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Et al.

COMBINED ACTIVE HUMORAL AND CELLULAR IMMUNIZATION APPROACHES FOR THE TREATMENT OF SYNUCLEONOPATHIES

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Objectives: Parkinson's Disease (PD), Dementia with Lewy bodies (DLB), and Multiple System Atrophy (MSA) are neurodegenerative disorders of the aging population characterized by the progressive accumulation of alpha-synuclein. Jointly these disorders have been denominated synucleinopathies and currently no disease modifying treatments are available. Previous *in vivo* studies in transgenic (tg) mice have shown that active and passive immunization targeting alpha-synuclein ameliorates to some extent deficits and synuclein accumulation, however it's unknown if combining humoral and cellular immunization might synergize and also reduce inflammation and improve microglial cell mediated synuclein clearance.

Methods: PDGF- alpha-synuclein tg mice and control non-tg mice were immunized with: 1) Glucan Particle (GP) adjuvant alone, 2) GP human (hu)- alpha-synuclein (active immunization), 3) GP plus rapamycin and 4) GP plus rapamycin and hu-alpha-synuclein (combined active and humoral) and analyzed by neuropathological and biochemical markers.

Results: Compared to tg mice treated with adjuvant alone, mice immunized with GP hu-alpha-synuclein displayed a 30% reduction in alpha-synuclein accumulation. Combined immunotherapy with GP plus rapamycin and hu-alpha-synuclein resulted in 50% reduction in alpha-synuclein accumulation which was accompanied by reduced neuro-inflammation (Iba-1, GFAP, IL6, TNFalpha), phospho and insoluble alpha-synuclein, microglia and astroglia cell numbers, and retention of CD25, FoxP3 and CD4 positive cells. Levels of TGFb1 were also increased. Serological studies showed that active immunization resulted in higher levels of total IgG, IgG1 and IgG2 titers, levels were slightly higher in the combined group.

Conclusions: *In vivo* studies targeting alpha-synuclein support the hypothesis that cellular immunization might enhance the effects of active immunotherapy for the treatment of synucleionopathies.

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