

## Mini Review

# Development of Alzheimer's Disease Vaccines: a Perspective

Marciani DJ\*

Qantu Therapeutics, USA

\***Corresponding author:** Marciani DJ, Qantu Therapeutics, Inc. 612 E Main Street, Lewisville, TX 75057, USA

**Received:** August 21, 2014; **Accepted:** September 08, 2014; **Published:** September 09, 2014

**Abstract**

Like infectious disease vaccines, effective Alzheimer's disease vaccines should elicit an antibody response similar to the natural autoantibodies found in serum and preparations of intravenous immunoglobulins, which recognize an array of amyloid- $\beta$  conformations. An immune response that is the result of a progressive formation over time of antibodies against toxic amyloid- $\beta$  conformations and that different from most vaccines under development, would require the whole protein as an antigen, including both B and T-cell epitopes. However, due to the presence of amyloid- $\beta$  T-cell epitopes and the fact that such a protein is a Th1 immune modulator, safe and effective vaccines, besides eliciting Th2 immunity, should inhibit but not abolish Th1 immunity, which is needed for protection against pathogens; a strategy that would apply to other potential Alzheimer's disease vaccine antigens, e.g. tau. Due to immunosenescence, these vaccines would be more effective for preventive rather than therapeutic purposes, as younger individuals produce a better immune response. Recently developed novel adjuvants that most probably act at the dendritic cell level and that can deliver such a selective Th2 immune modulation while inhibiting Th1 immunity, would be crucial for the development of these proposed vaccines.

**Keywords:** Alzheimer vaccine; Amyloid-beta; Intravenous immunoglobulin; Immunotherapy

**Abbreviations**

AD: Alzheimer's disease; A $\beta$ : Amyloid- $\beta$ ; A $\beta_{42}$ : Whole A $\beta$ ; DC: Dendritic Cell; Nabs: Natural Antibodies; IVIG: Pooled Immunoglobulins; mAb: Monoclonal Antibodies

**Introduction**

Due to the high prevalence of Alzheimer's disease (AD), 5.2 million cases in the US alone, which is expected to triple by the year 2050 to 16 million, it is apparent that an active immunization or vaccination to prevent and/or treat this disease would be the most effective way to manage it. Significant evidence supports the role of circulating antibodies against amyloid- $\beta$  (A $\beta$ ) in preventing and/or reducing toxic extracellular A $\beta$  oligomers, the main cause of AD [1-3]. Indeed, Schenk et al. showed that vaccination of a transgenic mouse model for AD with whole A $\beta$  (A $\beta_{42}$ ) and the Th1 adjuvant QS-21, prevented plaque formation and attenuated behavioral deficits [4,5]. However, clinical studies with a similar vaccine, AN-1792, resulted in serious side effects and some deaths, caused by a damaging Th1 inflammatory immune response elicited by the A $\beta_{42}$ 's T-cell epitopes plus QS-21 [6,7]. Hence, to prevent a harmful Th1 immunity, later AD vaccines contained truncated A $\beta$  antigens without T-cell epitopes, usually combined with Th1 adjuvants, a strategy that has yielded disappointing results in clinical studies (<http://www.clinicaltrials.gov>) [8-11]. While it was assumed that truncated A $\beta$  with Th1 adjuvants elicits a safe immune response, these adjuvants induce a systemic Th1 immune response that could affect microglia, magnifying the neuroinflammation linked to AD [12-15]. This situation may also occur also with other likely antigens for AD vaccines, as with the tau

protein, where the whole protein or some of its peptides with Th1 adjuvants may trigger a damaging inflammatory response [16,17]. Hence, there is a need to reassess the current AD vaccine paradigm and consider new approaches to its development.

