In a recent study reported and published last month in the Journal of Experimental Medicine by UCSF investigators Brian Fife, Ph.D. and Jeff Bluestone, Ph.D., it has been shown that insulin itself is a contributing factor in the progression of type 1 diabetes and to prevent the disease, we must selectively target the insulin-specific, autoimmune T cells.

By creating a powerful treatment protocol to target these insulin-specific cells in an animal model of diabetes, these researchers were able to re-educate the immune system, helping to restore a state of self-tolerance and preventing further beta cell destruction. The past decade has seen a significant increase in the number of potentially tolerogenic therapies for treatment of new-onset diabetes. However, most treatments are antigen nonspecific, and the mechanism for the maintenance of long-term tolerance remains unclear. In a recent study reported and published in the Journal of Experimental Medicine by UCSF investigators Brian T. Fife, Ph.D. and Jeffrey A. Bluestone, Ph.D., an antigen-specific therapy has been developed using insulin-coupled antigen-presenting cells to treat diabetes in non-obese diabetic mice after disease onset.

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder resulting from the T cell mediated destruction of the insulin producing cells within the pancreas. This research study focused on developing and understanding methods to induce antigen specific tolerance, to selectively target the T cells responsible for autoimmune diabetes without compromising the body’s ability to fight infectious agents. In this study, a powerful treatment protocol was created to target these cells. Using this type of approach allowed the researchers to re-educate the immune system to selectively silence destructive immune responses -- in effect, restore a state of self-tolerance and prevent further tissue destruction.

The discovery, from a mouse model of a human autoimmune condition, suggests that insulin is a major autoantigen during the progression of autoimmune diabetes and selectively targeting the insulin specific T cells is an effective strategy to treat autoimmune diabetes. The success of this treatment relies on a negative regulatory pathway for T cells. This pathway, Programmed Death-1 (PD-1), when engaged with PD-1 Ligand (PD-L1) inhibits T cell
function, including the destruction of beta cells. Blocking this pathway reversed tolerance weeks after tolerogenic therapy by promoting antigen-specific T cell activity directly in infiltrated pancreas. PD-1/PD-L1 blockade did not limit T regulatory cell activity, suggesting direct effects on pathogenic T cells. Finally, we describe a critical role for PD-1/PD-L1 in another powerful immunotherapy model using anti-CD3, suggesting that PD-1/PD-L1 interactions form part of a common pathway to selectively maintain tolerance within the target tissues.

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