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Orthogonal Anti-CD3 Antibody for Purification, Targeting, and Safety Control of Engineered T Cell Therapies

Researchers at Stanford have developed orthoTeplizumab, an antibody that selectively recognizes engineered T cells without binding a patient's own T cells. It targets orthogonal CD3 (orthoCD3), an engineered version of a receptor carried by cell therapy products and binds it with sub-nanomolar affinity while sparing the natural form of the receptor.

Cell therapies built on orthoCD3 are designed to survive antibody treatments that clear disease-causing T cells, making them useful in transplantation, autoimmunity, and cancer. These products have lacked a matched reagent that distinguishes engineered cells from the patient's own cells, which limits how the cells are purified during manufacturing and how they are controlled after infusion. The Stanford team addressed this by re-engineering teplizumab, a clinically approved anti-CD3 antibody, to switch its specificity to orthoCD3.

The antibody activates orthoCD3 cells while leaving normal T cells near background levels. This selectivity supports positive selection of edited cells during manufacturing, incorporation into bispecific T cell engagers that recruit only engineered cells to a target, and on-demand depletion of engineered cells in a patient as a safety switch.

Applications

- Kill switch to selectively deplete orthoCD3 engineered cells in vivo

- Bispecific T cell engagers that recruit only orthoCD3 engineered cells to a target antigen
- Positive selection and purification of edited cells during cell therapy manufacturing
- Selective activation and expansion reagent for orthoCD3 engineered cells
- Detection and tracking of orthoCD3 engineered cells for research and clinical monitoring

Advantages

- Sub-nanomolar binding to orthoCD3 with near-background activity on wildtype T cells
- Single reagent covering manufacturing, in vivo targeting, and safety control
- Positive selection of edited cells without adding a separate selection marker to the construct
- Built on teplizumab, an antibody scaffold with an established clinical safety record
- Confines bispecific engager activity to engineered cells, sparing endogenous T cells

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