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Immune Shaping and the Development of Alzheimer's Disease Vaccines

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Abstract

Given the emotional, social, and financial devastation wrought by Alzheimer's disease (AD), it is imperative that effective therapeutics be devised to ameliorate this presently incurable disorder. Vaccine-based approaches have been developed to target and eliminate amyloid-beta, a key peptide implicated in AD pathogenesis. Preclinical successes in AD mouse models created excitement and impetus for clinical application of an amyloid-beta based vaccine. Eliciting immune responses against a self-peptide, such as amyloid-beta, carries with it the potential to induce autoimmune and inflammatory conditions in the vaccinated individual, a caveat borne out in multiple patients enrolled as part of a recent clinical trial. These clinical adverse events seemingly overshadowed interesting behavioral stabilization and alterations of amyloid-beta burden in these and other vaccinated patients, thus speaking to the potential of immunotherapy for AD. Understanding the mechanisms by which vaccines reduce amyloid-beta burden in AD brain and the types of immune responses raised, as well as developing new modalities of vaccine delivery that facilitate the modulation of elicited immune responses, will undoubtedly lead to a new generation of efficacious amyloid-beta immunotherapeutics with improved safety profiles.

Keywords

Alzheimer's disease; amyloid beta; vaccine; immune shaping; gene transfer; viral vector

Introduction

As age is the greatest risk for **Alzheimer's disease**

<http://sageke.sciencemag.org/cgi/content/full/2001/1/dn2> (AD), it is anticipated that its prevalence will grow over the next four decades to become the number one cause of death in North America (see **Trojanowski Perspective**

<http://sageke.sciencemag.org/cgi/content/full/2005/17/pe11>). The economic burden attending this scourge will also grow to unprecedented levels. These considerations compel a systematic societal effort to identify the means to attenuate the emergence of and to slow the natural history of AD.

Late onset AD, the most common form, is not diagnosed pre-clinically and at the time of its presentation it is likely that the patient has already suffered extensive synaptic dysfunction and loss. This problem makes evident the need for improved diagnostic methods to detect disease earlier as well as therapeutic interventions that are synapse sparing. Work in many laboratories is devoted to achieving these important goals (see, for example, **Reddy Perspective** <http://sageke.sciencemag.org/cgi/content/abstract/2005/18/pe12>, **Geerts Perspective** <http://sageke.sciencemag.org/cgi/content/full/2005/6/pe4>, **Saito Perspective**

<http://sageke.sciencemag.org/cgi/content/full/2003/3/pe1>, and **“Plaques Aglow”** <http://sageke.sciencemag.org/cgi/content/full/2003/39/nw135>).

One of the central pathophysiological features of AD is the excessive accumulation of amyloid beta ($A\beta_{1-42}$), a 42-amino acid peptide, in extracellular senile plaques (see **“Detangling Alzheimer’s Disease”** <http://sageke.sciencemag.org/cgi/content/full/2003/43/oa2>). Multiple strategies are directed against the production of $A\beta$, notably small molecule inhibitors of the two enzymes, β and γ -secretases <http://sageke.sciencemag.org/cgi/content/full/2003/11/pe7>, which are responsible for liberating the toxic $A\beta$ peptide from its transmembrane substrate, the **amyloid precursor protein** [http://sageke.sciencemag.org/cgi/genedata/sagekeGdbGene; 197](http://sageke.sciencemag.org/cgi/genedata/sagekeGdbGene;197) (APP). Among its disease promoting properties, $A\beta$ induces inflammation, a state that persists throughout the disease course. This chronic inflammation is defined by activated microglia, reactive astrocytosis, complement activation, and elaboration of pro-inflammatory cytokines (see **McGeer Review** <http://sageke.sciencemag.org/cgi/content/full/2002/29/re3>). Efforts to attenuate the inflammation once AD has been diagnosed have proven unsuccessful, leaving open the possibility that presymptomatic blockade may be required to have an impact on disease emergence.

