Antibody therapy for Alzheimer's disease

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The economic, social and emotional impact of Alzheimer's dementia is increasing dramatically as greater numbers live to advanced ages. The dearth of effective therapies has led to innovative approaches to treat the disease. This review summarizes the rationale, progress and setbacks regarding the use of antibody-based therapies to treat Alzheimer's disease and discusses future directions for this approach in Alzheimer's and other disorders.

Alzheimer's disease is a dementing illness that has a typical onset late in life (70s–90s) and causes progressive loss of CNS functions over a 7–15-year period. Most Alzheimer patients will require professional caregiving and institutionalization that last for years. Alzheimer's disease affects roughly 4 million Americans. The direct costs for the disorder are $100 billion, with indirect costs associated with loss of caregivers from the workforce adding billions more. It is estimated that simply delaying Alzheimer's by 5 years would save $50 billion in medical care. As the baby boom generation approaches the age of risk and we continue to see gains in longevity due to successful treatment of cardiovascular diseases and cancer, the numbers of demented individuals filling our nursing facilities will rise dramatically and costs will approach $400 million in current dollars. It is difficult to overstate the magnitude of the problem society may face over the next quarter century. The greatest hope is for treatments that modify disease progression, rather than the largely palliative treatments presently available.

As with most disorders, the treatments for Alzheimer's have been developed from our incomplete (yet expanding) knowledge of the disease process. Two decades ago, the cholinergic hypothesis of Alzheimer's disease reigned, analogizing the relationship between acetylcholine loss and memory disorders in Alzheimer's to the relationship between dopamine loss and movement disorders in Parkinson's disease. Replacing the missing acetylcholine made sense in light of the success of L-dopa and other dopaminomimetics in diminishing the symptoms of Parkinsonism, at least transiently [1,2]. This led to the development of CNS active cholinesterase inhibitors which are the agents currently approved to treat the memory dysfunction found in dementing illnesses. These drugs are largely palliative agents. Not all patients respond to these agents and the effects are typically modest in magnitude (6–12 month reversal of symptoms). Patients continue to deteriorate on the drugs.

The Amyloid Hypothesis of Alzheimer's disease

A more recent hypothesis regarding Alzheimer's disease is based upon the pathologic features of the disease. All Alzheimer patients, by definition, have extracellular deposits of amyloid composed primarily of the Aβ peptide. Based largely on the study of genetic mutations that can cause Alzheimer's disease, the amyloid plaques have been increasingly viewed as a critical step in the pathogenesis of the disease leading to dementia (for a review of the amyloid hypothesis, see [3]). The Aβ peptide is a 40–42 amino acid fragment of a considerably larger protein called the amyloid precursor protein (APP). It is formed as a minor degradation product of APP by the conjoint activity of two proteases referred to as β-secretase (N-terminal cleavage) and γ-secretase (C-terminal cleavage) of APP.

APP is cleaved by β-secretase, which results in the release of Aβ and APP, a membrane-bound protein. The primary α-secretase, also known as α-secretase or α′-secretase, can cleave APP at the extracellular domain of APP, preventing the formation of Aβ. The γ-secretase cleaves APP at the C-terminal, forming a fragment called APP C-terminal domain (CTD) and a fragment called APP N-terminal domain (NTD).

