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Methods to improve CAR T cell efficacy and safety by modulating mediators of phagocytosis

There are several barriers to widespread use of CAR T-cell therapy. One of them is toxicity, primarily cytokine release syndrome (CRS) and neurologic toxicity, but also on-target off-tumor toxicity. Another barrier is the lack of CAR T cell persistence, and more efficacious CAR-T cell therapies are needed especially those targeting solid tumors.

The Mackall Lab at Stanford invented a novel way to harness the macrophage – CAR T cell interaction with the goal to address those two limitations: 1) Create a safety switch to quickly deplete CAR T cells in cases of toxicity, and 2) manipulate CAR T cells to enhance their persistence, improving their anti-tumor activity. The safety switch works by blocking "don't eat me" signals on the surface of CAR-T cells, resulting in efficient and fast elimination of CAR T cells by macrophages. Having an off-the-shelf antibody which can effectively deplete CAR T cells when they cause toxicity can be a valuable tool for immunotherapy. To obtain the opposite outcome and increase expansion and persistence exploiting the same CAR-T cell/macrophage regulatory axis, we over-express "don't eat me" signals on CAR T cells. This manipulation has no deleterious effect on their cytotoxic activity, but yields CAR-T cells more resistant to elimination by macrophages, leading to superior activity in models of solid and liquid tumors.

Applications

- CAR-T cell immunotherapies
- Other T cell based therapies

Advantages

- Capable of blocking or overexpressing "don't eat me" signals on the surface of CAR T cells depending on the purpose:
  - Off-the-shelf antibody can be used to effectively block the signal and deplete CAR-T cells when toxic
  - Overexpression of the signal in CAR-T cells increase their function, persistence and efficacy

Publications

- Yamada-Hunter SA, Theruvath J, et al. (2023). Engineered CD47 protects T cells for enhanced antitumor immunity. BioRxiv, 2023.06.20.545790.

Patents

- Published Application: WO2022232569

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