Vaccination Against AD

The landmark observation that $A\beta$ -directed vaccination of a mouse model of AD could prevent disease occurrence triggered a wave of interest in understanding the underlying immunological mechanism(s) (Fig. 1A) (1-3). In general, any substance that is capable of generating an immune response is termed an immunogen, while an antigen represents a substance that can be bound by antibody. Not all antigens are effective immunogens. In mouse models of AD and in humans, $A\beta$ peptide is a self-peptide that is not sufficiently immunogenic on its own, and thus this type of vaccination requires the co-administration with a substance termed an “adjuvant” to boost the immune response. Adjuvants can consist of a mixture of immunogenic substances or could be composed of a single gene product (termed ‘molecular adjuvant’). Co-delivery of $A\beta$ with a potent adjuvant leads to uptake by antigen presenting cells (APCs) such as dendritic cells that process the antigen and adjuvant via the major histocompatibility complex II (MHC II) pathway leading to the expression of proteins (cytokines and chemokines) that promote the proliferation and attraction of T cells. Depending upon the profile of cytokines and chemokines that are expressed as a result of APC and T-cell engagement, the adaptive immune response can proceed via T-cell helper 1 (T_H1)- or T helper 2 (T_H2)-dependent pathways. Immune responses driven by T_H1 T-cells (dependent upon interferon- γ (IFN- γ) and interleukin-1 (IL1) cytokines) lead to activation of B cells that express antibodies (humoral response) of the IgG2b (or related) isotype, but T_H1 T cells can also activate cellular responses that lead to activation of $A\beta$ -specific cytotoxic T-lymphocytes (CTL). Such responses are inherently more inflammatory, and are therefore unwanted activities for an AD vaccine. T-cell helper 2 (T_H2)-dependent responses (IL-4 and IL-10 cytokine-driven) are believed to be the safest for derivation of an $A\beta$ -specific immune response in the setting of an AD-afflicted individual. T_H2 -dependent pathways drive $A\beta$ -specific humoral responses that produce antibodies from isotype classes (IgG1 or similar) that are not as likely to participate in inflammatory reactions (see **“Immunity Challenge”** <http://sageke.sciencemag.org/cgi/content/full/2003/23/oa1> and **“Wollscheid-Lengeling Perspective”** <http://sageke.sciencemag.org/cgi/content/full/2004/1/pe2> for further discussion of the immune system).

Two schools of thought regarding the mode of action of the $A\beta$ peptide vaccine, each with supporting data, have evolved. The first holds that a humoral response characterized by production of anti- $A\beta$ antibodies promotes the egress of the toxic peptide from the brain to the vascular compartment where it is bound by antibody and eliminated peripherally (4). The

second posits that microglia interact with A β -specific antibodies in the brain via recognition of the Fc portion of the antibody, leading to phagocytosis and eventual clearance of A β (5). These are not mutually exclusive mechanisms and may operate in concert following A β vaccination.

On the strength of robust preclinical data Elan Pharmaceuticals http://www.elan.com/research_development/alzheimers/clinicaltrialinfo.asp commenced clinical trials to evaluate A β ₁₋₄₂ peptide vaccination in mild to moderate AD patients. Because adverse events were not observed in an initial Phase I trial, the company initiated a larger Phase IIa trial. During the vaccination of 300 patients, approximately 5% (18) of subjects developed an aseptic meningoencephalitis (inflammation of the brain and its surrounding membranes in the absence of a pathogenic microorganism); this result compelled termination of the trial [reviewed in (6)]. There was no correlation between elicited A β antibody responses or titers and the development of meningoencephalitis (7,8). Whereas some patients recovered, others remained compromised. Several such patients have come to post-mortem examination during which brain analysis revealed patchy clearance of A β deposits, infiltration of T cells, and evidence of exacerbated inflammation (9).

The adverse events associated with this trial were unexpected and unfortunate. However, analysis of a subset of the Phase IIa vaccinated subjects suggested that those in whom an antibody response included reactivity against senile plaque-associated aggregated A β exhibited an attenuation of disease progression (10). This observation among others portends the therapeutic utility of AD vaccination but underscore the associated challenges (see McGeer Perspective <http://sageke.sciencemag.org/cgi/content/full/2004/27/pe29>). Succinctly, the question becomes: Can vaccines be developed that protect against A β toxicity without promoting or exacerbating underlying brain inflammation?

