Drug Designing: Open Access
ISSN: 2169-0138

Carrera and Cacabelos, Drug Des 2013, 2:2
DOI: 10.4172/2169-0138.1000107

Research Article Open Access

Novel Immunotherapeutic Procedures for Prevention of Alzheimer's Disease

Ivan Carrera[1] and Ramon Cacabelos[2]*

[1]Department of Neurosciences, EuroEspes Biotechnology, Spain
[2]EuroEspes Biomedical Research Center, Institute for CNS Disorders and Genomic Medicine, Corunna, Chair of Biotechnology and Genomics, Camilo José Cela University, Madrid, Spain

Introduction

There are two main modalities of immunotherapy for Alzheimer's disease (AD) under investigation, based on previous results with animal models and clinical trials. The first approach was passive immunotherapy, with the administration of monoclonal Aβ-specific antibodies, although some disadvantages and side-effects were described in the literature [1]. A second approach is active immunization with the $A\beta_{42}$ antigen-tested mouse models [2]. Based on this methodology, posterior studies have tried to avoid the adverse activation of T-cell-mediated immune response that probably caused negative effects in patients. Although there are different immune compounds being given to APPswe/PS1dE9 double-transgenic mice to achieve the same goal, one particular study has taken a new approach by delivering $A\beta_{42}$ in a novel immunogen-adjuvant manner consisting of Sphingosine-1-Phosphate (S1P)-containing liposomes, administered to APP/PS1 transgenic mice before and after the detection of AD-like pathology in the brain [3]. The results from this novel vaccine (EB101) indicate that active immunization significantly prevents and reverses the progression of AD-like pathology and also clears prototypal neuropathological hallmarks in those transgenic mice studied. This new approach seemed to strongly induce T-cell, B-cell and microglial immune response activation, avoiding the Th1 inflammatory reaction. These beneficial effects were achieved by using a physiological adjuvant formed by naturally-occurring phospholipids, which have already been proven safe and efficient in several other types of vaccines, such as influenza. In the EB101 vaccine, the S1P-phospholipid plays a key role in the anti-inflammatory reaction, probably by acting as a neuronal regenerating agent in *in vitro* and *in vivo* studies [4].

Rationale for immunotherapy in AD

There are consistent reasons why immunotherapy should work in AD [5], based on studies published during the past decade. Some of these reasons are: (a) β-amyloid plaques and their aggregated, proto-fibrillar and oligomeric precursors contain immunologic neo-epitopes that are absent from the full-length Amyloid Precursor Protein (APP), as well as from its soluble proteolytic derivatives restricted to the brain tissue; therefore, β-amyloid-based immunotherapies designed to selectively target pathologic neo-epitopes present on Aβ oligomers, protofibrils or fibrils, should not cause autoimmune disease in unaffected tissues throughout the organism. (b) β-amyloid buildup precedes neurodegeneration and functional loss, and the prevention of its formation or its removal can be expected to result in the slowing or the prevention of neurodegeneration. (c) β-amyloid can cause the formation of neurofibrillary tangles *in vivo* and *in vitro*, as has been supported by animal models and tissue culture. These findings strongly suggest that the removal of β-amyloid bears the potential to correct not only β-amyloid-related toxicity but also to prevent the formation of neurofibrillary tangles. (d) Conformational changes of endogenously occurring proteins and the formation of insoluble aggregates are commonly associated with neurodegeneration and brain disease, so the removal or prevention of these pathologic protein aggregates is also a therapeutic goal in the principle of immunotherapy. (e) Immunotherapy works in experimental animals and in initial clinical trials: both active immunization and passive antibody transfer consistently reduce brain β-amyloid load, improve β-amyloid-related memory impairments, and protect neurons against degeneration in many independent experiments using different mouse models and primates.

Mechanisms of action in immunotherapy

Some hypotheses [6] concerning the basis of immunotherapeutic mechanisms are currently under investigational scrutiny, such as: (a) *Plaque breakdown*: A specific antibody is capable of entering the brain and opsonizing Aβ burden plaques, and during the immune response process the plaques are fragmented and phagocytized by microglial cells. (b) *Peripheral sink*: This is based on the hypothesis that antigen-antibody complex formation at the brain periphery isolates β-amyloid from the damaged brain areas and avoids the deposition of new Aβ plaques. The increased levels of Aβ in serum also raised another possibility, in which the Aβ is sequestered from the brain directly into the bloodstream by changing the Aβ blood-brain balance rate to enhance clearance of soluble Aβ. (c) *Aggregation inhibitor*: Aβ represents a key molecular target in AD intervention therapy, and agents that can efficiently prevent its aggregation and accumulation or potentiate its clearance might represent remarkable therapeutic benefits. Among the main potential inhibitors are those related to the β- and α-secretase enzymes which are required in the abnormal processing of Aβ [7].

