Docket #: S17-501

SMASh_CARs: A "drug off" chemogenetic system for regulating CAR T-cell therapy

Background
Researchers in Prof. Crystal Mackall's laboratory at Stanford University are focused on translational research related to cancer immunotherapy, including basic T-cell function and tumor immunology. These scientists and their collaborators have developed a variety of technologies aimed at improving CAR T-cell (chimeric antigen receptor T-cell) therapy. 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. The technologies to improve CAR T-cell therapy include: engineered TCR's to enhance tumor targeting; engineered CARs to enhance signaling activity; and “CAR T switch” systems which regulate signaling activity to improve patient safety and/or prevent T-cell exhaustion (a dysfunctional state that reduces the overall effectiveness of therapy).

Technology
This is a CAR T switch system that uses the SMASh-Tag technology to turn off T-cell signaling. Using this technology, protease inhibitor drugs could be used to selectively turn off engineered CARs to reduce the risk of adverse events from excessive immune activation (e.g., cytokine release syndrome, neurotoxicity or autoimmune effects). The system could also enhance efficacy by preventing T-cell exhaustion.

Related Technology
To review other inventions in this portfolio, click “Crystal Mackall” on the inventor to the right.

Stage of Research
Using this system in a mouse model of cancer, the inventors demonstrated that

administering a protease inhibitor drug can dramatically reduce the cytotoxic capacity of CAR T-cells in vivo. They showed similar levels of regulation using SMASH_CARs directed to four different tumor/leukemia targets.

Applications

- **Cancer immunotherapy (CAR-T-cell therapy)** - regulating CARs in vivo or ex vivo to enhance T-cell function for treating:
  - Solid tumors
  - Leukemia
  - Lymphoma
- **Research** - system could be could be used for regulating CARs to study basic T cell function and signaling

Advantages

- **Improves T cell-based immunotherapies:**
  - could enhance safety by preventing toxicity from unrestricted antigen driven proliferation (e.g., cytokine release syndrome and neurotoxicity)
  - could improve effectiveness of immunotherapy by preventing or reversing T-cell exhaustion
  - could improve cytotoxicity, proliferative capacity and/or cytokine secretion during ex vivo expansion
  - exhibits a wider dynamic range than other drug-regulatable systems
- **Transient regulation:**
  - administering drug can rapidly and potently diminish expression of SMASh-Tag regulated proteins
  - for T-cell exhaustion, transient and reversible effects provide a mechanism for T-cells to “rest” and then restore functionality
  - potential for localized regulation at a therapeutic site
- **“Drug off” system** - patient only receives drug in the case of an adverse event, would not require constant administration
- **FDA approved drugs** - chemogenetic switching achieved with protease inhibitors, a broad class of small molecule therapeutics with several agents that have been clinically validated as safe and tolerable

Patents

- Published Application: WO2020010239
- Published Application: 20210171602
- Published Application: 20260103504
- Issued: 12,473,344 (USA)

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