PROTEIN TAU, TARGET FOR IMMUNOTHERAPY: PRE-CLINICAL EVALUATION IN TRANSGENIC MICE

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Background: Alzheimer's disease is caused by excess amyloid and phosphorylation of protein tau, both presenting as a spectrum of protein-aggregates. Immunotherapy can alleviate the pathological impact of protein-aggregates, while contributing to understand the neurotoxic species molecularly. Immunotherapy was successful in amyloid mice, but clinical studies in humans pose problems. Interest in tauopathy in AD is growing, but only beginning to be assessed as target for immunotherapy.

Aims: We explored phosphopeptide-liposomes as active vaccines in pre-clinical Tau.P301L mice, and generated monoclonal antibodies with novel specificities as passive vaccines.

Results: Liposome-based vaccines (Muhs et al, 2007) carrying synthetic phospho-Tau peptides elicited robust antiserum responses in mice. The high specificity for pathological tau was visualized by TAUPIR on brain sections from biGT mice with proven tauopathy (Terwel et al, 2008). Abundant labeling of neurofibrillary tangles in hippocampus and cortex was corroborated biochemically by western blotting on mouse brain extracts and on isolated hP-Tau preparations (Vandebroek et al, 2005). Specific ELISA demonstrated high and stable antibody titers against synthetic phospho-Tau-peptides as opposed to negative reaction to non-phosphorylated Tau-peptides.

Mice with the most specific immune responses were boosted to generate monoclonal antibodies. Resulting hybridomas were screened by TAUPIR and ELISA for interesting specificities, yielding a selection of hybridomas that are characterized for specificity and avidity by various techniques.

Active immunotherapy is tested with these antibodies in different immunization schemes, using clinical and pathological read-outs to evaluate therapeutic effects on motor and cognitive dysfunctions of Tau.P301L and biGT mice (Terwel et al, 2005; 2008).