To confront and prove these hypotheses, different strategies involving Aβ immunotherapy are currently under investigation by the scientific community, such as: (a) Direct Aβ42 immunization in transgenic mouse models has already provided clinical feedback of Aβ immunotherapy [8]. This direct immunization approach aims to stimulate the immune system response, activating the T-cells, B-cells and microglia in the brain. (b) Another strategy of active immunization involves the administration of Aβ conjugated synthetic fragments

***Corresponding author:** Dr. Ramón Cacabelos, EuroEspes Biomedical Research Center, Institute for CNS Disorders and Genomic Medicine, Santa Marta de Babio, 15165, Corunna, Spain, Tel: +34 981 780 505; E-mail: rcacabelos@euroespes.com

Received April 30, 2013; **Accepted** May 24, 2013; **Published** May 26, 2013

Citation: Carrera I, Cacabelos R (2013) Novel Immunotherapeutic Procedures for Prevention of Alzheimer's Disease. Drug Des 2: 107. doi:10.4172/2169-0138.1000107

bound to a carrier protein, thus avoiding potential problems associated with mounting a T-cell response directly against Aβ [9]. (c) The third type of immunotherapeutic strategy involves the passive administration of monoclonal antibodies, developed outside the patient's body, directed against Aβ [10]. This method does not stimulate the immune system to play an active role in fighting the infection as do the previous two active methods.

Tau-based Immunotherapy

Recent studies have observed increased levels of tau oligomers in the early stage of AD, previous to detection of Neurofibrillary Tangles (NFT) formed by aggregation and accumulation of the microtubule-associated protein tau [11]. Since Aβ immunotherapy presents a limited clearance effect of tau aggregates in dystrophic neurites, the development of an alternative therapy that directly targets pathological tau has become crucial. In the last decade, several approaches have been taken to treat AD by targeting tau, such as (a) the inhibition of tau hyperphosphorylation, by using a kinase inhibitor of soluble aggregated tau formation, and also to prevent related motor deficits [12], although unwanted side-effects might be found due to its important physiological role; (b) Activation of the proteolytic pathway, by the degrading action of calpain [13] and puromycin-sensitive aminopeptidase [14]; (c) Stabilization of microtubules, treating tauopathies by functionally binding and stabilizing microtubule with MT-binding protein tau [15] and paclitaxel, a drug proven effective in restoring the affected axonal transport and motor impairments [16]; and (d) Tau clearance by immunotherapy. In this case, the tau active vaccination uses phosphorylated antigens of tau fragments associated with neurofibrillary tangles [17], that results in an efficient reduction of both soluble and insoluble tau active fragments, reducing phosphorylated NFTs in the AD-like mouse brains.

Pre-clinical findings

Pre-clinical studies have provided clear evidence that Aβ immunization therapy provides protection and reverses the pathological effects of AD in transgenic mouse models [18]. This strategy seems to improve cognition performance [19] after $A\beta_{42}$ immunization, in addition to causing an effective reduction in Aβ pathology. A recent immunization study has proven that a fragment of the Aβ peptide bound to polylysines activated the immune response that results in the diminishing of AD-like pathology in APP transgenic mice. This report reinforces the notion that the immune-conjugate approach is an effective means of Aβ immunotherapy and also that the entire Aβ peptide is not necessary for its efficacy, and is in accordance with the hypothesis that specific antibodies directed against the amino-terminal and/or central region of the amyloid peptide provide beneficial protection against amyloid pathology. Passive immunization studies have also been conducted with promising experimental results showing that a humoral response alone, without Aβ cellular response, is sufficient to reduce the β-amyloid burden and to reverse memory deficits [20].

