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INDUCTION OF TOLERANCE FOR ANTIGEN-SPECIFIC THERAPY OF GRAVES' DISEASE AND ORBITOPATHY

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Graives' disease is an autoimmune disorder, which is characterized by stimulatory antibodies targeting the human thyrotropin receptor (TSHR), resulting in hyperthyroidism and multiple organ damage. The disease can be modelled in mice using adenoviral immunizations with the extracellular A subunit of the TSHR, which induces a long-term stable disease state. TSHR binding cAMP-stimulatory antibodies, thyroid enlargement, elevated serum thyroxin levels, tachycardia, cardiac hypertrophy and orbitopathy are observed in these Ad-TSHR-immunized mice. T cell epitope-derived linear peptides have been identified using immunized HLA-DR3 transgenic mice, which may induce tolerance towards TSHR at the group of David Wraith, Birmingham, UK. A combination of such peptides have being investigated in a first clinical phase I trial with encouraging results in patients with Graves' disease at Apitope Inc. Alternatively, cyclic peptides derived from the interaction site of the TSHR A domain with stimulatory anti-TSHR antibodies were injected intravenously in monthly intervals into mice modelling Graves' disease. These administrations of cyclic peptides were each timed two weeks after the respective Ad-TSHR immunizations, and re-established tolerance towards the antigen, improving symptoms of Graves' disease within 3 – 4 months after starting these therapies. In immunologically naïve mice, administration of the cyclic peptides did not induce any immune response.

Biography

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