

## The Use of Peptide–Major-Histocompatibility-Complex Multimers in Type 1 Diabetes Mellitus

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### Abstract

Major histocompatibility complex (MHC) class I and MHC class II molecules present short peptides that are derived from endogenous and exogenous proteins, respectively, to cognate T-cell receptors (TCRs) on the surface of T cells. The exquisite specificity with which T cells recognize particular peptide–major-histocompatibility-complex (pMHC) combinations has permitted development of soluble pMHC multimers that bind exclusively to selected T-cell populations. Because the pathogenesis of type 1 diabetes mellitus (T1DM) is driven largely by islet-reactive T-cell activity that causes  $\beta$ -cell death, these reagents are useful tools for studying and, potentially, for treating this disease. When coupled to fluorophores or paramagnetic nanoparticles, pMHC multimers have been used to visualize the expansion and islet invasion of T-cell effectors during diabetogenesis. Administration of pMHC multimers to mice has been shown to modulate T-cell responses by signaling through the TCR or by delivering a toxic moiety that deletes the targeted T cell. In the nonobese diabetic mouse model of T1DM, a pMHC-I tetramer coupled to a potent ribosome-inactivating toxin caused long-term elimination of a specific diabetogenic cluster of differentiation 8+ T-cell population from the pancreatic islets and delayed the onset of diabetes. This review will provide an overview of the development and use of pMHC multimers, particularly in T1DM, and describe the therapeutic promise these reagents have as an antigen-specific means of ameliorating deleterious T-cell responses in this autoimmune disease.

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**Abbreviations:** (APC) antigen-presenting cell, (CD) cluster of differentiation, (CTL) cytotoxic T lymphocyte, (GAD65) glutamic acid decarboxylase 65 kD isoform, (HA) hemagglutinin, (IFN- $\gamma$ ) interferon gamma, (IGRP) islet-specific glucose-6-phosphatase catalytic subunit-related protein, (IL) interleukin, (MAB) monoclonal antibody, (MHC) major histocompatibility complex, (NOD) nonobese diabetic, (NRP) NOD-related peptide, (pMHC) peptide–major-histocompatibility-complex, (SAP) saporin, (TCR) T-cell receptor, (Tg) transgenic, (T<sub>H</sub>) T-helper, (T1DM) type 1 diabetes mellitus

**Keywords:** antigen-specific T cells, autoimmunity, immunomodulation, major histocompatibility complex, multimers, type 1 diabetes mellitus

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