Treating autoimmune diseases with tolerogenic peptides - apitopes®

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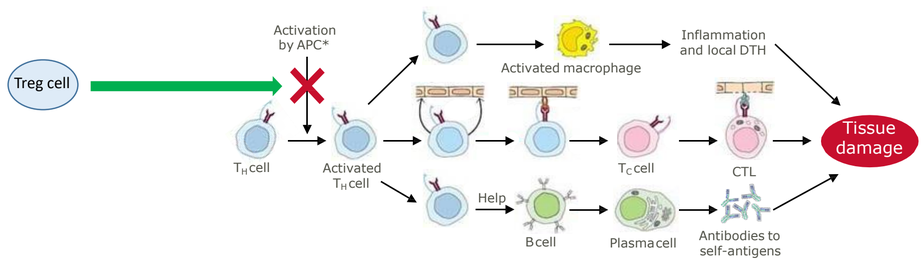
Introduction

Autoimmune diseases are often treated by general immune suppression which is associated with severe side effects and complications. Tolerogenic peptides, especially apitopes address the disease causing mechanism, the antigen-specific Th cells, and teach tolerance to the immune system through the induction of and activation of antigen-specific Treg cells.

Using this approach, Apitope has generated specific peptide immunotherapies for two different diseases, multiple sclerosis (MS) and Graves' disease and treated 78 patients in clinical trials.

Apitopes prevents autoimmunity at the earliest possible event in the immune response by activating T reg cells



The Apitope® Technology

Apitopes®:

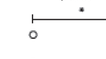
- Soluble synthetic peptides based on the human sequence which mimic the naturally processed T cell epitopes but do not require processing by antigen-presenting cells - antigen-processing-independent epitopes = Apitopes®.
- Apitopes® are identified using a proprietary discovery platform unique to Apitope comprising HLA-DR transgenic mice technology, human PBMC cultures and *in silico* prediction tools

Mode of action:

- Soluble apitopes® bind to empty MHC receptors and selectively trigger generation of IL-10 secreting regulatory Tr1-like cells which suppress pathogenic Th cells
- Soluble apitopes® administered without any adjuvants do not induce inflammation and have demonstrated good tolerability and safety profiles in clinical trials

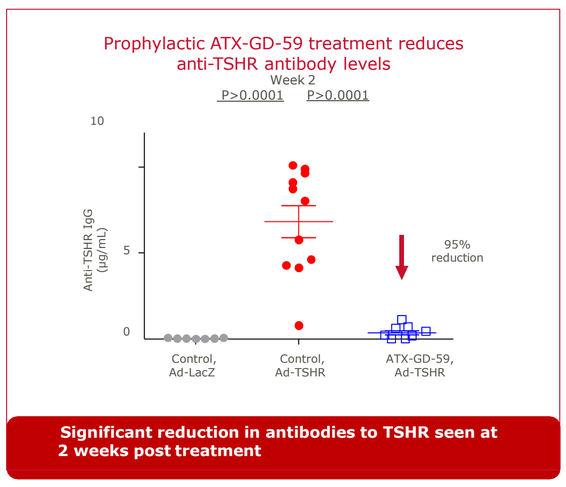
Wraith DC, CoCHE 2018
Burton BR et al., Nature communications 2014
Chataway et al., Neurology 2018
Jansson et al. Endocrinology 2018

Apitope propriety platform

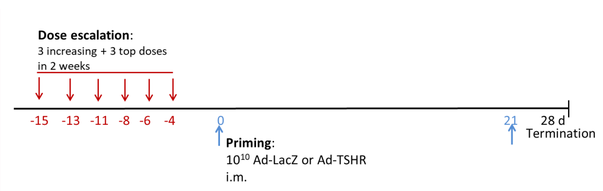
Apitope's patented discovery platform enables cost efficient selection of peptides which are proven to be safe and well tolerated		
Identify		Self antigen targeted in autoimmune disease, e.g. Thyroid Stimulating Hormone Receptor in Graves' disease or myelin basic protein (MBP) in multiple sclerosis
Design		Soluble tolerogenic (tolerance inducing) peptide that mimics naturally processed and presented epitopes from the self antigen
In vitro		Identify peptides that can bind to surface MHC class II of tolerogenic APCs without processing
Generate		Human and mouse T-cell reagent used to identify T-cell epitopes
In vivo		Determine capability to induce tolerance to full length antigen in different mouse models
Develop		Once a new candidate cocktail is found, it is patented and moved into preclinical development

