderating an errant immune response[112]. Since the termination of the pioneering Aβ vaccine trial[113], basic research has advanced the safety and efficacy of active immunization[114,115]. Although considerable challenges remain, if these can be overcome, active immunization could become a relatively simple, inexpensive, and accessible immunopreventive measure.

Finally, it should be emphasized that dementia can result from pathologies such as primary tauopathy, α-synucleinopathy, TDP-43 proteopathy, vascular disease[106,116] and many others. In older people, several of these degenerative processes can be comorbid with AD[29]. Prevention of AD *per se* thus won’t completely eliminate the risk of dementia. Even so, since AD is the most common cause of dementia[117], effective prevention would have considerable benefit for the world’s increasingly long-lived population.

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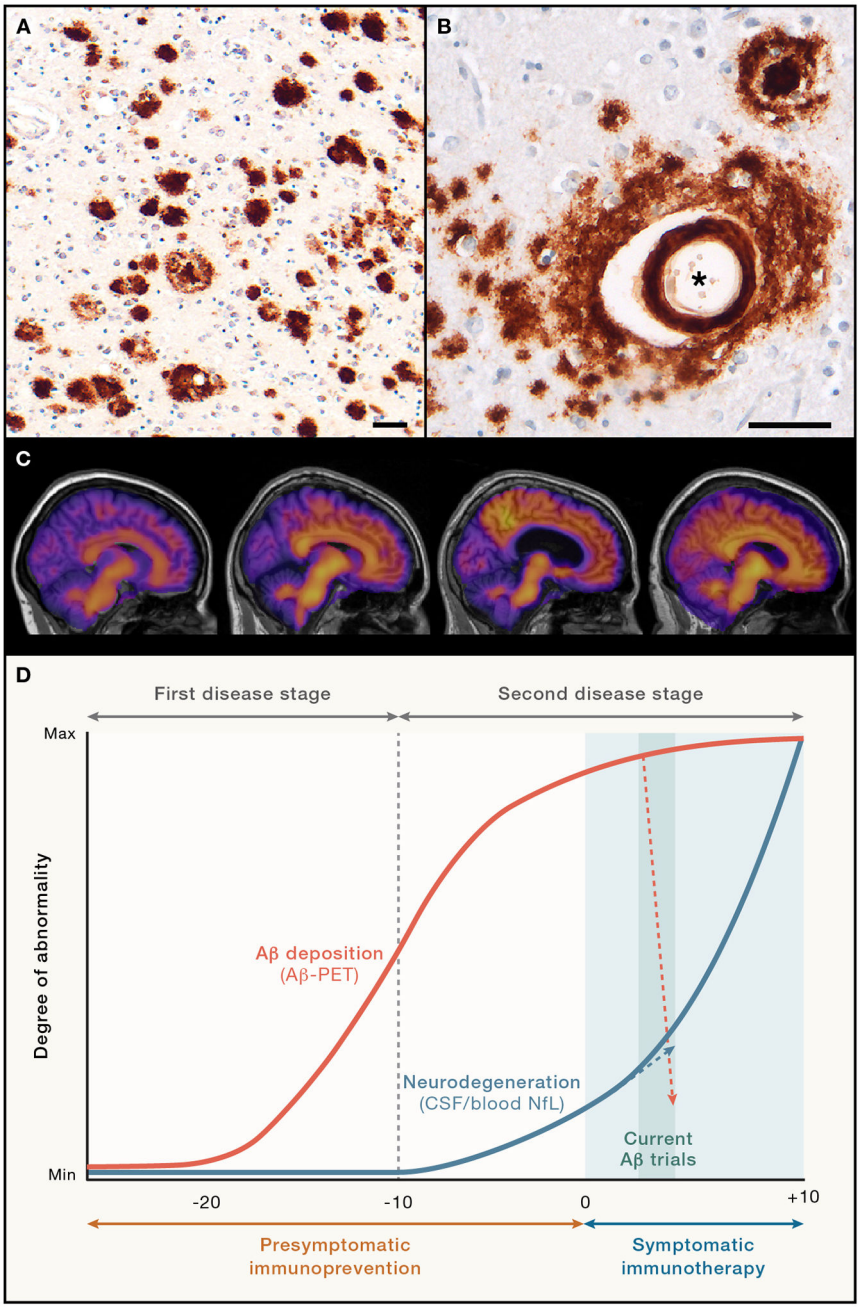

Figure 1. The pathologic progression of AD, immunoprevention, and the impact of immunotherapy in symptomatic patients.