Different from infectious disease vaccines where the number of Th1 adjuvants is large, vaccines against neurodegenerative proteinopathies, like AD, have a negligible selection of adjuvants that stimulate solely Th2 immunity, alum being the most common [18]. Still, that alum does not elicit an effective immunity in the elderly, as shown by the age-associated decrease in the efficacy of the flu and other vaccines [19] and have cumulative neurotoxicity [20], would preclude its use in AD vaccines. That certain bacterial toxins are "conditional" Th2 adjuvants, i.e. the stimulated immunity would depend on the age and mode of administration among other factors, adds an element of risk when used in large populations; for example, cholera toxin elicits Th2 immunity in young animals, but induces Th1 immunity in older ones [21], as well as a Th17 immune response [22]. The recent reports that some well-defined helminth glycans and plant-derived glycosides elicit Th2-only immunity [18,23], despite the absence or presence of T-cell epitopes, offer a new approach to develop safe and effective AD vaccines. Access to adjuvants that stimulate Th2 but inhibit Th1 immunity would allow the use of whole proteins, e.g. A $\beta_{42}$  and tau; antigens that are not used because of the damaging inflammatory immune response caused by their T-cell epitopes. Significantly, since A $\beta_{42}$  has an intrinsic Th1 immune modulatory activity [24,25], the use of adjuvants that inhibit Th1 immunity will be essential with this antigen.

Truncated A $\beta$  antigens lacking T-cell epitopes and representing 25 to 36% of the whole protein [8-11], i.e. the B cell epitopes within the first 15 amino acids, while safer do not allow i) the formation of conformational epitopes [26-29] and production of antibodies against those epitopes that may be important for A $\beta$ <sub>42</sub> disaggregation, and ii) the potential cooperativity between antibodies recognizing different epitopes [30]. Indeed, the epitopes targeted by most natural anti-A $\beta$  antibodies (Nabs) include the T-cell epitopes' sequences [31,32], which for safety are absent in truncated A $\beta$  [1-3]. This diversity of epitopes support the fact that A $\beta$ <sub>42</sub> is not a "static" structure, but a dynamic one with conformations and oligomerization states that change with time and progression of the disease, a condition that is shown by the presence of Nabs targeting diverse A $\beta$ <sub>42</sub> conformations [27,33,34]. Hence, it is improbable that truncated A $\beta$  would deliver the broad selection of Nabs elicited by the polymorphic A $\beta$ <sub>42</sub>, some of which may play a role in the elimination of this protein's toxic forms. Although, the evidence implies that various Nabs are conformation-dependent and sequence-independent [26-29,35,36], it is obvious that the A $\beta$ <sub>42</sub> primary structure, including T and B-cell epitopes, is driving this protein's folding and oligomerization, leading to formation of the conformational epitopes needed to stimulate production of conformation-dependent Nabs. An advantage of Nabs is that they can recognize "toxic" conformations of other proteins capable of forming amyloids [35,36]. However, that the conformation dependent antibodies induced by aggregated A $\beta$ <sub>42</sub> apparently bind better to amyloids from this protein than other proteins, upholds the use of this protein as a vaccine antigen [35]; an observation that can be extended to other proteins forming amyloids. Yet, the stimulation of Nabs production cannot be attained with Th1 adjuvants without generating damaging pro-inflammatory responses, notwithstanding that A $\beta$ <sub>42</sub> alone seems to be an effective Th1 immunity inducer [24,25,37,38]; hindrances that can be prevented by using adjuvants that solely stimulate Th2 while inhibiting Th1 immunity [18,23].

Although clinical evaluations of passive immunotherapy with pooled immunoglobulins from healthy donors (IVIG) containing various Nabs have not met the studies' primary outcome objectives, pre-clinical and clinical studies have shown some immune modulatory properties relevant to the treatment of neurodegenerative disorders [39-42]. Indeed, it has been shown that previous treatment with IVIG reduces the risk of AD by 42% [43]. While polyclonal IVIG preparations meet some standardization requirements due to the heterogeneity of their source and processing, they differ in their distribution of antibody's isotypes, and their binding to different regions of A $\beta$ <sub>42</sub> and tau [44-47]. For example, IgM antibodies that catalyze the degradation of A $\beta$ <sub>42</sub> and presumably tau, preventing their aggregation and toxicity, are inactivated during IVIG preparation; a situation that results in preparations containing different levels of specific antibodies [45,48-50]. Screening of IVIG preparations has shown that Nabs target the A $\beta$ <sub>42</sub> region between residues 28-40 where the T cell epitopes are located, as well as pathogenic conformation; but poorly recognize the N-terminal fragment, which is the basis for most of the AD vaccines under development [31,32]. Yet, immunization with A $\beta$ <sub>42</sub> in the AN-1792 vaccine study mainly yielded antibodies against the N-terminal region [8,51]; however, the damaging pro-inflammatory response induced by this vaccine [6] and the increase in Th1 cytokines in mice immunized with A $\beta$ <sub>42</sub>

