NATIONAL CANCER INSTITUTE
Technology Transfer Center

Chimeric Adaptor Proteins (CAPs) Containing a Linker for Activation of T Cells (LAT) and a Kinase Domain for Use in T Cell-Based Immunotherapy

Summary

There remains a need for effective immunotherapies to treat solid tumors as well as hematological malignancies. Researchers at the National Cancer Institute (NCI) have designed novel chimeric adaptor proteins (CAPs) consisting of signaling molecules downstream of the T cell receptor (TCR) for use in T cell-mediated immunotherapy. NCI is seeking parties interested in licensing and/or co-developing CAPs that can be used in immunotherapy for treating cancer, including both hematological and solid malignancies.

NIH Reference Number

E-210-2018

Product Type

- Therapeutics

Keywords

- Chimeric Adaptor Protein, CAP, Chimeric Antigen Receptor, CAR, T cell, Linker for Activation of T cells, LAT, Immunotherapy, Samelson

Collaboration Opportunity

This invention is available for licensing and co-development.

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Description of Technology

T cell immunotherapy is used in the treatment of various pathologies – including cancers and infections. Current therapies employ chimeric antigen receptors (CARs) consisting of the intracellular fragment of CD3-zeta as the signaling domain with varied combinations of co-stimulatory, transmembrane, spacer/hinge, and extracellular targeting domains. While effective in treating hematological malignancies, CAR T cells need to be activated through T cell receptor (TCR) activation. Such activation is subject to various regulatory and inhibitory mechanisms that can limit their full therapeutic potential. Moreover, CAR T cells are less effective in the treatment of solid tumors due to exhaustion. There remains

a need for effective immunotherapies to treat solid tumors as well as hematological malignancies. Researchers at the National Cancer Institute (NCI) have found that after T cell receptor (TCR) activation, the linker for activation of T cells (LAT) forms a distinct signaling complex and its formation is sufficient to cause full T-cell activation independent of the TCR complex. As activation of the TCR complex is highly regulated by a number of competing kinases and phosphatases, the downstream LAT molecule offers several advantages over CD3-zeta as the signaling domain in CARs.

Researchers at the NCI have developed chimeric adaptor proteins (CAPs) consisting of an extracellular targeting domain, transmembrane domain, intracellular LAT domain, and the kinase domain of ZAP70. The inventors have observed that the formation of these complexes is sufficient to cause full T-cell activation independent of TCR activation. It is expected that the circumvention of the regulatory mechanisms targeting upstream TCR activation will increase the potency of T-cell signaling and the sensitivity of immunotherapy. Furthermore, T cells prepared with these recombinant molecules may be more resistant to exhaustion by molecules targeting TCR activation, and tunable, as the activity of the kinase domain can be altered with small molecules.

The Laboratory of Cellular and Molecular Biology, is seeking statements of capability or interest from parties interested in licensing this invention and/or collaborative research to further develop, evaluate, or commercialize CAPs for the treatment of solid tumors and hematological malignancies.

Potential Commercial Applications

- Treatment of hematological malignancies and solid tumors
- Therapeutic use as a combination therapy with immune checkpoint inhibitors and/or chemotherapy

Competitive Advantages

- Potential for demonstrable efficacy against solid cancers previously refractory to cellular immunotherapy via:
  - Signaling through LAT allows circumvention of regulatory and inhibitory mechanisms involved in TCR activation
  - Directly triggering the downstream signaling cascade could cause more potent activation of T cells
  - LAT-based CAP-expressing T cells may be more resistant to PD-1-mediated T-cell exhaustion
  - Signaling from CAPs consisting of LAT and ZAP70 kinase domain may be tunable

Inventor(s)

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Development Stage

- Pre-clinical (in vivo)

Publications

Yi J, et al. TCR microclusters form spatially segregated domains and sequentially assemble in calcium-dependent kinetic steps [PMID 30655520]

Balagopalan L, et al. Plasma membrane LAT activation precedes vesicular recruitment defining two phases of early T-cell activation [PMID 29789604]

Patent Status

- **PCT:** PCT Application Number PCT/US2020/022752, Filed 13 Mar 2020

Related Technologies

- E-159-2009 - Use of a Modified Adaptor Molecule LAT to Improve Immunotherapy for Cancer and Other Diseases

Therapeutic Area

- Cancer/Neoplasm

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