Novel Aβ Oligomer-Specific Epitopes: A Hypothesis-Driven Approach to Alzheimer’s Immunotherapeutics

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Background: Alzheimer’s disease (AD) Aβ immunotherapeutics in humans have been hampered by negative side-effects including ARIA-E and cerebral microhemorrhage, mediated by antibody binding to non-toxic fibrils and/or monomers. Recent advances have demonstrated the fundamental role of amyloid-β oligomers (AβO) in disease onset, synaptotoxicity and progression. Together with promising results from clinical trials targeting aggregated Aβ, these data suggest that by targeting AβOs, a blockade of cognitive decline in humans is possible.

Methods: Proprietary algorithms have computationally predicted five AβO-specific epitopes (see Poster #12344, session P4-14). The epitopes were synthesized, structured through cyclization, and conjugated to immunogens, validated for sequence and structure, and used to produce monoclonal antibodies. ELISA was employed to screen clones against structured and unstructured epitopes and synthetic AβOs and monomers.

Objective: We used computational epitope discovery methods to identify immunologic targets on toxic and propagating AβO. The objective was to identify monoclonal antibodies that react with synthetic oligomers over monomers with an affinity of ~100/1, or react with native oligomers in brain and CSF with low affinity binding to monomers, and do not react with plaques.

Results: Together the five epitopes produced more than 300 clones. ELISA prescreen of hybridoma supernatants found specificity for the structured epitopes vs. unstructured epitopes was varied, and appeared to be maximal with the 301 epitope. A proportion of the clones were reactive to the KLH-epitope linker peptide. These were excluded from further investigation. The majority of the clones were of the IgG isotype.

Conclusions: The computational epitope discovery approach utilized here may produce multiple AβO-specific antibodies. If successful, the approach may be applicable to other proteins and protein misfolding diseases.

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