similarly to T_R1 cells, were found to be essential for the establishment of antigen-specific tolerance. The B regulatory cells did not present peptide to cognate CD4 T cells *ex vivo*, and produced IL-10 upon lipopolysaccharide stimulation. However, they were necessary for nanoparticle efficacy, which was abrogated when they were depleted using anti-CD20 monoclonal antibodies. Although antigen-presenting cells from the pancreatic lymph nodes of treated mice produced lower levels of pro-inflammatory mediators in response to lipopolysaccharide, nanoparticle treatment did not cause general immunosuppression. Treated mice were able to clear an acute viral infection and make antibodies to an exogenous antigen as readily as untreated mice. The authors also showed that nanoparticle therapy resolved autoimmune symptoms in immunodeficient non-obese diabetic mice (*Il2rg*$^{-/-}$) reconstituted with peripheral blood mononuclear cells from patients with type 1 diabetes.

Thus, the therapy appears to work by activating a known pathway of peripheral tolerance (**Fig. 1**). The nanoparticles induce the generation of T_R1 cells, which secrete the cytokines IL-10, IL-21 and TGF-β. The cytokines suppress local antigen-presenting cells that bear the cognate autoantigen and induce expansion of B regulatory cells, which also participate in suppressing the antigen-presenting cells. The result is a reduction in inflammation and in the presentation of peptides bound to major histocompatibility complex class II (pMHCII) complexes to autoreactive T cells, effectively halting disease progression.

Nanoparticles bearing pMHC complexes may provide a new class of therapeutics to treat autoimmunity in a disease- and organ-specific way without compromising systemic immunity. As this approach is advanced toward clinical trials, it will be important to consider several key issues. Potential toxicity over the short- and long-term is not well understood. Moreover, MHC class II molecules are highly polymorphic, and each individual carries only one of several dozen MHC class II variants, which means that tailored therapies might be needed to avoid immune responses to foreign MHC class II molecules. Crucially, for most autoimmune diseases, including the three studied by Santamaria and colleagues[1], multiple autoantigens have been identified, and some autoimmune diseases have no known dominant reactivity to a specific peptide. Finally, the progression of autoimmune diseases is marked by epitope spreading, in which the immune response changes from targeting a primary epitope to subsequently targeting additional epitopes. In principle, it should be possible to address this by administering nanoparticles with multiple specificities.

Which autoimmune diseases are most amenable to nanoparticle therapies? The low-hanging fruit are likely to be diseases that have single, defined auto-antigens, such as myasthenia gravis, thyroid autoimmunity and neuromyelitis optica. It is also necessary to consider how nanoparticles would be combined with existing therapies. For example, could they be administered together with one of the ten US Food and Drug Administration-approved drugs used to treat multiple sclerosis? For this and other autoimmune diseases, anti-CD20 antibody is effective, but Santamaria and colleagues[1] show that B cells are required for the nanoparticles to work and that anti-CD20 antibody abrogates the therapeutic effects. Another question concerns the efficacy of nanoparticles in the context of ongoing inflammatory processes, such as IL-17 responses.

Monitoring the status of the immune system will be necessary to assess the clinical benefit of nanoparticles and might require the use of tetramers or a more global measure of the immunoregulatory effect, for example by quantifying T_R1 cells or B regulatory cells. Nonetheless, the antigen specificity of the therapy and the absence of global immunosuppression suggest that nanoparticles could have a substantial impact on the treatment of autoimmune diseases.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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