The peripheral sink hypothesis of anti-Aβ antibody action

Rapid antibody effects on mouse behavior

Anti-Aβ Antibodies directly in the brain

Epitope specificity of anti-Aβ antibodies

Alternative Anti-Aβ vaccine strategies

Early phase clinical trials

Five-year view & future directions

Key issues

References

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cleavage). The major cleavage product of APP in this region occurs at Aβ amino acid 16 by α-secretase (90%), an action that precludes the formation of the Aβ peptide. Present evidence suggests the C-terminal cleavage performed by γ-secretase can be performed at either amino acid 40 or amino acid 42 by the same enzyme. Mutations leading to early onset Alzheimer’s disease in an autosomal dominant fashion all tend to increase either the length or total amount of the Aβ peptide formed. While the topic of much speculation, no one has yet identified a convincing functional role for Aβ in vivo. Under normal circumstances, the Aβ that is made in the CNS is cleared with a half-life of 1–2 h [4]. A key feature of the long form of the Aβ peptide is that it is more prone to assemble into amyloid fibrils than the shorter form. Thus, based upon the pathologic appearance of fibrillary amyloid and the genetic indications that more fibrin-prone forms of Aβ are linked with early onset disease, one major target for drug development in Alzheimer’s disease has been to block the formation of Aβ and its deposition into fibrillar amyloid plaques.

Antibodies as potential therapeutic agents

The first demonstration that antibodies may have use in Alzheimer’s disease was that antibodies raised against fragments of the Aβ peptide could block the formation of amyloid fibrils from Aβ in vitro [5]. Even at this early stage, some epitope specificity of the antibody’s action was demonstrated by the observation that antibodies against aa1–28 were effective in blocking fibrillogenesis, while antibodies against amino acids 8–17 were ineffective. Shortly after this first demonstration, these authors found that the anti-Aβ antibodies could even dissolve pre-existing amyloid fibrils [6]. In addition, these antibodies could prevent in vitro neurotoxicity of Aβ fibrils, indicating a functional benefit in dissolving the fibrils with antibodies. Again, antibodies against N-terminal portions of the peptide were active (amino acids 1–16) while others (amino acids 13–28; amino acids 33–40) were ineffective. Importantly, the stoichiometry of the antibody to Aβ ratio indicated a potential catalytic mechanism of action for the antibody, as 1:10 and even 1:100 ratios were effective in depolymerizing the fibrils [7]. Using phase display techniques, these authors have identified the amino acids 3–6 (EFRH) as being the minimal effective epitope in raising antibodies against the Aβ peptide [8].

The development of transgenic mouse models overexpressing APP and depositing Aβ fibrils as the mice aged (PDAPP [9]; Tg 2576 [10]) permitted in vivo evaluation of many agents directed towards blocking amyloid deposition. In the summer of 1999 Schenk et al. published the surprising finding that vaccinating transgenic mice against the Aβ peptide could dramatically reduce the deposition of fibrillar amyloid in the PDAPP transgenic mouse and possibly even remove deposits already formed [11]. They also noted activated microglia in the vicinity of the few remaining amyloid deposits and suggested that these cells were phagocytosing and eliminating the opsonized Aβ fibrils. This group quickly followed up on this finding with a second publication examining passive immunization protocols [12]. They demonstrated that monoclonal antibodies against Aβ were also effective in reducing amyloid loads when injected into transgenic mice. They also showed that, in vitro, antibodies could activate microglia and cause phagocytosis of preformed amyloid deposits, including those on slices of Alzheimer brain. Moreover, using a panel of antibodies, they demonstrated a correlation between the ability of anti-Aβ monoclonal antibodies to reduce amyloid and to stain fibrillar Aβ deposits on histological sections. Those antibodies with high affinity towards soluble Aβ but lacking the ability to stain Aβ plaques were ineffective in reducing amyloid load in transgenic mice in vivo or in activating microglia to remove plaque in vitro. The authors also noted that unlike active immunization with the Aβ vaccine, the passive administration of anti-Aβ antibodies did not elicit a T-cell response to Aβ when testing splenocytes. These authors concluded that the mechanism of anti-Aβ antibody action is to opsonize the fibrillar deposits and stimulate phagocytosis and elimination by resident microglia.

