Docket #: S21-195

Screening for Gene Modifications to Improve T Cell Function

A major barrier in CAR-T cell therapies has been T cell exhaustion, which affects the durability and effectiveness of treatments, particularly for solid tumors. This is caused by chronic tumoral T cell activation which limits their ability to kill the cancer cells due to impaired proliferation, cytotoxicity, and effector functions. Therefore, identifying methods to improve T cell function and resist exhaustion via genetic engineering of T cells represents a highly promising therapeutic approach and major focus of the cell therapy field.

Stanford researchers have developed an in vitro T cell exhaustion model with genome-wide CRISPR screens for genes that improve these T cell functions. Several of these genes have been identified that not only prevent exhaustion but also improve T cell survival in the presence of chronic antigen in vitro and persistence in tumor models in vivo. Modification of these genes can improve therapeutics in the CAR-T setting as well as other adoptive T cell-based therapies.

Stage of Development
Proof of concept with *in vitro* and *in vivo* data

Applications

- Researchers and companies could use the screening approach to dissect additional aspects of T cell function ie. perform screens based on cytokine secretion, surface receptor expression, and other phenotypes.
- Targeting of the identified genes may be directly therapeutically relevant to patients with cancer and other immune-mediated diseases ie. with engineered cell therapies (CAR-T cells) and/or as therapeutic targets for other drug modalities.

Advantages

- This screening approach enables screening at much larger scale than is feasible in mouse models (in vivo screening), which enables comprehensive and unbiased discovery of new factors in the setting of T cell exhaustion.
- Several of the discovered genes exhibit improved in vitro and in vivo function relative to unmodified T cells with the vast majority of these having not been previously described.

Publications

- Belk JA, Yao W, Ly N, Freitas KA, Chen YT, Shi Q, Valencia AM, Shifrut E, Kale N, Yost KE, Duffy CV, Daniel B, Hwee MA, Miao Z, Ashworth A, Mackall CL, Marson A, Carnevale J, Vardhana SA, Satpathy AT. "Genome-wide CRISPR screens of T cell exhaustion identify chromatin remodeling factors that limit T cell persistence." Cancer Cell. 2022 Jul 11;40(7):768-786.e7. Epub 2022 Jun 23.

Patents

- Published Application: WO2023010073
- Published Application: 20240327826

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