Abstract 1318

NOVEL ALPHA-SYNUCLEIN-BASED GLUCONEOCONJUGATE PARKINSON VACCINES INDUCE POTENT AND THERAPEUTIC ANTIBODY RESPONSES IN MICE

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Aims

The progressive accumulation of misfolded α-Synuclein (aSyn) in the brain is widely considered to be causal for the debilitating clinical manifestations of synucleinopathies including, most notably, Parkinson's disease (PD). Vaccines targeting aSyn have been developed and are promising novel treatment strategies for such disorders. PD vaccines representing the current generation of vaccines are limited in their immunogenicity. To increase the potency and specificity of PD vaccination, we created the 'Win the Skin Immune System Trick' (WISIT) vaccine platform.

Methods

This novel class of gluconeoconjugate vaccines is specifically designed to leverage the potential of skin dendritic cells by targeting their C-type lectin receptors. WISIT PD vaccines were benchmarked to conventional aSyn-based, adjuvanted conjugate vaccines using immunological parameters including the strength of the specific antibody (Ab) response and the specificity of the Abs elicited for aggregated aSyn. Moreover, we tested their therapeutic efficacy in an established synucleinopathy seeding model in vivo.

Results

WISIT PD candidates elicited significantly stronger specific Ab responses compared to conventional peptide-carrier conjugate PD vaccines in BALB/c mice. This was evident over the entire dose range tested. Importantly, WISIT vaccine-induced Abs displayed higher selectivity for aSyn aggregates than those induced by conventional vaccines. Furthermore, Abs induced by selected WISIT candidates were shown to inhibit aSyn aggregation in a dose dependent manner in vitro. Most importantly, our top candidate vaccine was found to significantly reduce the propagation of synucleinopathy in vivo in a therapeutic setting. A strong negative correlation between the titers of aSyn-specific Abs and the level of pathology supports the therapeutic role of the Abs elicited.

Conclusions

Our studies provide proof-of-concept for the immunological efficacy of aSyn-targeting WISIT vaccines and support their further development.

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