Current perspectives

Among the drugs and vaccines currently under development to treat the pathological effects of AD, bapineuzumab, solanezumab, CAD106 and EB101 are the most promising ones. Solanezumab is a monoclonal antibody raised against $A\beta_{13-28}$, recognizing an epitope in the core of the amyloid peptide, binding selectively to soluble Aβ and with low affinity for the fibrillar Aβ form [21], presenting fewer adverse events than bapineuzumab, which binds to Aβ amyloid plaques more strongly than soluble Aβ [22]. There are a few other monoclonal antibodies against Aβ that present properties different from those of bapineuzumab, such as (a) PF-04360365, which specifically targets the free carboxy-terminus of $A\beta_{1-40}$; (b) MABT5102A, which binds with equally high affinity to Aβ monomers, oligomers and fibrils; (c) GSK933776A, which targets the N-terminus of Aβ. Specific anti-Aβ antibodies are present in pooled preparations of intravenous immunoglobulin (IVIg or IGIV), which has already been approved by the FDA for the treatment of a variety of other neurological aspects. Current results from these studies have shown that IVIg treatment may also be an efficacious alternative approach in the treatment of AD neuropathologies [23].

Avoiding both the strong Th1 effects of QS-21 adjuvant and the T-cell epitopes at the C-terminus of Aβ, CAD106 consists of a short N-terminal fragment of Aβ attached to a virus-like particle, with no additional adjuvant [24]. This therapeutic agent is currently in phase II trials. Affiris is testing two short 6-amino-peptides (AD01, AD02), administered with aluminum hydroxide as adjuvant, that mimic the free N-terminus of Aβ and therefore cause cross-reactivity with the native peptide in phase I trials [25]. In terms of prevention and therapeutic treatment approach, the EB101 vaccine showed for the first time the effectiveness of combining a liposomal immunogen-adjuvant with an Aβ antigen to induce an effective immunological response combined with an anti-inflammatory effect in preclinical studies using APP/PS1 transgenic mice [3]. The EB101 vaccine immunization process has shown a marked positive effect as a preventive and therapeutic treatment, reducing amyloidosis-induced inflammation as an effective Th2 immunomodulator. Moreover, this vaccine proved to stimulate innate immunity and enable effective phagocytosis to clear amyloid and neurofibrillary tangles, among the major hallmarks of AD-like neuropathology observed. Phase I clinical trials are expected to reinforce these consistent results. However, a few other vaccines are currently under development, and recent studies have opened new perspectives in the immunization approach to AD pathology, in particular, the gene-gun-mediated genetic immunization with $A\beta_{42}$ gene [26], showing that self-tolerance can be broken in order to produce a humoral response to the $A\beta_{42}$ peptide with minimal cellular response.

Conclusion

The current experimental studies to develop anti-amyloid treatments using immunological approaches are expected to provide a framework based on the amyloid hypothesis in a near future. This approach will be tested in transgenic AD animal models and it is expected to be an effective therapy method to prevent the AD neuropathological effects. Active immunization strategies are being planned and developed in order to maximize endogenous antibody production as well as to minimize T lymphocyte reactions. However, there is still a void in the identification and validation of AD biomarkers for the diagnosis of early pathological effects in the brains of AD patients. Together with the evaluation of the therapeutic efficacy of immunotherapies currently under development, are major hurdles to be addressed in the near future by researchers and investigators worldwide. In conclusion, based on studies reported over the past two decades, there is a strong and solid evidence to suggest that Aβ immunotherapy may have disease-modifying potential leading to an effective therapy in AD both in animal models and in AD patients. However, alternative emerging

neuroprotective approaches such as neurotrophic factor enhancers, neurotrophins, and stem-cell treatments are also under investigation.

