Docket #: S20-397

Modulating BHLHE40 in the differentiation of type 1 regulatory T cells and controlling T cell exhaustion

Exhausted T cells are T cells that become dysfunctional after a period of time and play a role in reduced efficacy of T cell targeted immunotherapies. Sometimes the cell product is no longer detectable in the peripheral blood, due to potential exhaustion or lack of engraftment. Additionally, most T cells become exhausted when they cannot properly differentiate into effector memory T cells, thereby disrupting their persistence in the body. Current approaches to address this issue have been limited, as they rely on restarting from different T cell progenitors instead of trying to manipulate the underlying molecular pathways that are involved in T cell memory.

Inventors at Stanford have developed a method to show how modulating certain transcription factors can improve adaptive immunity. They demonstrated that memory T cells highly express the BHLHE40 transcription factor and modulating the expression of BHLHE40 can lead to the development of novel cancer immunotherapies. Through modulation of BHLHE40 transcription factor, the Roncarolo Lab was able to decrease the frequency of T cells becoming exhausted. BHLHE40 is required for efficient expression of cytokines including: IFNg, IL4, and IL-2. Knocking out BHLHE40 in human naive CD4+ T cells leads to an increase in IL-10 production but does not have a significant effect in IL10 production when knocked out in total CD4+ T cells.

By inhibiting a transcription factor (e.g. through genetic manipulation), the invention can be used to prevent the differentiation of a subset of cells and skew the differentiation into another subset of cells. By identifying the transcription factors involved in the differentiation, cells can more easily differentiate in vitro and in vivo and be leveraged for the development of novel immunotherapies.

Applications

- Cell manufacturing by upregulating transcription factors during the production of CAR-T cells or in vivo post infusion.
- Cell control and targeting
- Immunotherapy and CAR-T cell therapy

Advantages

- Targets underlying molecular pathways involved in T-cell memory instead of T-cell progenitors
- Reduces cell manufacturing time
- Increases Tr1 cell yield

Publications

- Uyeda, M. J., Freeborn, R. A., Cieniewicz, B., Romano, R., Chen, P. P., Liu, J. M. H., ... & Roncarolo, M. G. (2021). "BHLHE40 Regulates IL-10 and IFN-? Production in T Cells but Does Not Interfere With Human Type 1 Regulatory T Cell Differentiation". Frontiers in immunology, 12, 2705.

Patents

- Published Application: WO2022104056
- Published Application: 20240018474

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