Anti-Aβ antibodies protect transgenic mice from memory loss

At the time that the Schenk et al. paper demonstrated the capacity of Aβ vaccines to reduce amyloid loads in transgenic mice, a major question regarding how the vaccine would affect learning and memory in the mice emerged [11]. One corollary of the inflammation hypothesis of Alzheimer’s disease is that activation of the microglia by Aβ deposits results in a vicious cycle of inflammation that ultimately causes toxicity of bystander neurons. Given the activation of microglia by the vaccine reported by Schenk et al., we predicted that although the vaccine may clear amyloid, it might disrupt normal memory function in the process. In collaborative work, we had established a doubly transgenic APP+PS1 transgenic mouse line [13] combining the Tg2576 APP mouse with a presenilin-1 (PS1) transgenic mouse generated by Duff et al. [14]. At the time the Schenk et al. study was published, we had just finished demonstrating a strong relationship between amyloid deposition and a working memory deficit in the radial arm water maze in our APP+PS1 mouse model of amyloid deposition [15]. We had also identified that this was a progressive change that developed slowly and was not consistently observed until the mice reached 15 months of age [16]. We were aware that behavioral testing of the PDAPP mice was complicated by the observation that they were deficient in most learning and memory tasks at all ages, even before any amyloid deposits could be detected [17,18]. Later work established this was in association with reduced hippocampal volumes and callosal agenesis in PDAPP mice [19,20]. Thus, in July of 1999 we began inoculating a cohort of transgenic mice with the intention of testing them for premature memory deficits associated with inflammatory reactions caused by the vaccine.

After 5 months of vaccination, the mice were tested for radial arm water maze performance at 11–12 months of age. At this age, we found that the nontransgenic mice could perform this task, which requires learning a new submerged platform location each day, almost perfectly, with less than half an error on average by the last trials of the day [21]. We also found that the
transgenic mice given control inoculations performed very well on the task and were not yet distinguishable from the nontransgenic littersmates. To our surprise, the same was true of the mice inoculated with Aβ vaccines. They too could learn the task, indicating to us that any microglial activation that was caused by the vaccine was not sufficient to result in disruption of learning and memory functions. Given that our initial hypothesis was disproved, we decided to continue inoculating the mice until they reached an age (15–16 mo) at which we had previously found memory deficits [15]. These mice were then tested again in the radial arm water maze, during which a memory deficit was observed in the transgenic mice injected with the control vaccine, as expected. We also found virtually flawless performance in the nontransgenic animals. However, the transgenic mice inoculated with the vaccine against Aβ, although slower to learn platform location, ultimately performed as well as nontransgenic animals [21]. In an independent series of experiments, using yet another APP transgenic mouse model (Tg CRND8), Janus et al. found that vaccination against the Aβ peptide partially reversed an early learning deficit in a reference memory version of the water maze [22]. As in our study, Janus et al. also failed to observe any adverse consequences of the vaccine. The amount of Aβ deposited in the APP+PS1 and Tg CRND8 transgenic models is greater than in the PDAPP or Tg2576 mice and in both of the above studies the reduction of amyloid was only partial. Yet the fact that behavioral benefits could still be obtained, implies either a threshold amount of deposited Aβ needed before memory is disrupted, or there is another pool of Aβ not readily detected by histochemical or immunoassay methods that is most directly responsible for the impairments.

In a further series of studies, evaluating mice vaccinated with 3, 5 or 9 inoculations at monthly intervals, we found that the activation of microglia in association with the vaccine was complex. In mice inoculated over 3 or 5 months there was an activation of microglia compared with mice given control inoculations, yet by 9 months, the microglial activation had abated and if anything there was tendency for reduced microglial activation in the vaccinated mice [23]. We also found considerable variation in the extent of microglial activation in individual mice in this study and in untreated mice [24]. Within the transgenic cohorts for the Wilcock et al. study, we found a bimodal distribution of microglial activation, with roughly half the mice inoculated with Aβ failing to demonstrate microglial activation using CD45 or major histocompatibility complex (MHC)-2 as markers [23]. When we correlated the extent of microglial activation with Aβ loads in these mice, we found a significant negative correlation, such that those mice with greater microglial activation had reduced amyloid loads. This is contrary to what might be expected if the stimulus for microglial activation was the amyloid deposits themselves. Although we are cautious about assigning causality from correlations, we felt that together with the other data collected, that the most likely mechanism of vaccine action was to somehow accelerate the microglial-mediated clearance of Aβ deposits.

