Docket #: S17-119

Transiently Regulated CAR-T Cells Engineered to Prevent T-cell Exhaustion and Improve Immunotherapy

A Stanford research team has patented methods that can prevent or reverse T cell exhaustion, thereby increasing the effectiveness of adoptive T cell therapies to fight cancer or chronic infections. These include engineering regulatable chimeric antigen receptors (CAR) as well as identifying a group of small molecules that can modulate or inhibit TCR signaling. Immunotherapy using CAR-T cells relies on endogenous T cell receptor (TCR) signaling which is responsible for optimal T cell activation and potent antitumor or anti-infective effects. However, continuous activation of CAR T cells can result in a dysfunctional state called "T cell exhaustion", reducing the overall effectiveness of therapy. To address this overstimulation problem, the inventors genetically engineered a regulatable CAR by attaching a protein domain that allows for control over CAR surface expression via addition of an FDA-approved small molecule drug. This system is designed such that CAR T cells can undergo temporary periods of rest during which the CAR T cell ceases to signal, thus mitigating T cell exhaustion and restoring therapeutic efficacy. In addition, the inventors showed that certain small molecules that inhibit protein kinases can also address the overstimulation problem through transient inhibition of TCR signaling. Both inventions have applications in basic research or immunotherapy for infectious disease or cancer.

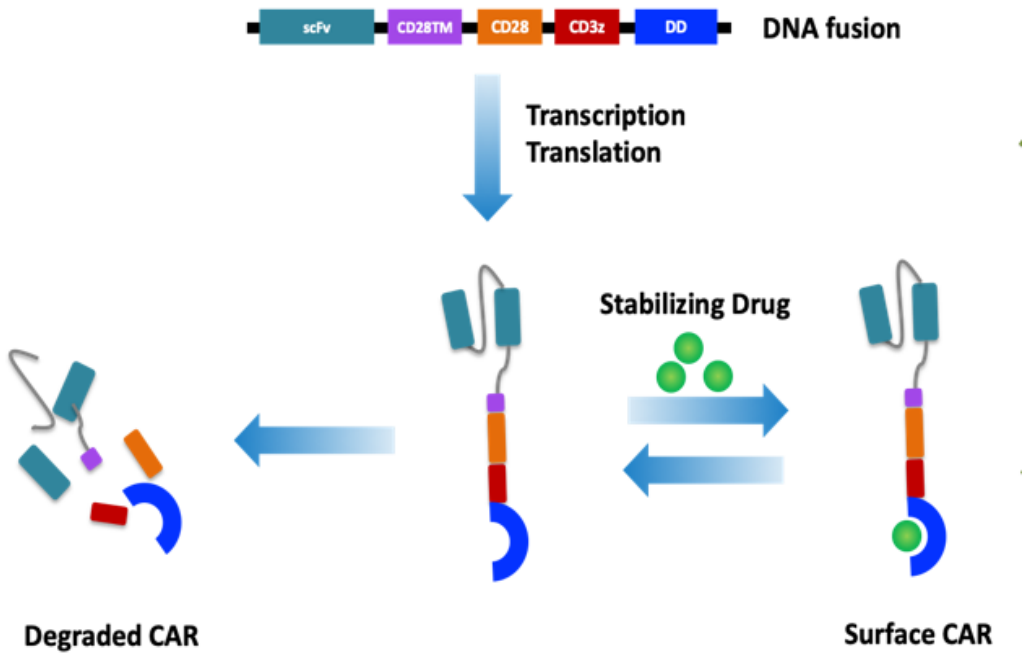

Image courtesy the Mackall Lab

Stage of Development - Proof of Concept

The inventors have established an animal model of regulating CAR surface expression and demonstrated proof-of-concept for the engineered regulatable CAR system *in vitro* and *in vivo*:

- *In vitro* - Transient rest (i.e., removing the engineered chimeric antigen receptors from the cell surface for 72-96 hours) can reinvigorate T cells following exhaustion. This substantially enhances their function.
- *In vivo* – Engineered chimeric antigen receptor and activity can be regulated. Culturing CAR T cells in the absence of the small molecule drug in order to "hide" surface CAR mitigates CAR tonic signaling/exhaustion and improves in vivo efficacy.

The inventors also used a known, FDA-approved drug to demonstrate the effects of tyrosine kinase inhibitors on reversing T cell exhaustion and augmenting T cell function in vivo. Further studies and collaborations with additional Stanford researchers have demonstrated similar or stronger effects using different, novel compounds:

- *Ex vivo* - CAR-T cells expanded ex vivo in the presence of tyrosine kinase inhibitors and infused into mice: a) had profoundly augmented proliferative capacity in vivo and b) could cure mice engrafted with osteosarcoma.

Applications

- **Immunotherapy** - prevent or reverse T cell exhaustion in cell therapy for cancer or chronic infection, including:
  - *Ex vivo* expansion for adoptive transfer
  - *In vivo* modulation of T cell receptor signaling
- **Research** - engineered T cell receptors and methods using protein kinase inhibitors could be used to study basic T cell function, signaling and exhaustion reversibility

Advantages

- **Enhanced CAR-T immunotherapy:**
  - preventing or reversing T cell exhaustion could improve effectiveness of immunotherapy for cancer or chronic infections
  - could improve cytotoxicity, proliferative capacity, cytokine secretion and formation of memory T cells
- **Transient effects** - Controlled CAR expression (and thus CAR signaling) as well as compounds' inhibitory effect on TCR signaling both provide mechanisms for T cells to "rest" and then restore functionality
- **Direct modulation:** - addresses root cause of T cell exhaustion (i.e., persistent antigen exposure leading to continuous TCR signaling) instead of relying on accessory pathways (such as PD-1/PD-L1)

Publications

- Weber EW, Parker KR, Sotillo E, Lynn RC, Anbunathan H, Lattin J, Good Z, Belk JA, Daniel B, Klysz D, Malipatlolla M, Xu P, Bashti M, Heitzeneder S, Labanieh L, Vandris P, Majzner RG, Qi Y, Sandor K, Chen LC, Prabhu S, Gentles AJ, Wandless TJ, Satpathy AT, Chang HY, Mackall CL (2021). Transient rest restores functionality in exhausted CAR-T cells through epigenetic remodeling. *Science*,

372(6537), eaba1786.

Patents

- Published Application: WO2018183888
- Published Application: 20210032363
- Published Application: 20240293461
- Issued: 11,938,153 (USA)

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