Alzheimer's & Dementia 11 (2015) 1246-1259

Perspective

A fresh perspective from immunologists and vaccine researchers: Active vaccination strategies to prevent and reverse Alzheimer's disease

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Abstract Traditional vaccination against infectious diseases relies on generation of cellular and humoral immune responses that act to protect the host from overt disease even though they do not induce sterilizing immunity. More recently, attempts have been made with mixed success to generate therapeutic vaccines against a wide range of noninfectious diseases including neurodegenerative disorders. After the exciting first report of successful vaccine prevention of progression of an Alzheimer's disease (AD) animal model in 1999, various epitope-based vaccines targeting amyloid beta (Aβ) have proceeded to human clinical trials, with varied results. More recently, AD vaccines based on tau protein have advanced into clinical testing too. This review seeks to put perspective to the mixed results obtained so far in clinical trials of AD vaccines and discusses the many pitfalls and misconceptions encountered on the path to a successful AD vaccine, including better standardization of immunologic efficacy measures of antibodies, immunogenicity of platform/carrier and adjuvants.

Keywords: Vaccine; Alzheimer's disease; β-amyloid; Tau protein; B cell epitope; Th cell epitope; Antibody titers; Clinical trials

1. Conventional and unconventional vaccines

The history of vaccination began in 1798 when Edward Jenner published his study showing that a person previously infected by cowpox (the Latin root "*vaccinus*" meaning "from the cow") was protected from smallpox and, moreover, deliberate infection with cowpox could protect against smallpox too [1,2]. Eighty years later Louis Pasteur used a similar strategy based on attenuated bacteria to fight chicken cholera (anthrax bacteria) [2].

Today, we have two categories of conventional vaccines: "attenuated live vaccines" and "inactivated or subunit vaccines." Attenuated live vaccines stimulate strong cellular and humoral (antibody) immunity but have the disadvantage being "live," thereby running the risk of causing serious infection in immunosuppressed individuals. They are also less stable than inactivated or subunit vaccines. Inactivated or recombinant vaccines are more stable and safe, but often at the price of reduced immunogenicity. To compensate for this reduced immunogenicity, they are formulated with immune-boosting compounds called adjuvants [3].

The major goal of conventional vaccines is to generate protective immunity, thereby protecting against overt clinical disease, even if not sterilizing. Different types of immune cells are involved in generation of such protective immunity. Normally, after administration of vaccines, professional antigen-presenting cells engulf, process, and present vaccine-derived peptides through their major histocompatibility complex (MHC) class I and II molecules. Subsequently, $CD8^+$ and $CD4^+$ T cells are activated when their antigen receptors (Th cell receptor) bind these peptides presented by MHC class I and II molecules, respectively. The $CD4^+$ T cells become T helper (Th) cells that assist

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http://dx.doi.org/10.1016/j.jalz.2015.06.1884

B-cell to produce antibodies and CD8 T-cell to differentiate into cytotoxic T lymphocytes. However, first B cells must receive an activating signal via cross-linking of their B-cell receptors (BCR) by the relevant antigen. B cells internalize and present the processed antigen via their MHC class II to Th cells (so called antigenic bridge), thereby obtaining the second signal which they need to start producing antigen-specific antibodies.

Although conventional vaccines target foreign antigens expressed by infectious organisms, it is now recognized that the same basic process can be used to generate immune responses against either self-antigens, such as expressed for instance by cancer cells, or against completely synthetic antigens such as nicotine or cocaine. This has led to the field of "unconventional vaccines." Thus, vaccines are no longer restricted to infectious disease applications, but potentially can be applied to treatment of a wide range of chronic diseases that include cancer, allergy, asthma, diabetes mellitus, autoimmunity, atherosclerosis, obesity, drug addiction, and degenerative neurologic diseases [4]. These vaccines work by stimulating neutralizing antibodies, or in some cases T cells, against relevant self- or nonself-molecules. Currently, the vast majority of approved vaccines are conventional [5–8]. Only two therapeutic vaccines (one conventional and one nonconventional) have been approved by food and drug administration so far. More specifically, a conventional varicella zoster vaccine is used for treatment of herpes zoster in infected adults [9]. In addition, sipuleucel-T is an approved therapeutic vaccine for advanced prostate cancer that targets the self-antigen, prostatic acid phosphatase and increases the median survival time by up to 4.5 months [10].

