Research Number: 300000-4895

Title: Immunotherapy targeting pathological phosphorylated tau conformers in Alzheimer's disease and other tauopathies - a study in transgenic mouse-models

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Year (Start): 2009 Year (End): 2012

Working hypothesis and aims: Immunotherapy targeting pathologically phosphorylated (phos)-tau conformers may reduce the neurofibrillary tangles (NFT) burden and ameliorate the cognitive deficits, yet may be unsafe under certain conditions. Our aim was to explore both the efficacy (anti-NFT effect and cognitive improvement) and safety (free of encephalitis) of a phos-tau peptide vaccine, particularly to identify the conditions causing adverse effects. For this purpose we studied the efficacy and safety aspects as well as mechanistic aspects of phos-tau immunization in various AD-mouse models (NFT-models presenting mature NFTS; an amyloid-model presenting amyloid plaques and also early tau-pathology; NFT/amyloid-model and WT-mice), using different immunization protocols (single vs repeated vaccine injections) in different age groups (young, adult and aged).

Background: The drawbacks of amyloid immunotherapy in terms of both safety and efficacy, including the lack of effect on NFTs, the neuropathology which correlates best with clinical dementia, point that immunotherapy targeting directly the NFT-pathology maybe a preferential therapeutic approach. Yet, the encephalitogenicity of full-length unphos-tau protein vaccine under a proinflammatory CNS milieu [with complete-Freund's-adjvant and pertussis-toxin (CFA-PT)], reported by us in WT-mice, demanded to carefully and selectively target pathological tau and address not only efficacy but also safety of such immunotherapy. Our preliminary results showed that a single immunization of young NFT-mice with phos-tau peptides presents high efficacy (reduced NFT burden) and safety profile (no adverse effects).

Methods: Mice were immunized with phos-tau peptides in CFA-PT, or with CFA-PT only. Clinical follow-up, behavioral, pathological as well as immunological studies were performed.

Results: Safety: A single injection (with one booster) of phos-tau vaccine in CFA-PT was safe (free of neuroinflammation) in NFT-models, amyloid-model, NFT/amyloid-model mice and in WT-mice. However, repeated immunization resulted in encephalitis in 66.7% of the adult WT-mice, and in 26.7% of the adult NFT-mice (following 7 times repeated immunization), as well as in 17% of aged WT-mice (following 4 times repeated immunization). Efficacy: A single injection resulted in a robust (40%) decrease in NFT-pathology in NFT-models, and improved cognitive performance. It also showed a decrease in amyloid-burden in amyloid-mice and improved cognitive performance. Similarly, an improved cognitive performance was noticed following repeated immunization in NFT-mice, both adult and aged mice; however, it worsened the performance of WT-mice. Mechanism: Anti-phos-tau Abs were detected in serum and blood vessels in CNS of immunized mice, with serum immunoreactivity specific for NFT-pathology; with altered levels of lysosomal proteases, suggesting Ab and lysosomal involvement.

Conclusions: While phos-tau immunization shows encouraging efficacy, it maybe unsafe under certain conditions, such as repeated immunization in a proinflammatory milieu, particularly in WT-mice. Identification of the conditions causing adverse effect will allow to develop safer anti-NFT-vaccines.

Key words: Alzheimer's-disease, tauopathy, neurofibrillary-tangles, immunotherapy, Tg-mice.
Publications associated with the project:
