Vaccine for Alzheimer's Disease (BGN)

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Alzheimer's disease (AD) is a progressive neurological disorder that begins with short-term memory loss and proceeds to disorientation, impairment of judgment and reasoning and, ultimately, dementia. Alzheimer's disease is characterized by the progressive accumulation of the amyloid-beta (A) protein in limbic and association cortices, where some of it precipitates to form a range of amorphous and compacted (fibrillar) extracellular plaques. Vaccination against amyloid-beta is pursued in full force by Biotech and Pharma companies. In one of the major clinical trial conducted recently, active amyloid peptide (A) immunization of patients with Alzheimer's disease resulted in meningoencephalitis in 6% of immunized patients stopping the further development of the vaccine. As of today, all vaccination approaches in AD are aimed at producing A-beta antibodies, while depleting the T cell epitopes associated with the response. We have previously found that these T cells are naturally stimulated in patients with AD and if boosted properly, they can qualitatively advance the vaccination approaches taken today.

The Technology

We examined the immune-response variations to active vaccination against amyloid-beta by assessing the T cell reactivity, epitope specificity, and immunogenicity and the contribution of various HLA-DR alleles to the response. Analysis of blood samples from 133 individuals disclosed that the abundant DR haplotypes DR15 (found in 36% of subjects), DR3 (in 18%), DR4 (12.5%), DR1 (11%), and DR13 (8%) were associated with A-specific T cell responses elicited via distinct T cell epitopes within residues 15-42 of A. Because the HLA-DRB1*1501 occurred most frequently, we examined the effect of A challenge in humanized mice bearing this allele. The observed T cell response was remarkably strong, dominated by secretion of IFN- and IL-17, and specific to the same T cell epitope as that observed in the HLA-DR15-bearing humans. Furthermore, following long-term therapeutic immunization of an AD mouse model bearing the DRB1*1501 allele, A was effectively cleared from the brain parenchyma and brain microglial activation was reduced. We conclude that based on the HLA alleles expressed by the Alzheimer's patient, circulating A-beta-specific T cells will have different specificities i.e., will recognize a different portion of A-beta peptides presented by the HLA complex. In order to stimulate only the specific T cells in each individual, one needs to determine the HLA alleles expressed in the patient and vaccinate accordingly.

Applications

We aim to generate the first individual-based (personalized) immunotherapeutic approach in AD based on the HLA alleles of the individual and the specific A-beta peptide presented to T cells. Thus we suggest a method of treatment of Alzheimer's patients with specific amyloid beta peptides according to the HLA-DR alleles they expresses.

Patent Status

Patent Pending

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