without an adjuvant [24,25], indicate that the A $\beta$ <sub>28-40</sub> peptide region has an intrinsic Th1 immune modulatory activity. In effect it has been shown that Dendritic Cells (DCs) generated *in vitro* in the presence of A $\beta$ <sub>42</sub> show an increase in the production of inflammatory molecules [52], which would aggravate AD. Thus, because of the likelihood that the A $\beta$  regions containing T cell epitopes would induce Th1 inflammatory responses, even without adjuvants, the use of A $\beta$ <sub>42</sub> as an antigen would require vaccine formulations that prevent Th1 immunity while stimulating antibodies' production.

The fact that Nabs target various A $\beta$ <sub>42</sub> epitopes suggests cooperative effects between different antibodies, where binding of a Nab causes A $\beta$ <sub>42</sub> conformational changes that allow binding of other antibodies [30], a process that may facilitate the disaggregation and degradation of the protein, which may also be extended to antigens like tau. The fact that two anti-A $\beta$  monoclonal antibodies (mAbs), solanezumab that binds to the central region, and crenezumab a conformational antibody, failed to recognize A $\beta$  in human brain tissue, has been explained as result of the mAbs' lack of specificity [53]. Another explanation may be that some mAbs require other antibodies to exert their action via cooperative effects. Nevertheless, IVIG studies strengthen the notion that the production of an effective, protective array of Nabs requires A $\beta$ <sub>42</sub> rather than its fragments, to obtain antibodies against both linear and conformational epitopes, including catalytic antibodies [54]. While linear epitopes can be readily available by using A $\beta$  fragments [55,56], the fact that the delivery of conformational epitopes that include T cell epitopes are apparently necessary for a "protective" immunity, is more challenging due to the myriad of A $\beta$ <sub>42</sub> non-covalently bound aggregates that can be reorganized depending on various factors. Even so, there are several A $\beta$  constructs apparently with the desired conformations needed to develop effective vaccines [55-58] that can be readily synthesized. Another approach could be the use of DNA vaccines encoding for A $\beta$ <sub>42</sub>; however, attaining an effective immune response would require a prime boost of A $\beta$ <sub>42</sub> with Quil A, a strong Th1 adjuvant [38]. Of interest is that wild-type mice immunized six times with human A $\beta$ <sub>42</sub> plus 20  $\mu$ g of Quil A, did not develop neuroinflammation [59], results that contrast with those of the human AN-1792 vaccine having 50  $\mu$ g of QS-21 [6,7,60], a significantly less toxic compound than Quil A with a mouse acute toxic dose of over 250  $\mu$ g [61]. While the difference between the immune responses in humans and mice cannot be explained by differences between the A $\beta$ s that are very similar, these results stress the need to avoid adjuvants that elicit even a poor Th1 immunity. However, regardless of the antigen's source, an effective AD vaccine should induce a broad immune response, which is analogous or better than that found in IVIG, which means eliciting antibodies targeting a variety of components from the A $\beta$  cascade.

Similar to immunity against pathogens, the various anti-A $\beta$  Nabs found in IVIG indicate previous exposure of the immune system to a broad variety of antigens. Thus, a successful AD vaccine would probably have an assortment of antigens, which besides A $\beta$ -derived antigens may include tau as evidently there is synergism between this protein and A $\beta$  in AD development [62-66]. Yet, the vaccine must elicit only Th2 without residual Th1 immunity; a difficult endeavor when considering the intrinsic A $\beta$ <sub>42</sub> Th1 immune modulatory activity and limited access to Th2 adjuvants that inhibits Th1 immunity. Since AD shows a constant progression, its prevention/treatment could

require regular immunizations for the rest of the patient's life in order to sustain an effective level of protective antibodies against a diversity of antigens; a complex situation because of immunosenescence that affects the elderly population and increases inflammation [67]. An important observation for AD sub-unit vaccines is that prolonged immunization of aged dogs with A $\beta$ <sub>42</sub> resulted in a drift of the antibody response from the linear epitopes of the amino terminus toward conformational epitopes [68]; an observation that may also be relevant to long-term immunization with A $\beta$ <sub>42</sub> DNA vaccines [38]. This finding shows that regular vaccination with A $\beta$ <sub>42</sub>, probably for the rest of a patient's life, could stimulate the production of presumably protective antibodies that recognize new A $\beta$ <sub>42</sub> abnormal conformations; an approach that in preventive AD vaccines could avoid or limit the need for a large number of A $\beta$ <sub>42</sub> isoforms in the vaccine formulation.

