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Engineered orthogonal CD3 T cells: A Novel Prevention and Treatment Strategy for Transplantation, Autoimmunity, and Cancer Therapy

Stanford researchers have created the orthoCD3 T cells, by engineering T cells to resist depletion from anti-CD3 antibodies during lymphodepletion, thereby, enhancing the efficacy of T cell therapies for cancer, autoimmune disorders, and transplant rejection.

Current T-cell therapies are essential for treating conditions like cancer, autoimmune diseases, and transplant complications, however, they face significant limitations due to lymphodepletion caused by anti-CD3 antibodies, such as Muromonab (OKT3) and Teplizumab. These antibodies, while essential for lymphodepletion to eliminate existing T cells and make space for therapeutic T cells, interferes with T cell therapies as they also deplete the therapeutic T cells, thereby reducing the treatment's effectiveness and compromising potential synergies of anti-CD3 and T cell adoptive therapy. Furthermore, the timing of T cell administration is crucial —too early, and the anti-CD3 antibodies will deplete the therapeutic cells; if too late, then the patient's T cells may recover, leaving less room for the therapeutic cells, leading to suboptimal treatment outcomes.

To address this issue, Stanford researchers have leveraged advanced genetic engineering approaches to create the orthoCD3 T cells, which are resistant to lymphodepletion. Using techniques like yeast surface display, site-directed mutagenesis and CRISPR-Cas9-mediated homology-directed repair, Stanford researchers have engineered a mutant version of the CD3 epsilon molecule that does not bind to anti-CD3 antibodies. This allows orthoCD3 T cells to evade depletion by anti-CD3 antibodies, ensuring their survival and functionality during treatment.

By integrating orthoCD3 technology with existing treatments, we can significantly enhance the efficacy and reliability of T-cell therapies for prevention and treatment of cancer, autoimmune disorders, and transplant rejection.

Stage of Development:

Preclinical. The next steps to market include validation in preclinical models to demonstrate preserved T cell performance, validation of gene modification approaches pre-clinically and establishing GMP grade cell therapy manufacturing and validation runs.

Applications

- Prevention of allograft rejection in solid organ and tissue transplantation
- Prevention of Graft-Versus-Host Disease (GVHD) after bone marrow transplantation
- Treatment of autoimmune disorders, specifically but not limited to Type 1 diabetes
- Improving CAR T cell therapies in cancer treatment
- Improve immunity by allowing the adoptive transfer of T cells specific for responding to infections during lymphodepletion

Advantages

- Allows for better engraftment and proliferation of therapeutic T cells by selective depletion of undesired T cells leading to vacated space and nutrients
- Enhanced therapeutic outcomes
- Anti-CD3 makes inflammatory T cells more tolerogenic, making its use in combination with orthoCD3 regulatory T cells more effective for autoimmune diseases.
- Provides enhanced timing and efficacy by eliminating the problematic timing window for administering T cell therapies post-anti-CD3 treatment

Patents

- Published Application: WO2025024281

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