(A, B) Immunohistochemical detection of Aβ deposition in AD brain as plaques (A) and cerebral β-amyloid angiopathy (CAA; black asterisk in B); the affected vessel is surrounded by diffuse parenchymal Aβ deposits, and a dense-core plaque is in the upper right. CAA is moderate-to-severe in nearly half of all AD cases, and CAA has been linked to the side effects of Aβ-immunotherapy; antibody 4G8, Nissl counterstain; scale bars are 50 μm.

(C) Representative Aβ-PET images (left to right) from a control person (non-mutation carrier), a mutation carrier about 10 years before symptom onset, and two mutation carriers

that are symptomatic (Pittsburgh compound B [PiB] tracer; shown are participants with familial AD[23]). The increase in PiB retention primarily occurs in the presymptomatic phase. **(D)** In the two-stage model of AD,[24–26] the first stage is dominated by Aβ deposition. The second stage commences approximately 10 years before symptom onset and becomes partly independent of Aβ deposition with the emergence of clear signs of neurodegeneration (as assessed, e.g., by NfL levels in CSF or blood) and, eventually, behavioral impairments.[26] Targeting aberrant Aβ as immunoprevention (prevention of the disease) is likely to be most successful when initiated during or prior to the first stage. Given the growing pathologic complexity of the disease, it is not clear how much clinical benefit can be expected from Aβ-removing therapies alone beyond this time point. Indeed, Aβ-immunotherapy trials for 18 months with aducanumab, lecanemab, or donanemab removed >60% of the deposited Aβ, but NfL continued to rise (albeit at a reduced pace), paralleling the slowed - but not stopped - cognitive decline in treated subjects.

