Docket #: S17-119B

Methods to Prevent T-cell Exhaustion and Improve CAR-T Cell Immunotherapy with Small Molecules

A team of Stanford researchers has identified a group of small molecules that can prevent or reverse T cell exhaustion, thereby increasing the effectiveness of adoptive T cell therapies to fight cancer or chronic infections. Immunotherapy using CAR-T cells relies on T cell receptor (TCR) signaling to activate the cells that will mediate potent antitumor or anti-infective effects. However, over time, chronic signaling through the endogenous TCR or CAR can induce a dysfunctional state called "T cell exhaustion", reducing the overall effectiveness of therapy. Moreover, CARs are prone to antigen independent signaling in vitro and in vivo, further underscoring the need to modulate CAR signaling to preserve CAR T function. The inventors utilized small molecules to inhibit protein kinases and address this overstimulation problem. Since proximal kinases are necessary to transmit TCR and CAR signaling, modulating their effects in a rational manner can enhance CAR-T cell function. This approach could be used in vivo or ex vivo to expand genetically engineered T cells that are less exhausted and therefore more potent. This reversible "CAR-T switch" system transiently inhibits TCR or CAR signaling to prevent or reverse T cell exhaustion and restore T cell function, with applications in basic research or immunotherapy for infectious disease or cancer.

Stage of Research

The inventors initially 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 effects using different, novel compounds (*further described in* Stanford Docket S18-061: Small Molecule modulators of chimeric antigen receptors (CAR) T cells).

CAR-T cells expanded ex vivo in the presence of tyrosine kinase inhibitors maintained a memory-like phenotype, which is associated with improved clinical responses in patients. When these cells were infused into mice, they: a) demonstrated profoundly augmented proliferative capacity and persistence in vivo and b) exhibited durable control of leukemia or osteosarcoma compared to CAR-T cells expanded in the absence of the inhibitors.

Applications

- **Immunotherapy** - Prevent or reverse T cell exhaustion in cell therapy for cancer or chronic infection for:
  - Ex vivo expansion of engineered CAR-T cells
  - In vivo modulation of CAR or T cell receptor signaling
- **Research** – methods using protein kinase inhibitors could be used to study basic T cell function and signaling

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 and/or cytokine secretion
- **Transient effects** – Transient and reversible effects on CAR and T cell receptor signaling, providing a mechanism for T cells to "rest" and maintain or restore functionality
- **Direct modulation** - addresses root cause of T cell exhaustion (i.e., 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. Transient rest restores functionality in exhausted CAR-T cells through epigenetic remodeling. *Science*. 2021 Apr

2;372(6537):eaba1786. PMID: 33795428; PMCID: PMC8049103.

Patents

- Published Application: 20200101108

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