From the available information it is possible to assume that to obtain an immune response similar to that from IVIG, an effective AD vaccine must have A $\beta$ <sub>42</sub> and perhaps other relevant antigens, like tau, to stimulate the production of a broad array of protective antibodies. While a diverse antibody response may be attained by a prolonged vaccination schedule with A $\beta$ <sub>42</sub> and/or a combination of A $\beta$  antigens, a most likely situation with an AD vaccine would be the stimulation of only Th2 with the concomitant inhibition of Th1 immunity. This would be a prerequisite for the safe induction of humoral immunity without damaging inflammatory responses. Furthermore, because of the ageing recipient population, the vaccine should be able to ameliorate to some degree the immune system's decline, a result of immune senescence, in order to stimulate an effective immune response [18]. Consequently, it is evident that vaccines would be more effective to prevent than to treat AD, starting immunization when the immune system is still competent. To attain these objectives, the development of these vaccines would need, in addition to the antigens, unique immune modulators that would be different from those used in the infectious disease vaccines.

## References

- Lemere CA. Immunotherapy for Alzheimer's disease: hoops and hurdles. *Mol Neurodegener*. 2013; 8: 36.
- Wang YJ, Zhou HD, Zhou XF. Clearance of amyloid-beta in Alzheimer's disease: progress, problems and perspectives. *Drug Discov Today*. 2006; 11: 931-938.
- Lannfelt L, Relkin NR, Siemers ER. Amyloid- $\beta$ -directed immunotherapy for Alzheimer's disease. *J Intern Med*. 2014; 275: 284-295.
- Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature*. 1999; 400: 173-177.
- Schenk DB, Seubert P, Lieberburg I, Wallace J. beta-peptide immunization: a possible new treatment for Alzheimer disease. *Arch Neurol*. 2000; 57: 934-936.
- Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, et al. Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. *Neurology*. 2003; 61: 46-54.
- Uro-Coste E, Russano de Paiva G, Guilbeau-Frugier C, Sastre N, Ousset PJ, da Silva NA, et al. Cerebral amyloid angiopathy and microhemorrhages after amyloid beta vaccination: case report and brief review. *Clin Neuropathol*. 2010; 29: 209-216.
- Lemere CA. Developing novel immunogens for a safe and effective Alzheimer's disease vaccine. *Prog Brain Res*. 2009; 175: 83-93.
- Delrieu J, Ousset PJ, Caillaud C, Vellas B. 'Clinical trials in Alzheimer's disease': immunotherapy approaches. *J Neurochem*. 2012; 120: 186-193.
- Fu HJ, Liu B, Frost JL, Lemere CA. Amyloid-beta immunotherapy for Alzheimer's disease. *CNS Neurol Disord Drug Targets*. 2010; 9: 197-206.
- Winblad B, Andreassen N, Minthon L, Floesser A, Imbert G, Dumortier T et al. Safety, tolerability, and antibody response of active A $\beta$  immunotherapy with CAD106 in patients with Alzheimer's disease: randomized, double-blind, placebo-controlled, first-in-human study. *Lancet Neurol*. 2012; 11: 597-604.