Development of a Safer Vaccine

Work in several fields impinges on the development of a safer vaccine strategy: (i) determining the types of immune responses that are elicited in response to different forms of A β vaccination, (ii) developing animal models that are reflective of human AD to test vaccine responses, and (iii) understanding the role of immune shaping in these responses. We discuss each of these issues in more detail below.

Mode of antigen delivery

Most AD vaccine studies, including the human clinical trials, have employed peptide-based means for immunization. This approach involves prior formation of higher-order A β aggregates (termed 'fibrils') and co-delivery with a potent adjuvant. Pre-formed fibrillar A β is believed, in the immunogenic sense, to better mimic the pathogenic form of A β found in plaques in AD brain than use of soluble monomeric A β . Resultant immune responses from peptide-based vaccination can be somewhat modulated through the use of different segments (epitopes) of A β and by varying adjuvants. Newer vaccine approaches have sought to exploit gene transfer to engender more controlled immune responses. Genetic sequences encoding A β and molecular adjuvants (DNA sequences that code for immunostimulatory gene products) can be delivered to antigen presenting cells by two broad classes of vectors: viral and non-viral. Viral vectors exploit the evolutionary achievements of viruses to propagate, package and transfer genetic material from cell to cell and organism to organism. Via genetic modification of mammalian viruses, it is possible to specifically target gene expression in desired cellular populations. Adeno-associated virus (AAV) and Herpes simplex virus (HSV)-based vectors have been tested as immunotherapeutics in mouse models of AD (described in more detail below). AAV vectors exhibit above-average safety profiles and express transgenes essentially lifelong, but have a small transgene size capacity (<4.5 kb). HSV vectors, especially those of

the amplicon type, have been shown to efficiently transduce dendritic cells, induce strong transgene-specific immune responses, and carry transgene segments up to 130 kb in size. Non-viral or plasmid DNA-based vaccination are less efficient in delivering the gene encoding an A β antigen *in vivo*, but could be employed to prime the adaptive immune response when combined with another of the vaccination modalities.

Animal models

A β vaccination has been extensively evaluated in mice, in both models of AD (transgenic animals that produce variant forms of APP) and non-transgenic strains. In non-transgenic mice in which A β is a foreign protein, vaccination can elicit different immune responses that are dependent on (i) adjuvant composition, (ii) route of vaccine administration (e.g., intradermal, intraperitoneal, subcutaneous, intranasal, or intramuscular), and (iii) mode of antigen delivery. In addition, the genetic background of the mouse strain also affects the nature of the immune response to vaccination. In only one case out of nearly 100 reports did investigators observe encephalitis in C57BL/6 mice. This occurred when the mice were vaccinated with A β peptide plus the adjuvant pertussis toxin, which is known to promote autoimmunity (11). This vaccination paradigm may thus serve as an informative mouse model in which to study A β -vaccine mediated brain inflammation and encephalitis.

Numerous investigators have evaluated A β vaccine efficacy in mouse models of AD. All such models harbor and express a familial AD APP mutant transgene that results in the accumulation of excess human amyloid in the brain. Most strains do not recapitulate the varied pathologies, such as chronic inflammation, seen in the human AD brain. In these mice, the transgenically expressed human A β is a self-peptide (that is, a peptide produced by the organism itself) to which tolerance must be broken to elicit an immune response. Immune tolerance refers to the failure of an organism, including humans, to make an immune response to an antigen to which it has been exposed early in life. A β -based vaccine assessments using a recently developed AD mouse model that harbors genes encoding variant forms of human APP, **presenilin 1** <http://sageke.sciencemag.org/cgi/genedata/sagekeGdbGene;198> (a component of the γ -secretase complex), and the microtubule binding protein **tau** <http://sageke.sciencemag.org/cgi/genedata/sagekeGdbGene;282> [**3 $\times$ Tg-AD** [http://sageke.sciencemag.org/cgi/content/full/2003/32/tg7; \(12\)](http://sageke.sciencemag.org/cgi/content/full/2003/32/tg7; (12))], have yet to be reported.

