Docket #: S18-286

SNIP: A "drug on" chemogenetic system for regulating of CAR T-cell therapy

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
SNIP is a CAR T switch system that turns on T-cell signaling using a protease inhibitor drug. The system exhibits robust activity in the ON state and does not suffer from "leaky" activity in the OFF state. Furthermore, CAR-T cells containing the SNIP switch have improved efficacy, as determined by functional assays, compared to control CAR T cells. SNIP provides a mechanism to regulate CAR T-cell therapy to intervene in the case of adverse events; to reduce susceptibility to T-cell exhaustion; or to otherwise optimize the response profile of transferred T-cells.

Related Technology
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Stage of Development-Research In Vivo
Using this system in a mouse model, the inventors demonstrated that T-cells

engineered with SNIP kill leukemia cells when the drug is present but have no observable cytotoxicity in the absence of drug. They are constructing and testing additional SNIP proteins, including TCRs that target solid tumors.

Applications

- **Cancer immunotherapy (CAR-T , NK cell, TCR, stem cell)** - regulating CARs to enhance T-cell function for treating:
  - Solid tumors
  - Leukemia
  - Lymphoma
- **Research** - system could be used for regulating CARs to study basic T cell function and signaling

Advantages

- **Improves T cell-based immunotherapies**
  - could enhance safety by intervening in the case of adverse events
  - could improve effectiveness of immunotherapy by preventing or reversing T-cell exhaustion
  - could optimize the response profile of transferred T-cells
- **Tight regulation** - SNIP system has a wide dynamic range, no leaky activity and fast on/off kinetics
- **FDA approved drugs** - chemogenetic switching is achieved with protease inhibitors, a broad class of small molecule therapeutics with several agents that have been clinically validated as safe and tolerable

Publications

- Labanieh, L., Majzner, R. G., Klysz, D., Sotillo, E., Fisher, C. J., Vilches-Moure, J. G., Pacheco K. Z. B., Malipatlolla, M., Xu, P., Hui, J.H., Murty, T., Theruvath, J., Mehta, N., Yamada-Hunter, S. A., Weber, E.W., Heitzeneder, S., Parker, K. R., Satpathy, A. T., Chang, H. Y., Lin, M. Z., Cochran, J.R., Mackall, C.L. (2022). Enhanced safety and efficacy of protease-regulated CAR-T cell receptors. *Cell, 185*(10), 1745-1763. doi: 10.1016/j.cell.2022.03.041.

Patents

- Published Application: WO2020118076
- Published Application: 20220041686
- Published Application: 20260078164
- Issued: 12,454,562 (USA)

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