- Cazareth J, Guyon A, Heurteaux C, Chabry J, Petit-Paitel A. Molecular and cellular neuroinflammatory status of mouse brain after systemic lipopolysaccharide challenge: importance of CCR2/CCL2 signaling. *J Neuroinflammation*. 2014; 11: 132.
- Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. *Biol Psychiatry*. 2010; 68: 930-941.
- Solito E, Sastre M. Microglia function in Alzheimer's disease. *Front Pharmacol*. 2012; 3: 14.
- Town T, Nikolic V, Tan J. The microglial "activation" continuum: from innate to adaptive responses. *J Neuroinflammation*. 2005; 2: 24.
- Rozenstein-Tsalkovich L, Grigoriadis N, Lourdopoulos A, Nousiopoulos E, Kassis I, Abramsky O, et al. Repeated immunization of mice with phosphorylated-tau peptides causes neuroinflammation. *Exp Neurol*. 2013; 248: 451-456.
- Rosenmann H. Immunotherapy for targeting tau pathology in Alzheimer's disease and tauopathies. *Curr Alzheimer Res*. 2013; 10: 217-228.
- Marciani DJ. New Th2 adjuvants for preventive and active immunotherapy of neurodegenerative proteinopathies. *Drug Discov Today*. 2014; 19: 912-920.
- Aspinall R, Del Giudice G, Effros RB, Grubeck-Loebenstien B, Sambhara S. Challenges for vaccination in the elderly. *Immun Ageing*. 2007; 4: 9.
- Khan Z, Combadière C, Authier FJ, Itier V, Lux F, Exley C, et al. Slow CCL2-dependent translocation of biopersistent particles from muscle to brain. *BMC Med*. 2013; 11: 99.
- Cai Y, Kurita-Ochiai T, Kobayashi R, Hashizume T, Yamamoto M. Nasal immunization with the 40-kDa outer membrane protein of *Porphyromonas gingivalis* plus cholera toxin induces protective immunity in aged mice. *J Oral Sci*. 2013; 55: 107-114.
- Lee JB, Jang JE, Song MK, Chang J. Intranasal delivery of cholera toxin induces th17-dominated T-cell response to bystander antigens. *PLoS One*. 2009; 4: e5190.
- Tundup S, Srivastava L, Harn DA Jr. Polarization of host immune responses by helminth-expressed glycans. *Ann N Y Acad Sci*. 2012; 1253: E1-1E13.
- Szczepanik AM, Rampe D, Ringheim GE. Amyloid-beta peptide fragments p3 and p4 induce pro-inflammatory cytokine and chemokine production *in vitro* and *in vivo*. *J Neurochem*. 2001; 77: 304-317.
- Vollmar P, Kullmann JS, Thilo B, Claussen MC, Rothhammer V, Jacobi H, et al. Active immunization with amyloid-beta 1-42 impairs memory performance through TLR2/4-dependent activation of the innate immune system. *J Immunol*. 2010; 185: 6338-6347.
- Ahmed M, Davis J, Aucoin D, Sato T, Ahuja S, Aimoto S, et al. Structural conversion of neurotoxic amyloid-beta(1-42) oligomers to fibrils. *Nat Struct Mol Biol*. 2010; 17: 561-567.
- Masters CL, Selkoe DJ. Biochemistry of amyloid  $\beta$ -protein and amyloid deposits in Alzheimer disease. *Cold Spring Harb Perspect Med*. 2012; 2: a006262.
- Ladiwala AR, Litt J, Kane RS, Aucoin DS, Smith SO, Ranjan S, et al. Conformational differences between two amyloid- $\beta$  oligomers of similar size and dissimilar toxicity. *J Biol Chem*. 2012; 287: 24765-24773.
- Habicht G, Haupt C, Friedrich RP, Hortschansky P, Sachse C, Meinhardt J, et al. Directed selection of a conformational antibody domain that prevents mature amyloid fibril formation by stabilizing Abeta protofibrils. *Proc Natl Acad Sci USA*. 2007; 104: 19232-19237.

