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Multi-Pass Scaffold Technology for Modular CAR T-Cell Therapies

Stanford researchers have developed the Broadly Usable Multi-Pass Engineered Receptor (BUMPER) architecture, a novel protein engineering platform for assembling stable, multifunctional cell surface receptors. BUMPER technology enables separate anchoring of multiple functional domains, such as antigen-binding regions, within distinct transmembrane segments of a single protein — reliably supporting homogeneous expression and overcoming misfolding and domain-interference issues commonplace in current multi-specific chimeric antigen receptor (CAR) T-cell therapies.

Single-target CAR T therapies for cancer have exhibited promise but often fail in solid tumors due to antigen loss and tumor heterogeneity, prompting the need for multi-specific approaches. Existing methods to generate multi-targeting CAR T cells face challenges including decreased expression, misfolding, and unpredictable efficacy, particularly when combining multiple binding domains in a single protein. BUMPER eliminates these issues by providing a modular, plug-and-play scaffold for integration of diverse protein domains at flexible sites and spacings, all while supporting robust *in vivo* expression and performance.

The inventors' stable scaffold architecture supports efficient production of multifunctional proteins that maintain in vivo efficacy, expanding possibilities for next-generation CAR T therapies targeting multiple tumor antigens simultaneously, as well as broader applications in immune cell signaling and therapeutic protein delivery.

Stage of Development
Preclinical, with *in vitro* and *in vivo* validation data obtained

Applications

- Multi-specific CAR T-cell therapies for treating cancers with complex or heterogeneous antigen expression profiles
- Delivery of diverse membrane-bound functional domains, including cytokines and death signals
- Modular engineering of cell and protein therapies addressing challenging disease targets

Advantages

- Robust expression of engineered proteins without inter-domain interference or misfolding
- Modular, plug-and-play domain incorporation enables accelerated design and testing
- Stable scaffold ensures high in vivo expression and therapeutic efficacy
- Compatible with existing CAR T-cell manufacturing protocols for scalable translation

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