### The Peripheral Sink Hypothesis of anti-Aβ antibody action

In the summer of 2001, a remarkable paper appeared which found that peripheral injections of anti-Aβ high affinity monoclonal antibodies caused a massive elevation of Aβ in the plasma and that repeated injections were associated with dramatic reduction in amyloid load in vivo [25]. DeMattos et al. were unable to detect anti-Aβ antibody in the brain and argued that the circulating antibodies were acting as a ‘sink’ for Aβ and altering the equilibrium between blood and brain Aβ to favor its distribution into the blood. In a related publication, these authors found that the initial rate at which Aβ accumulated in the blood after injection of anti-Aβ antibodies was highly correlated with the amyloid load found in the brains of these mice [38]. In this manner, measuring the initial rate of Aβ efflux may be a good marker of brain Aβ load and could be useful for diagnostic purposes and for evaluation of the efficacy of antiamyloid therapeutics. Thus, this introduced a third possible mechanism for the antibody-mediated clearance of Aβ from brain in addition to dissolving the fibrils catalytically or opsonizing them for microglial mediated clearance.

### Rapid antibody effects on mouse behavior

The behavioral studies in vaccinated mice had suggested that complete removal of the amyloid deposits was not required in order to see behavioral benefits [21,22]. Still, this was interpreted as indicating a threshold phenomenon was present, with the functional reserve of the brain being adequate to tolerate some degree of amyloid deposition. Both we and others have demonstrated a meaningful correlation between brain amyloid levels in individual mice and their performance on learning and memory tasks, suggesting reductions of these values should be required to obtain behavioral benefits of treatments [27,28]. Thus, it was quite unexpected when it was found that single injections of monoclonal anti-Aβ antibodies (passive immunization) into transgenic mice were sufficient to reverse memory deficits [29,30]. Moreover, these reversals of memory loss were obtained without any measurable change in brain Aβ levels. These demonstrations argue that the memory disruptive form of Aβ is most likely not the fibrillar deposits but hard to measure intermediates between soluble and fibrillar amyloid, the so-called oligomeric or protofibrillar Aβ [31]. Moreover, these data suggest that anti-Aβ immunotherapy in early stage Alzheimer’s disease might succeed in rapidly reversing memory impairments already manifest. Towards this end, it has been demonstrated that antibodies can be specifically generated against oligomeric forms of the Aβ peptide [32], conceivably permitting identification of which form(s) of Aβ might be most responsible for the memory loss in transgenic mice.

### Anti-Aβ Antibodies directly in the brain

In a technological tour de force, Bacskai et al. developed a method to longitudinally monitor Aβ plaque distribution in vivo using multiphoton microscopy and a craniotomy [33]. They were able to identify the same pattern of amyloid staining in multiple sessions over weeks, apply anti-Aβ antibody topically and then
monitor the disappearance of amyloid deposits over days. They found a virtually complete loss of deposits in the several hundred microns beneath the craniotomy, confirmed at necropsy by standard immunocytochemical techniques. They also observed a remarkable activation of microglial cells in the vicinity of the deposits, implying that antibody opsonized Aβ led to microglial activation and phagocytic removal of the material. However, in a follow-up study, these authors found that F(ab')2 antibodies were equally effective as their intact Fc-bearing versions in clearing Aβ [34]. This observation argues that Fc receptor-mediated clearance via microglial-mediated phagocytosis is not necessary for the clearance of Aβ deposits. The degree of microglia activation caused by F(ab')2 antibodies was not reported.