30. Roguin LP, Retegui LA. Monoclonal antibodies inducing conformational changes on the antigen molecule. *Scand J Immunol*. 2003; 58: 387-394.
31. Dodel R, Balakrishnan K, Keyvani K, Deuster O, Neff F, Andre-Selmer L-C, et al. Naturally occurring autoantibodies against  $\beta$ -amyloid: Investigating their role in transgenic animal and *in vitro* models of Alzheimer's disease. *J Neurosci*. 2011; 31: 5847-5854.
32. Welzel AT, Williams AD, McWilliams-Koeppen HP, Acero L, Weber A, Blinder V, et al. Human anti-A $\beta$  IgGs target conformational epitopes on synthetic dimer assemblies and the AD-brain derived peptide. *PLoS ONE*. 2012; 7: e50317.
33. Reitz C. Alzheimer's disease and the amyloid cascade hypothesis: a critical review. *Int J Alzheimers Dis*. 2012; 2012: 369808.
34. Hoozemans JJ, Chafekar SM, Baas F, Eikelenboom P, Scheper W. Always around, never the same: pathways of amyloid beta induced neurodegeneration throughout the pathogenic cascade of Alzheimer's disease. *Curr Med Chem*. 2006; 13: 2599-2605.
35. O'Nuallain B, Wetzel R. Conformational Abs recognizing a generic amyloid fibril epitope. *Proc Natl Acad Sci USA*. 2002; 99: 1485-1490.
36. Kaye R, Head E, Sarsoza F, Saing T, Cotman CW, Neucula M, et al. Fibril specific, conformation dependent antibodies recognize a generic epitope common to amyloid fibrils and fibrillar oligomers that is absent in prefibrillar oligomers. *Mol Neurodegener*. 2007; 2:18.
37. Lambracht-Washington D, Rosenberg RN. Active DNA A $\beta$ 42 vaccination as immunotherapy for Alzheimer disease. *Transl Neurosci*. 2012; 3: 307-313.
38. Lambracht-Washington D, Qu B-X, Fu M, Anderson LL, Eager TN, Stuve O, et al. A peptide-prime DNA boost immunization protocol provides significant benefits as a new generation A $\beta$ 42 DNA vaccine for Alzheimer's disease. *J Neuroimmunol*. 2013; 254: 63-68.
39. Kaye R, Jackson GR, Estes DM, Barrett AD. Alzheimers disease: review of emerging treatment role for intravenous immunoglobulins. *J Cent Nerv Syst Dis*. 2011; 3: 67-73.
40. Magga J, Puli L, Pihlaja R, Kanninen K, Neulamaa S, Malm T, et al. Human intravenous immunoglobulin provides protection against A $\beta$  toxicity by multiple mechanisms in a mouse model of Alzheimer's disease. *J Neuroinflammation*. 2010; 7: 90.
41. Moreth J, Mavoungou C, Schindowski K. Passive anti-amyloid immunotherapy in Alzheimer's disease: What are the most promising targets? *Immun Ageing*. 2013; 10: 18.
42. Loeffler DA. Intravenous immunoglobulin and Alzheimer's disease: what now? *J Neuroinflammation*. 2013; 10: 70.
43. Fillit H, Hess G, Hill J, Bonnet P, Toso C. IV immunoglobulin is associated with a reduced risk of Alzheimer disease and related disorders. *Neurology*. 2009; 73: 180-185.
44. O'Nuallain B, Williams AD, McWilliams-Koeppen HP, Acero L, Weber A, Ehrlich H, et al. Anti-amyloidogenic activity of IgGs contained in normal plasma. *J Clin Immunol*. 2010; 30: S37-42.
45. Klaver AC, Finke JM, Digambaranath J, Balasubramaniam M, Loeffler DA. Antibody concentrations to A $\beta$ -42 monomer and soluble oligomers in untreated and antibody-antigen-dissociated intravenous immunoglobulin preparations. *Int Immunopharmacol*. 2010; 10:115-119.
46. Britschgi M, Olin CE, Johns HT, Takeda-Uchimura Y, LeMieux MC, Rufibach K, et al. Neuroprotective natural antibodies to assemblies of amyloidogenic peptides decrease with normal aging and advancing Alzheimer's disease. *Proc Natl Acad Sci USA*. 2009; 106: 12145-12150.
47. Smith LM, Coffey MP, Loeffler DA. Specific binding of intravenous immunoglobulin products to tau peptide fragments. *Int Immunopharmacol*. 2014; 21: 279-282.
