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Using de novo protein design to target MHC-1 and MR-1 antigens

Stanford scientists have created a de novo protein design platform that designs binding proteins that specifically target antigens in the major histocompatibility complex (MHC). Designing proteins capable of specific targeting of antigens can be transformative and enhance CAR-T treatments.

Technology Summary:
Stanford scientists have created a de novo protein design platform that designs binding proteins that specifically target antigens in the major histocompatibility complex (MHC). Designing proteins capable of specific targeting of antigens can be transformative and enhance CAR-T treatments.

MHCs are protein molecules that bind pathogen-associated or damage-associated molecular patterns and display them on the surface of cells for recognition by the immune system. T cell receptors (TCRs) have evolved to recognize the peptide identities on the MHC-peptide complexes via interaction with both the antigenic peptide and the MHC. There have been significant efforts to engineer TCRs to allow improved recognition and destruction of virus-infected cells or cancer. However, TCR engineering remains a challenge due to its structural complexity.
The creation of a non-TCR protein platform to design functional mimetics of TCRs that recognize the MHC-peptide complexes can overcome the challenges associated with TCR engineering. Proteins that specifically bind to an MHC-peptide complex of interest are designed using computer-based protein engineering and high throughput screening assays. The designed binding protein, or TRACeR, is simpler in structure than TCRs, and comprises an antigenic peptide recognition element and an MHC recognition element. Selected binders are screened for binding strength against thymic epithelial cells to minimize cross-reactivity with self-MHC-peptides. Importantly, TRACeRs have been tested in CAR-T cells and have positive killing results. Consequently, TRACeRs have the potential to drastically improve CAR-T

therapy efficacy and transform the CAR-T field by facilitating the design of binding proteins that specifically target relevant antigens.

Stage of Developement:
Preclinical – *in-vitro*

Applications

- Development of antigen binders for CAR-T therapy
- De novo protein design for liquid biopsy tests and other diagnostics

Advantages

- TRACeRs are straightforward to design and optimize
- TRACeRs are specific for the selected antigen
- TRACeRs are simpler in structure than TCRs

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