Multiple vaccination approaches ranging from peptide only to DNA and virus or virus-like particles have proven effective in breaking tolerance to transgenic A β and conferring either protection against and/or reduction of accumulated brain amyloid [reviewed by (13)]. In one instance the use of an HSV amplicon A β vaccine resulted in a marked increase in brain inflammation in the AD model **Tg2576** <http://sageke.sciencemag.org/cgi/content/full/2004/5/tg1> (14). This robust upregulation of a number of pro-inflammatory cytokines occurred after several vaccinations. More relevant to the vaccine safety profile issue was the mortality of greater than 50% of the herpes amplicon A β vaccinated Tg2576 mice. Given the limited number of observations demonstrating A β vaccine-elicited inflammatory effects in AD mouse models, it seems imperative that AD immunotherapeutics be assessed in models that more closely mimic the immune system of an elderly individual. In this regard, aged non-human primates may represent more optimal candidates for assessing vaccine safety profiles relating to untoward brain inflammatory responses.

Immune shaping

Immune shaping has become a goal of vaccine strategies. Elaboration of an immune response is characterized by a blending of two types of T cell responses: T_H1 and T_H2. The intent is to direct a skewed response towards one or the other. T_H1 responses are associated with the

elaboration of the cytokines interferon- γ (IFN- γ) and interleukin-1 (IL1) and a cell-mediated immune response. T_H2 responses are accompanied by a different cytokine profile, usually by increases in the concentrations of IL4 and IL10. This latter profile favors a humoral immune response. In the setting of neuroinflammation it would be desirable to promote a T_H2-biased response whereby an advantageous IgG1 antibody response is elicited. Several issues are pertinent to this strategy. Selection of the A β epitopes that strongly elicit a B-cell response, for example, one encompassing amino acids 1-15, may enhance humoral efficacy (Fig. 1B) (15). Similarly, fusion of A β sequences to chimeric peptides that engender strong T-cell help can also augment the elicitation of a robust antibody response. Examples of the latter are the “C” fragment of tetanus toxin (Tt $\times$ FC) (14) and the synthetic Pro-Ala-Asp-Arg-Glu sequence (Fig. 1C) (15). In one study the A β peptide was fused to the “C” fragment (A β /Tt $\times$ FC) and delivered with a herpes amplicon platform in the Tg2576 AD mouse model (14). By contrast to the morbidity and mortality seen with the A β herpes vaccine described above, the vaccination with the herpes amplicon expressing A β -Tt $\times$ FC chimera elicited no adverse outcomes, induced the elaboration of A β -specific IgG1 isotypic antibodies, and significantly attenuated A β accumulation, a measure of vaccine efficacy. These studies highlight the utility of the vaccine platform, like the herpes amplicon, that affords experimental control of antigen type, levels of expression, modulation with co-delivered immune modulating proteins, and efficient transfer to antigen presenting dendritic cells (Fig. 1D).

Previous studies have shown that A β peptides undergo spontaneous conversion in vitro from soluble monomeric forms to less well-characterized intermediates, referred to as A β -derived diffusible ligands (ADDLs) (16), to protofibrillar forms, and finally to insoluble fibril conformations. Mid-level oligomeric A β forms/ADDLs alter the normal physiology of neuronal cells, often leading to neuronal dysfunction and death (17) (see, for example, [Lashuel Perspective](http://sageke.sciencemag.org/cgi/content/full/2005/38/pe28) <http://sageke.sciencemag.org/cgi/content/full/2005/38/pe28>). Delivery of mutant A β forms known to more rapidly adopt oligomeric structures and thus achieve the pathogenic protein conformation may result in enhanced vaccine efficacy. Antibodies can be generated specifically against soluble oligomeric A β (18). These polyclonal antibodies not only recognize and neutralize the toxicity of ADDLs but also neutralize soluble oligomers of **prion** <http://sageke.sciencemag.org/cgi/content/full/2005/43/pe32> protein and **α -synuclein** <http://sageke.sciencemag.org/cgi/genedata/sagekeGdbGene;193>, indicating the existence of a shared structural epitope(s) among these pathogenic proteins. Antigenic conformation is also crucial for the elicitation of T_H1-mediated responses, as iteratively modifying the structure of a vaccine antigen has been demonstrated to influence resultant T-cell responses significantly (19).

