The complexity of autoimmune diseases is a barrier to the design of strategies that can blunt autoimmunity without impairing general immunity. We have shown that systemic delivery of nanoparticles (NPs) coated with autoimmune disease-relevant peptide-major-histocompatibility-complex (pMHC) molecules triggers the formation and profound expansion of antigen-specific T-regulatory T-cells in different mouse models, including mice humanized with lymphocytes from patients, leading to resolution of a broad range of established autoimmune phenomena. I will highlight the engineering principles impacting biological activity, will illustrate how these nanomedicines interact with cognate T-cells and will describe the pharmacokinetic behavior and toxicological profile of this novel class of drugs, potentially useful for treating a broad spectrum of autoimmune conditions in a disease-specific manner.