**ABSTRACT**

**Purpose:** Modulation of T cell responses provides new opportunities for the treatment of autoimmune and inflammatory diseases. Tregitopes are regulatory T cell (Treg) epitopes endogenously found in IgG that are presented on MHC II to regulatory T cells (Treg) and provide beneficial immunomodulatory effects, paralleling effects attributed to intravenous immunoglobulin (IVIG) therapy. In this presentation, we will provide evidence that Tregitopes derived from human IgG can reproduce immunomodulatory effects of IVIG in vitro and in vivo that may bypass the harmful side effects of this current treatment.

**Methods:** More than six collaborating laboratories have evaluated the mechanisms of action and beneficial effects of Tregitopes in mouse models of MS (EAE), OVA-induced allergic airway disease, enzyme replacement therapy in mice lacking acid alpha-glucosidase (GAA) as a model of Pompe disease, and AAV-mediated gene transfer.

**Results:** Tregitopes cause CAD4+CD25+Foxp3+ Treg to expand and produce IL-10 in vitro, and Treg to be induced in vivo. Induction and functions of Tregs have been examined in vivo and in vitro; the mechanisms of action and beneficial effects of Tregitopes in mouse models of MS (EAE), OVA-induced allergic airway disease, enzyme replacement therapy in mice lacking acid alpha-glucosidase (GAA) as a model of Pompe disease, and AAV-mediated gene transfer.

**Conclusions:** Tregitopes, by inducing Tregs and tolerance, are promising for the treatment of autoimmune and inflammatory disorders and may be a powerful tool for the design of safer, more effective protein therapeutics, monoclonal antibodies, novel scaffolds, replacement therapies or biosimilars.

**RESULTS**

1. **Tregitopes suppress antigen-specific CD8+ responses**

2. **Tregitopes suppress EAE comparable to IVIG**

3. **Tregitopes suppress T1 type allogeneic responses in vivo**

4. **Tregitopes suppress T1 type allogeneic responses in vitro (human MLR model)**

**CONCLUSIONS**

- These studies are an exciting first step towards understanding tolerance induction by Tregitopes. The data indicate that Tregitopes induce tolerance by:
  - Activating Treg populations.
  - Shifting cytokine production from inflammatory (IFNγ) to tolerogenic (IL-10).
  - Modulating APC phenotypes.
- The studies suggest a parallel mechanism of action for IVIG and Tregitopes.
- Tregitope-induced tolerance is antigen-specific; its effects can be long lasting.
- Tregitopes may improve therapeutic approaches in autoimmune disease, transplantation, gene transfer and allergy as well as enabling safer, more effective protein therapeutics.

**Tregitopes Elicit Antigen Specific Tolerance**

- Highly conserved linear peptide sequences derived from autoelements such as immunoglobulin.
- Bind multiple MHC class II haplotypes with high affinity.
- Activate Treg cells to dampen immune response to antigens.
- Mechanism of Treg cells may be contact-dependent or mediated by cytokines.

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