Docket #: S18-448

Optimized CAR T cell hinge regions enhance CAR functionality

Disease Indication Oncology, hematological cancers, breast cancer, solid tumors

Drug Format Cell therapy

Drug Class Best-in-class

Target CD19, HER2, B7-H3, GPC2 and all other tumor antigens

Research stage and Preliminary data
in vitro:
T-cells expressing a CD19-targeting CAR construct incorporating a hinge/transmembrane region derived from CD28 but a costimulatory domain from 4-1BB showed greater activity than CAR without the modified region while retaining enhanced persistence unique to 4-1BB costimulatory CARs.

in vivo:
In a mouse xenograft model using low expression of the CD19 antigen, animals treated with the modified CAR construct has increased survival, showing greater antitumor activity than approved CD19-targeting CAR-Ts tisagenlecleucel or axicabtagene ciloleucel. Responses were also sustained, with greater persistence than axicabtagene ciloleucel. In addition to CD19, in vivo activity was also extrapolated to CARs targeting HER2 and B7-H3.

Background
Existing CAR-T cell therapies have greatly improved outcomes for difficult to treat blood cancers. However, the treatments have shortcomings in their susceptibility to disease relapse and resistance, which can be driven by low expression of the CAR's targeted tumor antigen. Researchers at Stanford have modified the extracellular 'hinge' region of the CAR construct to enable activity against even low-expression targets. Optimizing various domains of the CAR-T construct- hinge and

transmembrane regions, as well as co-stimulatory domains– produced responses in a mouse model that had greater anti-tumor activity and longer persistence than existing clinical options.

Mode of action
Optimized structural elements on a CD19-targeting CAR-T- a CD28-derived hinge region and a 4-1BB-derived co-stimulatory domain- offer stronger activity against low-frequency target antigens, paired with increased persistence versus existing CAR-T products. Researchers have demonstrated preclinical antitumor activity with CARs targeting CD19, HER2, and B7-H3, with potential applications across a broader range of tumor antigens.

Related Technologies:
Stanford docket S18-453 - "Chimeric Antigen Receptors Targeting Glycipan-2"
This invention describes CARs that selectively target GPC2. GPC2 has very restricted expression in normal tissue but is expressed on many hard-to-treat pediatric and adult solid tumors. This technology provides new CARs that may be used as therapeutics for difficult to treat solid tumor cancers.

Applications

- Cancer immunotherapeutics
- Blood cancers
- Solid tumors

Advantages

- Responds to lower levels of target antigen expression
- Prevents immune escape and relapse
- Longer treatment persistence

Publications

- Robbie G. Majzner, Skyler P. Rietberg, Elena Sotillo, Rui Dong, Vipul T. Vachharajani, Louai Labanieh, June H. Myklebust, Meena Kadapakkam, Evan W.

Weber, Aidan M. Tousley, Rebecca M. Richards, Sabine Heitzeneder, Sang M. Nguyen, Volker Wiebking, Johanna Theruvath, Rachel C. Lynn, Peng Xu, Alexander R. Dunn, Ronald D. Vale, Crystal L. Mackall; Tuning the Antigen Density Requirement for CAR T-cell Activity. *Cancer Discov* 1 May 2020; 10 (5): 702–723.

Patents

- Published Application: WO2020227446
- Published Application: 20220218751

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