Our group has also administered anti-Aβ antibodies directly to the CNS and found a biphasic response in the clearance of Aβ deposits following the injection [35]. We observed an initial phase within the first 24 h that is independent of microglial activation and clears primarily diffuse Aβ deposits, with no effects on deposits that are fibrillar (Thioflavin S positive). Microglia remain quiescent during this initial phase. Between 1 and 3 days there is a second phase of clearance associated with an activation of microglia in mice administered the anti-Aβ antibody injections (but not control antibodies) and a further removal of Aβ deposits including those that are labeled by Thioflavin S. One week following the injections, the area surrounding the injection has a greatly reduced amount of amyloid and the microglial reaction has resolved with markers of microglial-mediated phagocytosis no longer apparent. This suggests that the antibody and the microglial reaction has resolved with markers of microglial activation no longer apparent. This suggests that the antibody and the microglial reaction has resolved with markers of microglial-mediated phagocytosis is not necessary for the clearance of Aβ deposits. The degree of microglia activation caused by F(ab')2 antibodies was not reported.

Epitope specificity of anti-Aβ antibodies

In the development of vaccines, one important question regards the epitope on Aβ that is most responsible for the amyloid clearing effects. Our own work using the entire Aβ1–42 molecule as antigen, found that the bulk of antigenicity was localized to the amino terminal in competition assays with synthetic Aβ peptides [36]. While the bulk of immunogenicity towards Aβ1–42 was competed by Aβ1–16, Aβ10–20 had little capacity to compete for the antisera with the intact Aβ peptide. Peptides ranging from amino acids 20 to 40 were also ineffective, while the intact Aβ1–40 and Aβ1–42 fully competed with Aβ1–42 bound to the microtiter plate. Thus, the primary epitope appeared to reside within the first 10 amino acids when full length Aβ was used as antigen in a vaccine prepared according to the method of Schenk et al. [11]. This same conclusion was reached by McLaurin et al. [37] using methods different from those used by Dickey et al., yet again examining a vaccine preparation using the entire Aβ1–42 peptide as antigen. Bard et al. also found that monoclonal antibodies against the N-terminal portion of Aβ were the only ones effective in mediating the clearance of Aβ by microglia [12]. BAM-10, a monoclonal antibody found effective in reversing behavioral deficits also recognizes the N-terminal amino acids of Aβ [30]. Thus, for many purposes, it would appear that N-terminal antibodies are the most effective. However, it should be noted that DeMattos et al. found very effective passive immunization responses in transgenic mice using an antibody (m266) directed against the central domain of the Aβ peptide [25,38]. Whether this antibody activates CNS microglia, or is effective when administered into the brain is not yet known.

Alternative anti-Aβ vaccine strategies

There have been a number of reports indicating development of alternative vaccines to the one first described by Schenk et al. using Aβ1–42. Using a phage display of Aβ residues 3–6 as the antigen, Frenkel et al. showed that this was a very potent antigen and that antibodies generated in this manner were very effective in dissolving Aβ fibrils into monomers [39]. In response to concerns that the intact Aβ1–42 molecule may be toxic when administered to humans, Sigurdsson et al. [40] found that a modified Aβ1–30 peptide was a very good antigen and that vaccines using this peptide were effective in reducing Aβ loads in transgenic mouse brains. Another alternative vaccine was reported by Nicolau et al. using Aβ1–16 in a liposome-based vaccine to aide in breaking self-tolerance [41]. This vaccine was found to be effective in removing pancreatic Aβ deposits in the transgenic NORBA mouse model (TABLE 1).

Self-tolerance may be a significant issue in the development of vaccines against the Aβ peptide for use in humans. There are several polymorphisms between human and mouse Aβ, especially in the antigenic N-terminal portion of the molecule. We have found that APP+PS1 transgenic mice are less capable of mounting an antibody response against the Aβ1–42 vaccine than nontransgenic littermates when given 3–5 inoculations [23]. However, after nine inoculations this self-tolerance is overcome with all mice possessing very high titers against the human Aβ peptide. Das et al. in parallel noted that Aβ vaccines were less effective in mice already possessing substantial Aβ deposits [42].