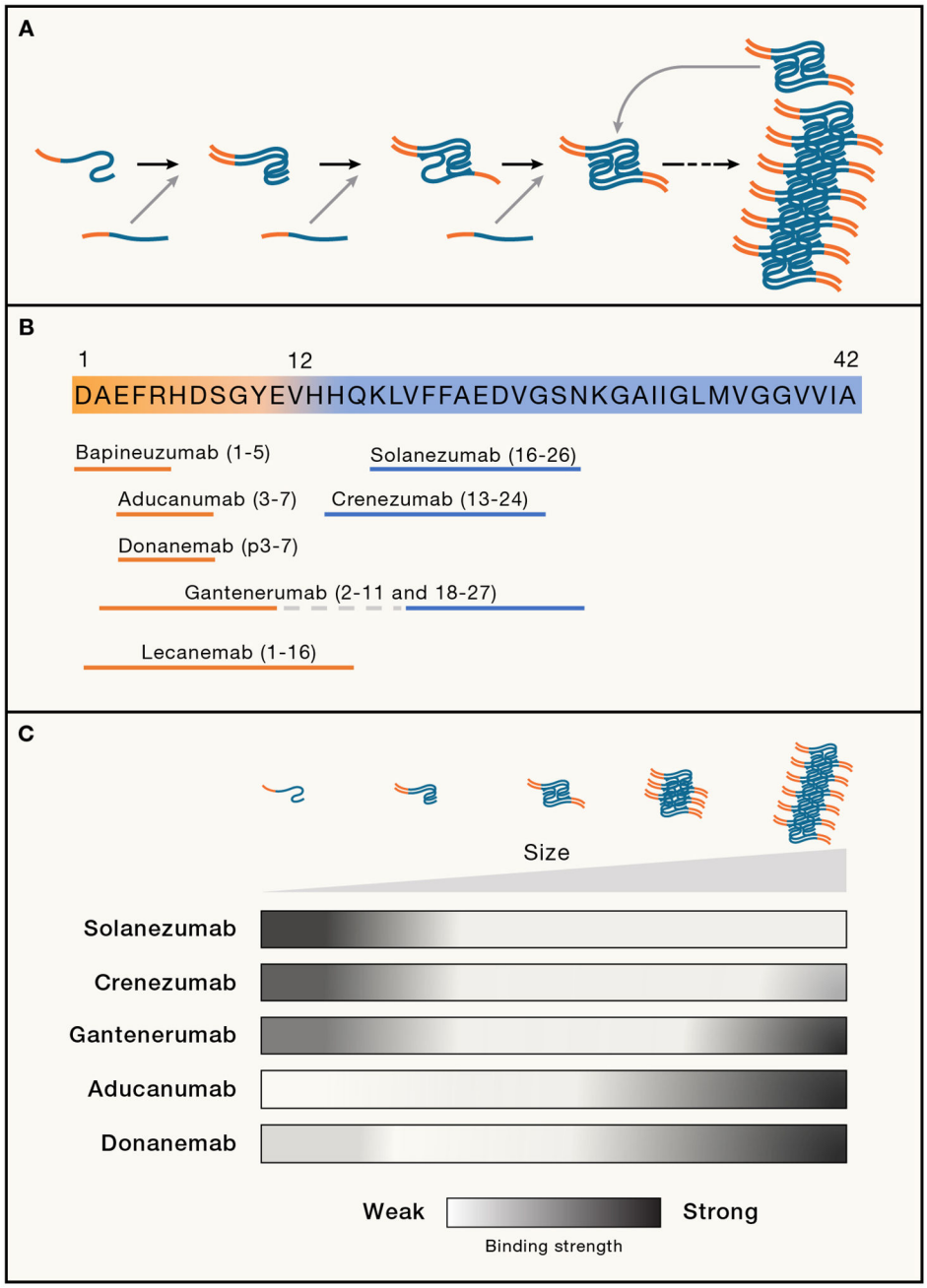

Figure 2. Aβ aggregation and the epitopes recognized by therapeutic antibodies.

(A) Aβ aggregation starts with a slow nucleation phase during which Aβ assumes an alternative conformation that converts and binds to other Aβ molecules to form the initial segment of the amyloid fibril. With increasing length, the growing fibril eventually breaks and releases seeding-active Aβ multimers, at which stage the process becomes self-propagating (based on Jucker and Walker[11]). As deposition progresses, Aβ comprises a mixture of multimers, ranging from small soluble oligomers to long amyloid fibrils, which differ in their cytotoxicity and ability to seed further aggregation.[18,19,40,41] The growing amyloid fibril schematically depicted here consists of two twisted protofilaments (based on

Yang et al.[42] for brain-derived Aβ42 fibrils). Note that the N-terminal amino acids (orange) are exposed from the hydrophobic amyloid core (blue).

(B) Diagram of Aβ42 showing the amino acid epitopes that therapeutic antibodies are thought to recognize (based on Plotkin and Cashman[43]). Common to the antibodies that cleared Aβ deposits in clinical trials (gantenerumab, aducanumab, donanemab, lecanemab) is that they recognize N-terminal amino acids (orange), i.e., epitopes that are exposed on mature amyloid fibrils. In contrast, solanezumab and crenezumab only recognize mid-sequence epitopes that are buried within the amyloid fibril; hence, these antibodies mainly recognize monomeric Aβ.

(C) Schematic illustration of the binding strength of five different antibodies to Aβ that was derived from native amyloid-laden brain samples (AD and mouse models) and fractionated according to size. The two antibodies that most effectively remove Aβ from the brain (donanemab, aducanumab) recognize predominantly large amyloid aggregates (based on Uhlmann et al.[44]).