References

1. Panza F, Frisardi V, Solfrizzi V, Imbimbo BP, Logroscino G, et al. (2012) Immunotherapy for Alzheimer's disease: from anti-Î²-amyloid to tau-based immunization strategies. Immunotherapy 4: 213-238.
2. Singh S, Kushwah AS, Singh R, Farswan M, Kaur R (2012) Current therapeutic strategy in Alzheimer's disease. Eur Rev Med Pharmacol Sci 16: 1651-1664.
3. Carrera I, Etcheverría I, Fernández-Novoa L, Lombardi V, Cacabelos R, et al. (2012) Vaccine Development to Treat Alzheimer's Disease Neuropathology in APP/PS1 Transgenic Mice. Int J Alzheimers Dis 2012: 376138.
4. Maceyka M, Harikumar KB, Milstien S, Spiegel S (2012) Sphingosine-1-phosphate signaling and its role in disease. Trends Cell Biol 22: 50-60.
5. Galimberti D, Ghezzi L, Scarpini E (2013) Immunotherapy against amyloid pathology in Alzheimer's disease. J Neurol Sci .
6. Morgan D (2006) Immunotherapy for Alzheimer's disease. J Alzheimers Dis 9: 425-432.
7. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, et al. (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 9: 119-128.
8. Grill JD, Cummings JL (2010) Current therapeutic targets for the treatment of Alzheimer's disease. Expert Rev Neurother 10: 711-728.
9. Tabira T (2010) Immunization therapy for Alzheimer disease: a comprehensive review of active immunization strategies. Tohoku J Exp Med 220: 95-106.
10. Wisniewski T, Konietzko U (2008) Amyloid-beta immunisation for Alzheimer's disease. Lancet Neurol 7: 805-811.
11. Maeda S, Sahara N, Saito Y, Murayama S, Ikai A, et al. (2006) Increased levels of granular tau oligomers: an early sign of brain aging and Alzheimer's disease. Neurosci Res 54: 197-201.
12. Boutajangout A, Sigurdsson EM, Krishnamurthy PK (2011) Tau as a therapeutic target for Alzheimer's disease. Curr Alzheimer Res 8: 666-677.
13. Johnson GV (2006) Tau phosphorylation and proteolysis: insights and perspectives. J Alzheimers Dis 9: 243-250.
14. Kudo LC, Parfenova L, Ren G, Vi N, Hui M, et al. (2011) Puromycin-sensitive aminopeptidase (PSA/NPEPPS) impedes development of neuropathology in hPSA/TAU(P301L) double-transgenic mice. Hum Mol Genet 20: 1820-1833.
15. Trojanowski JQ, Smith AB, Huryn D, Lee VM (2005) Microtubule-stabilising drugs for therapy of Alzheimer's disease and other neurodegenerative disorders with axonal transport impairments. Expert Opin Pharmacother 6: 683-686.
16. Zhang B, Maiti A, Shively S, Lakhani F, McDonald-Jones G, et al. (2005) Microtubule-binding drugs offset tau sequestration by stabilizing microtubules and reversing fast axonal transport deficits in a tauopathy model. Proc Natl Acad Sci U S A 102: 227-231.
17. Boutajangout A, Quartermain D, Sigurdsson EM (2010) Immunotherapy targeting pathological tau prevents cognitive decline in a new tangle mouse model. J Neurosci 30: 16559-16566.
18. Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, et al. (1999) Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. Nature 400: 173-177.
19. Janus C, Pearson J, McLaurin J, Mathews PM, Jiang Y, et al. (2000) A beta peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease. Nature 408: 979-982.
20. Bacskai BJ, Kajdasz ST, Christie RH, Carter C, Games D, et al. (2001) Imaging of amyloid-beta deposits in brains of living mice permits direct observation of clearance of plaques with immunotherapy. Nat Med 7: 369-372.
21. Imbimbo BP, Ottonello S, Frisardi V, Solfrizzi V, Greco A, et al. (2012) Solanezumab for the treatment of mild-to-moderate Alzheimer's disease. Expert Rev Clin Immunol 8: 135-149.
22. Panza F, Frisardi V, Imbimbo BP, D'Onofrio G, Pietrarossa G, et al. (2010) Bapineuzumab: anti-Î²-amyloid monoclonal antibodies for the treatment of Alzheimer's disease. Immunotherapy 2: 767-782.
23. Magga J, Puli L, Pihlaja R, Kanninen K, Neulamaa S, et al. (2010) Human intravenous immunoglobulin provides protection against AÎ² toxicity by multiple mechanisms in a mouse model of Alzheimer's disease. J Neuroinflammation 7: 90.
24. Kingwell K (2012) Alzheimer disease: Amyloid-Î² immunotherapy CAD106 passes first safety test in patients with Alzheimer disease. Nat Rev Neurol 8: 414.
25. Delrieu J, Ousset PJ, Caillaud C, Vellas B (2012) 'Clinical trials in Alzheimer's disease': immunotherapy approaches. J Neurochem 120 Suppl 1: 186-193.
26. Qu BX, Xiang Q, Li L, Johnston SA, Hynan LS, et al. (2007) Abeta42 gene vaccine prevents Abeta42 deposition in brain of double transgenic mice. J Neurol Sci 260: 204-213.

This article was originally published in a special issue, **Preventive Therapy of Mental Disorders** handled by Editor. Dr. Tatiana Lipina, Samuel Lunenfeld Research Institute, Canada