In a detailed study, Monsonego et al. [43] found that the self-tolerance was primarily due to inadequate T-cell help and could be

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<tr>
<th>Investigator(s)</th>
<th>Immunogen</th>
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<tbody>
<tr>
<td>Schenk</td>
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<td>[11]</td>
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<td>Frenkel, Solomon</td>
<td>Aβ3–6; phage display</td>
<td>[39]</td>
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<tr>
<td>Weiner, Lemere</td>
<td>Aβ1–42; nasal mucosa</td>
<td>[50]</td>
</tr>
<tr>
<td>Sigurdsson, Wisniewski</td>
<td>K6Aβ1–30 NH₂</td>
<td>[40]</td>
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<td>Monsonego, Weiner</td>
<td>Aβ1–15 conjugated to BSA</td>
<td>[43]</td>
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<td>Nicolau</td>
<td>Palmitoylated Aβ1–16 in liposomes</td>
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<td>Lambert, Klein</td>
<td>Oligomeric Aβ</td>
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BSA: Bovine serum albumin
overcome by conjugating the Aβ peptide with bovine serum albumin as a hapten.

**Early phase clinical trials**

On the basis of the efficacy of the vaccine in the transgenic mouse models and *in vitro* and safety in multiple animal studies, Elan Pharmaceuticals, NY, USA teamed with Wyeth Laboratories, NJ, USA, to initiate clinical trials in humans. A Phase I study included close to 100 patients and found the vaccine was well-tolerated by all patients and that a subset developed an antibody response to the vaccine [44]. A Phase IIa study followed involving 375 patients (300 receiving treatment) in the early stages of Alzheimer’s disease. Within several months of beginning the trial, about 5% of the patients developed symptoms consistent with brain inflammation (meningoencephalitis). All inoculations were halted in January of 2002 and all patients exhibiting symptoms ultimately responded to therapy. At least 375 patients (300 receiving treatment) in the early phases of the study included close to 100 patients and found the vaccine was well-tolerated by all patients and that a subset developed an antibody response to the vaccine [44]. A Phase IIa study followed involving 375 patients (300 receiving treatment) in the early stages of Alzheimer’s disease.

In a very recent publication, it has been demonstrated that passive Aβ immunization can accelerate cerebral microhemorrhage in a transgenic mouse model that is already quite susceptible to this type of damage [47].

**Five-year view & expert opinion**

If there is to be additional testing of immunotherapy in Alzheimer patients, it is likely this will need to use passive immunization approaches. While admittedly expensive, the safety problems found in the Phase IIa trial will dictate some demonstration of efficacy before active immunization protocols are attempted again. The problem is that active immunization is difficult to regulate. First, the individual responses against vaccines are variable even in a young population. Our work has found that old mice are considerably less capable of mounting an antibody response against the Aβ vaccine than young mice. Indeed the experience in the clinical trial indicates considerable variability in the response [44,45]. Passive immunization permits careful titration of antibody dosage, avoiding any excessive responses that might cause adverse reactions and permitting a graded ramp up of dosage while monitoring patients for adverse events. A second problem with active immunization is termination of the response. Once the plunger goes down, the patient is on for the whole ride. If the endogenous amyloid starts to act as an antigen, the immune response could become excessive with no means of terminating the response. Passive immunization permits the antibody levels to drop over weeks after the injection, a condition not guaranteed with active immunization. A third issue regards cellular immune responses. It has been speculated that the problem with the subset of patients showing CNS inflammation was development of a T-cell response against the Aβ peptide [48]. Since the passive approach only provides antibody, this would preclude a cellular immune reaction. Alternatively, any vaccine that does not elicit a cellular immune reaction may also prove beneficial, if the cellular response is the problem in the patients with adverse events in the clinical trial.

