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MANIPULATING T CELL REGULATORY GENES TO IMPROVE CAR T CELL THERAPY

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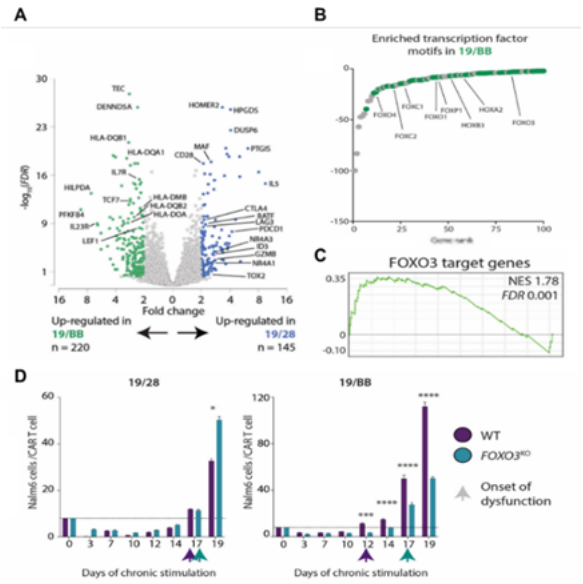
Value proposition: *An advanced CAR-T cell therapy engineered to reduce T cell exhaustion, enhancing durability and effectiveness in cancer treatment by overcoming one of the leading causes of long-term treatment failure.*

Technology Description

Researchers at Washington University in St. Louis have developed a composition of edited CAR-Ts containing modulated levels of regulatory transcription factors to enhance T cell persistence despite repeated antigen stimulation. T cell exhaustion occurs when the TCR is repeatedly stimulated by the same antigen. As a result, all the T cell's effector functions become attenuated, and the T cell permanently differentiates into the exhausted phenotype, to reduce continual activation of the adaptive immune system. For CAR-Ts, exhaustion similarly weakens the cells' responses to tumor, and is a leading cause of long-term failure in the treatment of cancer.



Above Figure: *Figure to the left shows A) Volcano plot of genes differentially expressed in exhausted CD19/4-1BB (19/BB) or CD19/CD28 (19/28) CAR-T cells. B) Enriched motifs in exhausted vs non-exhausted 19/BB CAR-T cells, as determined by transposase accessible chromatin sequencing. C) Geneset analysis showing FOXO3 target genes are generally upregulated in exhausted 19/BB CAR-T. D) Knockout of FOXO3 delays the onset of exhaustion in 19/BB but not 19/28 CAR-Ts, when incubated the Nalm6 (CD19+) leukemia line.*

Publications

Inducing T cell dysfunction by chronic stimulation of CAR-engineered T cells targeting cancer cells in suspension cultures. STAR Protocols (2023)

Stage of Research

This invention shows that the transcription factor forkhead family O3 (FOXO3) plays a central role in promoting the dysfunction of 41BB costimulated, but not CD28 costimulated, CAR T cells. Disruption of the gene encoding this protein significantly improves anti-tumor CAR T cell function and delays the onset of dysfunction that results from chronic antigen exposure.

Applications

- Cancer Treatment
- Car T cell therapy

Key Advantages

- Enhances T cell fitness without compromising efficacy
- Can rescue already exhausted T cell functions
- Simple to implement method

Patents

Patent application filed

Related Web Links – Nathan Singh Profile**;** Singh Lab