ATX-GD-59 prevents generation of anti-TSHR antibodies in both mice and Graves' disease patients

in mice

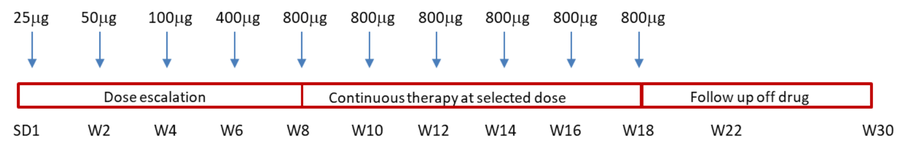


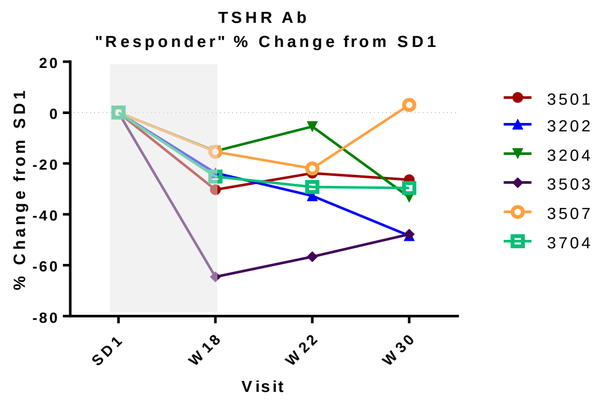
Significant reduction in antibodies to TSHR seen at 2 weeks post treatment

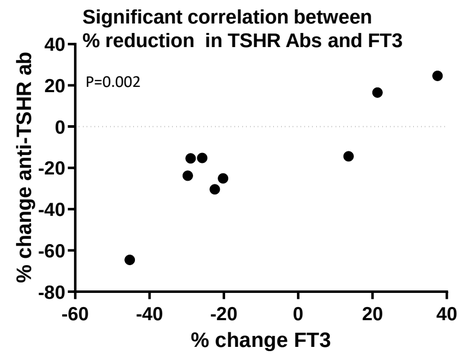


HLA-DRB1*0301 Tg mice were treated prophylactically with Apitope® ATX-GD-59 or PBS according to a dose escalation scheme as indicated. Animals were then primed with 10^{10} adenoviral vector particles expressing β-galactosidase (Ad-LacZ) or TSHR AA1-289 (Ad-TSHR) on week 0 and 3. At week 4, anti-TSHR antibodies were determined by ELISA and shown as mean ± SEM. Significance by one-way ANOVA + Bonferroni post-hoc testing: **= p<001; **** = p<0.0001.

in Graves' disease patients







12 Graves' disease patients not currently treated with anti-thyroid drugs were recruited and 8 completed the study per protocol (PP). 6 patients out of the 8 PP demonstrated reduced anti-TSHR abs levels, free T3 and free T4 levels. Primary end-point was met demonstrating the ATX-GD-59 to be both safe and well tolerated in that no treatment related serious adverse events were reported and the levels of T3 and T4 returned to normal (euthyroid) in a majority of patients.

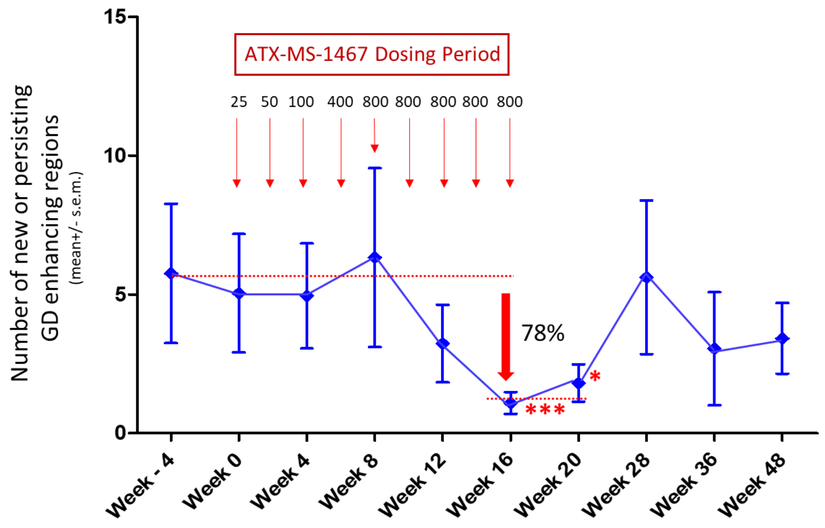
ATX-MS-1467 prevents new brain lesion formation in both mice and MS patients

in mice

ATX-MS-1467 treatment shows reduced lesion formation which translates into disease improvement in the EAE model

Treatment with ATX-MS-1467 100ug sc 3x/week from day 0 to day 14 in the (HLA-DR2xOb1)F1 double transgenic mouse. Experimental autoimmune encephalomyelitis (EAE) was induced with 200 ug mouse spinal cord homogenate in Freund's complete adjuvant.

in MS patients



Highly significant reduction of new lesion formation in MS patients (n=21) after intradermal administration of ATX-MS-1467 in a dose escalation regime every 2 weeks demonstrated with MRI.
*** P<0.001 vs. Week 0; * P<0.05 vs. Week 0

Apitope immunotherapy

- A highly targeted approach treating underlying cause of disease by selectively reinstating immune tolerance rather then global immune suppression
- The Apitope platform has proven efficacy in two different human diseases, multiple sclerosis and Graves' disease
- Proven efficacy of the platform in mouse models translates to human disease
- The administration of disease-specific peptide cocktails using a dose escalation protocol facilitates safe and efficacious products

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