In spite of these favorable considerations, the passive immunization approach is not without drawbacks. Such a therapy would involve frequent (monthly) injections with antibody. Humanized antibodies are particularly expensive to make when faced with GLP requirements and available production facilities are limited in their capacities. Another concern with monoclonal antibodies is that because they are all identical, any minor cross-reactivity may have considerable effects. A polyclonal antibody response, because it contains multiple clones, is unlikely to have as significant a cross-reactivity profile unless multiple clones share affinity for the inappropriate antigen.

A second important issue regards the mechanisms by which the antibodies act. There are three mechanisms presently being considered and these are not mutually exclusive. Evidence supporting all three approaches is available. The first involves a catalytic disaggregation of Aβ fibrils leading to monomeric Aβ and clearance form the brain. Evidence supporting this approach has been summarized by Solomon et al. [7]. A second mechanism is antibody-mediated phagocytosis and degradation of Aβ by activated microglia. Evidence supporting this mechanism has been summarized by Schenk [44]. A third mechanism doesn’t even require the antibodies to enter the brain but simply to bind Aβ in plasma (amyloid-sink hypothesis) altering the kinetics of Aβ flux into and out of the CNS [25]. Elucidating the relative contributions of these three mechanisms to the overall amyloid-lowering properties of Aβ vaccines in transgenic mice will be essential to designing rational modifications of the immunotherapeutic approach that are safe and effective. For example, were the amyloid-sink mechanism the dominant effect, then other agents that bind Aβ in plasma may be equally efficacious, without many of the concerns associated with vaccination or costs of passive immunization. One such approach has already shown preliminary promise, using a nonantibody-sequestering agent [49].

In conclusion, immunotherapy holds considerable promise as an amyloid-reducing therapy in Alzheimer’s disease. Work in mouse models show remarkable efficacy in reducing amyloid loads and restoring cognitive function. Once the dominant mechanism underlying these actions of immunotherapy are determined and alternative immunotherapeutic approaches designed which avoid the adverse events detected in a subset of patients, this approach will hold promise for modifying the course of this chronically debilitating disorder.
Key issues

- Antibodies against the Aβ peptide, the molecule which forms amyloid plaques in Alzheimer’s disease, appear effective in lowering the amyloid load in transgenic mouse models of the disease and overcoming memory deficits in these mice. This occurs with both active and passive immunization approaches. Recently, trials of active immunization were halted due to a small proportion of patients which developed central nervous system inflammation. A critical issue is to determine the relative contributions of antibodies, cellular immunity and, possibly, the adjuvant in these adverse reactions. Secondly, identifying unique characteristics of the sensitive patient population may also have merit to exclude this population from future trials. These steps will be important to guide further development of either passive immunization regimes, or revised vaccines which might lack the cellular immune response.

- A second question regards how immunotherapy acts to lower amyloid and improve memory. Three hypotheses, none mutually exclusive, have been proposed. One proposed mechanism suggests that the antibodies act to catalytically modify the Aβ conformation to one that is less prone to fibril formation. This would suggest that Aβ immunotherapy may even dissolve preformed fibrils. A second mechanism proposes that the antibodies opsonize the Aβ deposits, leading to degradation and removal of the material by phagocytes or other activated immune components. A third mechanism suggests that the antibodies act as a sink to pull Aβ into the circulation thereby reducing its content in the brain through modifying the equilibrium between these compartments. Resolving which of these mechanisms is most active in mouse brain and then verifying this in humans will be a critical step in the development of this therapeutic approach.

- Finally, the epitope specificity of anti-Aβ antibodies which are most effective will be a critical concern. Most antibodies developed with active immunization are directed against the N terminal amino acids of the Aβ peptide. Peptides with this epitope specificity have been found effective in mouse models. However, antibodies directed against central domains of the Aβ peptide have been effective in passive immunization protocols. Determining the optimal antibody specificity will be an important future issue.

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