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Anti-Idiotypic Antibodies for Controlled Reversal of Anti-CD3 Lymphodepletion

Researchers at Stanford have developed anti-idiotypic antibodies that reverse anti-CD3 monoclonal antibody therapy, giving clinicians control over the depth and timing of T cell depletion before adoptive cell therapy. These reversal agents bind the anti-CD3 antibody itself and block its engagement of CD3, allowing residual circulating antibody to be neutralized on demand. Two lead agents bind teplizumab with high affinity, block teplizumab binding to human peripheral blood mononuclear cells, and inhibit teplizumab-driven T cell activation in a concentration-dependent manner. The two agents recognize distinct epitopes on teplizumab and differ in the extent of blockade they achieve, so the degree of reversal can be tuned.

In mouse studies, a single dose of either agent accelerated teplizumab clearance from serum, and in a humanized graft-versus-host disease model the agents restored human cell engraftment that teplizumab had suppressed. This capability addresses a core limitation of anti-CD3 therapy: serum levels vary widely between patients and circulating antibody can persist for days to weeks, producing inconsistent depletion and leaving residual antibody that destroys infused cell products. By clearing that antibody at a defined point, the reversal agents open a therapeutic window for pairing anti-CD3 lymphodepletion with regulatory T cell and other engineered T cell therapies.

Applications

- On-demand reversal of anti-CD3 antibody therapy such as teplizumab
- Conditioning regimens that pair anti-CD3 lymphodepletion with infused regulatory T cell products

- Prevention and treatment of graft-versus-host disease following bone marrow transplantation
- Immune tolerance induction for organ and tissue transplantation
- Type 1 diabetes and other autoimmune indications treated with anti-CD3 antibodies
- Safety and rescue agent for patients experiencing adverse effects during anti-CD3 therapy

Advantages

- Provides control over the depth and duration of anti-CD3 mediated T cell depletion
- Reduces patient-to-patient variability in lymphodepletion caused by differences in anti-CD3 pharmacokinetics
- Clears residual circulating anti-CD3 antibody that would otherwise deplete infused cell therapy products
- Opens a defined therapeutic window for adoptive transfer of regulatory T cells and other engineered T cells
- Two lead candidates bind distinct epitopes on teplizumab, allowing the degree of reversal to be tuned
- Applicable to approved and investigational anti-CD3 antibodies across immunology and cell therapy pipelines

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