Tregitopes: The active ingredient in IVG-mediated tolerance induction?

Leslie P. Cousens¹, Leonard Moise¹, William Martin⁵, and Anne S. De Groot²,³

¹Epivax, Inc., Providence, RI
²Institute for Immunology and Informatics, University of Rhode Island, Providence, RI

ABSTRACT
Purpose: In the course of screening IgG sequences for T cell epitopes, we identified regulatory T cell (Treg) epitope peptides, now called Tregitopes, contained in the conserved framework regions of Fab and FC. The distinguishing characteristics of Tregitopes include in silico signatures of high-affinity binding to multiple human HLA class II DR, and conservation across IgG isotypes as well as mammalian species. Tregitopes induce expansion of CD4⁺CD25⁺Foxp3⁺ T cells and suppress immune responses to co-administered antigens in vitro. Tregitopes may provide one explanation for the expansion and stimulation of Treg following intravenous immunoglobulin (IVG) therapy. Harnessing tolerogenic effects of Tregitopes provides a novel tool to suppress unwanted immune responses and maintain antigen-specific tolerance, thus changing treatment paradigms in autoimmunity.

Methods: To identify the mechanism(s) by which Tregitopes induce immune tolerance, expression of MHC II, CD80, CD86, and ILT3 expression on APCs, proportions of CD25⁺Foxp3⁺CD4⁺ Tregs, and IL-10 production were measured when mouse and human leukocyte populations were incubated with or without Tregitopes.

Results: We provide evidence that when APCs present Tregitopes to natural (n) Treg, APC expression of MHC II, CD80, and CD86 are decreased; expression of tolerance-associated marker ILT3 is increased. These results are consistent with reported effects of IVG (Bayat et al. Blood, 2003, 101:1756) and of the IgG-derived peptide NC21R (Sera et al. Immunol, 2009, 128:395). Moreover, Tregitopes increase IL-10-producing Treg.

We hypothesize that the observed effects of Tregitopes may be explained by the following sequence of events:
- APCs present Tregitopes to Tregs.
- Treg function and proliferation are induced.
- Tregs down-regulate co-stimulatory signals in the APCs.
- The combination of APC phenotype and activated Treg will reduce effector T cell functions.

CONCLUSIONS
- This represents an exciting first step towards understanding the mechanism of action of tolerance induction by Tregitopes and suggests a role for Tregitopes in the mechanism of action of IVG.
- Tregitopes modulate APC phenotype and induce Treg proliferation & IL-10 secretion. This effect is Tregitope specific: negative control peptides had no effect on CD86, CD80, MHC II, or ILT3 on APCs.
- Results indicate Tregitopes modulate antigen-specific T cell and B cell responses in vivo.
- Future studies will explore Tregitope-mediated tolerance induction at the cytokine milieu (e.g., IL-10, TGF-β) in vitro and in vivo mice.