Characterization of patient population

Another important consideration in the evolution of a safe AD vaccine should include efforts to characterize the patient population to be vaccinated. Aged individuals exhibit progressive alterations in humoral and cellular immunity that lead to reduced vaccine responses and increased generation of auto-antibodies. In fact, recent data indicate that a fraction of AD patients harbor A β -reactive T cells and systemic markers consistent with inflammation (20). Moreover, deficiencies in immunoglobulin class switching have also been demonstrated in the elderly, which results in diminished maturation of vaccine-elicited humoral responses to secondary isotypes [reviewed by (21)]. The question regarding implementation of an AD vaccine then becomes: Does the intended cohort have AD, mild cognitive impairment, central nervous system or systemic inflammation, and/or age-related immunological alterations? As some of these variables can be evaluated, their inclusion in future AD trial design may be warranted. Although immunological profiling may prove impractical in the context of a large-scale clinical trial, such an approach could be possibly streamlined for larger study designs.

Conclusion

The graying of our population and the growth of AD prevalence underscore the vital nature of discovering disease-modifying therapeutics for this scourge. The potential for vaccination of at-risk individuals remains a promising approach but concerns of exacerbating underlying brain inflammation and aggravating disease progression compel the derivation of safer vaccines. Through use of vaccine platforms that support immune shaping it is possible to identify optimal antigens to elicit the most protective responses. Near term research must focus on the systematic evaluation of parameters and testing in animal models of AD where brain inflammation is present. The successful maturation of these vaccines from pre-clinical studies to clinical trials warrants examination in the context of differences in patient immune status to A β and the propensity for worsening brain inflammation. Adherence to such a step-wise and deliberate process may portend the arrival of a truly new therapeutic.

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Fig. 1.

Schematic representation of Aβ-based immunotherapeutic approaches for Alzheimer's disease with predicted immune responses and clinical outcomes. **(A)** The initial Aβ₁₋₄₂ peptide-based vaccine approach for AD involved the pre-fibrillarization of Aβ and co-administration of a potent adjuvant. Newer modalities have targeted oligomeric Aβ structures. In AD mouse models these approaches resulted in (i) engagement of the TH2 arm of the immune response, (ii) elicitation of anti-Aβ antibodies primarily of the IgG1 isotype, (iii) prevention of and/or dissolution of amyloid plaque-like deposits in the brain, and (iv) correlative improvement of learning/memory behaviors. Translation of this vaccine approach to Phase I clinical trials resulted in a subset of immunized patients developing encephalitic symptoms likely due to the elicitation of TH1-like responses that ultimately led to robust cellular infiltration and inflammatory conditions within the brains of these individuals. **(B)** A subsequent vaccine approach employed a characterized B-cell epitope that encompassed amino acids 1-15 of Aβ in combination with potent TH2 adjuvants. In AD mouse models, this approach led to the

elaboration of potent anti-A β humoral responses and functional improvement. **(C)** Other studies have used A β in the context of fused molecular adjuvants such as Tt $\times$ FC to induce skewed T_H2-like responses to the A β antigen. **(D)** More recent iterations of AD vaccines point to the utility of DNA plasmid- and viral vector-based vaccines, which provide the means to co-express immunomodulatory cytokines such as IL-4 along with A β epitopes to expand the pool of T_H2 T-cells that participate in anti-A β immune responses. This approach, in theory, would subsequently lead to elaboration of humoral responses that are overwhelmingly skewed toward T_H2-related antibody isotypes that are believed to be efficacious but inherently less inflammatory. TCR, T-cell receptor; MHC, major histocompatibility complex; TNF- β , tumor necrosis factor-beta; NK cell, Natural killer cell.