The generation of effective and safe therapeutic vaccines (both conventional and unconventional) is not simple and requires knowledge of the mechanism(s) involved in activation and inhibition of cellular and humoral immune responses. As an alternative, passive vaccination strategies with humanized or fully human monoclonal antibodies (Mabs) are widely used, for example, in therapy of cancers, pneumonia due to respiratory syncytial virus, psoriasis, multiple sclerosis, with over 40 Mab-based immunotherapeutics on the market or under review in the United States and European Union [11], with many additional Mabs in phase II–III trials [12]. Other therapeutic approaches include adoptive cell transfer (ACT), where *ex vivo* activated/engineered and expanded clones of antigen-specific T cells are used for therapy of infections or cancer. However, passive administration of Mab and/or immune T cells is unlikely to be applicable to people not yet suffering from a disease even if at increased risk, because of the inconvenience, as passive vaccination generally provides only short-lived effects, thereby requiring regular injections as frequently as monthly in some cases. In addition, administrations of high concentrations of Mab (3–10 mg/kg), or large numbers of immune T cells in the case of ACT, can have serious side effects including hypertension, nausea, vomiting, diarrhea, bleeding, blood clotting, and organ damage. In addition, these remedies are extremely expensive, the cost of treatment with Mab being more than $150,000 and cost of ACT potentially ~10 times higher again. We believe that, if safe and effective, an active immunization approach could potentially overcome many of these obstacles.

2. Active vaccines for Alzheimer's disease

To develop successful immunotherapeutic interventions for Alzheimer's disease (AD), it is first necessary to identify the molecules that are the key drivers of AD development and that can then be targeted by immune therapy. For more than 2 decades, amyloid beta (Aβ) peptides have been thought central to the onset and progression of AD, through the "amyloid cascade hypothesis". This hypothesis suggests that toxic forms of Aβ (oligomers and fibrils) are associated with synaptic failure and neuronal death and initiate AD pathology [13–16]. Support for this hypothesis was spurred by the identification of mutations in amyloid precursor protein (APP) in patients with AD [17] and also by development of AD-like pathology in mouse models overexpressing APP [18,19]. Based on these findings, therapeutic strategies have been directed to reducing the level of Aβ in the brain and/or blocking the assembly of Aβ peptides into pathologic forms that disrupt cognitive function [20–22]. The seminal report of Schenk et al. [23,24] demonstrated that active immunization of APP transgenic (APP/Tg) mice with fibrillar $A\beta_{42}$ antigen induced antibodies specific to Aβ and prevented the development of AD-like pathology in older animals. In addition, when older mice with preexisting Aβ plaques were immunized with $A\beta_{42}$, they were able to clear the Aβ deposits from the brain [23–25]. Active immunization with $A\beta_{42}$ protected APP/Tg mice from developing functional memory deficits [25–27], and passive administration of anti-Aβ monoclonal antibodies to APP/Tg mice reduced Aβ levels in the brain [28,29] and reversed memory deficits [30,31]. Two possible mechanisms for antibody-mediated clearance of Aβ have been suggested: "Aβ clearance by entry of anti-Aβ antibodies into the central nervous system (CNS)" [23,28,32–38] and "Aβ clearance by a peripheral sink whereby reduced systemic levels of Aβ result in increased transport of Aβ out of the CNS" [29,39–42]. Regardless of the exact mechanism of action, such immunotherapeutic strategies have displayed strong disease-modulating effects in animal models of AD, leading to attempts by industry to use active or passive anti-Aβ immunotherapy strategies in AD clinical trials [42–49]. Although these trials have had mixed results, recent excitement has been generated by early results from a BIIB037 phase I trial using a natural human Aβ Mab (aducanumab) cloned from a healthy human subject that recognized the disease-causing fibrillar form of Aβ [50,51]. Hence, this recent trial provides strong support for the ongoing use of Aβ as a therapeutic target, but in