48. Paul S, Planque S, Nishiyama Y. Immunological origin and functional properties of catalytic autoantibodies to amyloid beta peptide. *J Clin Immunol*. 2010; 30 Suppl 1: S43-49.
49. Taguchi H, Planque S, Nishiyama Y, Symersky J, Boivin S, Szabo P, et al. Autoantibody-catalyzed hydrolysis of amyloid beta peptide. *J Biol Chem*. 2008; 283: 4714-4722.
50. Siegel J. Immune Globulins: Therapeutic, pharmaceutical, cost and administration considerations.
51. Lee M, Bard F, Johnson-Wood K, Lee C, Hu K, Griffith SG, et al. Abeta42 immunization in Alzheimer's disease generates Abeta N-terminal antibodies. *Ann Neurol*. 2005; 58: 430-435.
52. Ciaramella A, Salani F, Bizzoni F, Orfei MD, Langella R, Angelucci F, et al. The stimulation of dendritic cells by amyloid beta 1-42 reduces BDNF production in Alzheimer's disease patients. *Brain Behav Immun*. 2013; 32: 29-32.
53. Watt AD, Crespi GA, Down RA, Ascher DB, Gunn A, Perez KA, et al. Do current therapeutic anti-A $\beta$  antibodies for Alzheimer's disease engage the target? *Acta Neuropathol*. 2014; 127: 803-810.
54. Taguchi H, Planque S, Nishiyama Y, Szabo P, Weksler ME, Friedland RP, et al. Catalytic antibodies to amyloid beta peptide in defense against Alzheimer disease. *Autoimmun Rev*. 2008; 7: 391-397.
55. Roeder AM, Roettger Y, Stündel A, Dodel R, Geyer A. Synthetic dimeric A $\beta$ (28-40) mimics the complex epitope of human anti-A $\beta$  autoantibodies against toxic A $\beta$  oligomers. *J Biol Chem*. 2013; 288: 27638-27645.
56. Lemere CA, Masliah E. Can Alzheimer disease be prevented by amyloid-beta immunotherapy? *Nat Rev Neurol*. 2010; 6: 108-119.
57. Hoogerhout P, Kamphuis W, Brugghe HF, Sluijs JA, Timmermans HA, Westdijk J, et al. A cyclic undecamer peptide mimics a turn in folded Alzheimer amyloid  $\beta$  and elicits antibodies against oligomeric and fibrillar amyloid and plaques. *PLoS One*. 2011; 6: e19110.
58. Verdoliva A, Rivieccio V, Rossi M. Simplified  $\beta$ -amyloid peptides for safer Alzheimer's vaccines development. *Hum Vaccin*. 2010; 6: 936-947.
59. Lambracht-Washington D, Qu BX, Fu M, Eager TN, Stuve O, Rosenberg RN. DNA beta-amyloid(1-42) trimer immunization for Alzheimer disease in a wild-type mouse model. *JAMA*. 2009; 302: 1796-1802.
60. Gilman S, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, et al. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. *Neurology*. 2005; 64: 1553-1562.
61. Kensil CR, Patel U, Lennick M, Marciani D. Separation and characterization of saponins with adjuvant activity from Quillaja saponaria Molina cortex. *J Immunol*. 1991; 146: 431-437.
62. Jin M, Shepardson N, Yang T, Chen G, Walsh D, Selkoe DJ. Soluble amyloid beta-protein dimers isolated from Alzheimer cortex directly induce Tau hyperphosphorylation and neuritic degeneration. *Proc Natl Acad Sci USA*. 2011; 108: 5819-5824.
63. Huang HC, Jiang ZF. Accumulated amyloid-beta peptide and hyperphosphorylated tau protein: relationship and links in Alzheimer's disease. *J Alzheimers Dis*. 2009; 16: 15-27.
64. Golde TE, Petrucelli L, Lewis J. Targeting Abeta and tau in Alzheimer's disease, an early interim report. *Exp Neurol*. 2010; 223: 252-266.
65. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. *Nat Rev Mol Cell Biol*. 2007; 8: 101-112.
66. Nicoll J. The prospects for a vaccine for Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2014; 85: e3.
67. Martorana A, Bulati M, Buffa S, Pellicanò M, Caruso C, Candore G, et al. Immunosenescence, inflammation and Alzheimer's disease. *Longev Healthspan*. 2012; 1: 8.
68. Vasilevko V, Pop V, Kim HJ, Saing T, Glabe CC, Milton S, et al. Linear and conformation specific antibodies in aged beagles after prolonged vaccination with aggregated Abeta. *Neurobiol Dis*. 2010; 39: 301-310.