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Chimeric Cytokine Receptors for Enhancing the Efficacy of Cell Therapies

Stanford researchers have engineered chimeric cytokine receptors that are expressed in therapeutic cells to enhance their activity and therapeutic potential. To prevent toxicity from hyperactivity, the activation state of these receptors can be regulated by a drug that acts on proteases.

While chimeric antigen receptor T-cell (CAR-T) therapy effectively treats liquid cancers, further improvements in persistence and potency are needed to combat solid cancers clinically. Regulating cytokine-triggered intracellular signaling cascades related to growth and proliferation could help augment CAR-T cell activity, enhancing anti-tumor efficacy.

To achieve this, Stanford researchers developed chimeric cytokine receptor (CCR) systems capable of constitutive signaling in the absence of their cognate cytokines. Their CCR system is comprised of two subunits, each including a heterologous dimerization domain and a cytokine receptor intracellular signaling domain (ICD). Because a cognate for the first dimerization domain is selected as the second dimerization domain and the two domains are in proximity, therapeutic cells with these CCRs have active intracellular signaling associated with persistence and potency downstream. The signaling cascade can be interrupted by regulating protease activity on ICDs to avoid exceeding the therapeutic window and causing toxicity. Cells with these CCRs could demonstrate sufficient anti-tumor activity to fight solid tumors.

Stage of Development
In vivo data

Applications

- Immunotherapy for cancer, autoimmune diseases, neurodegenerative diseases, and more:
  - CAR-T therapy
  - TCR therapy
  - CAR NK cell therapy

Advantages

- Has a wide dynamic range of control
- Safe, with no leaky activity in the off state
- Utilizes an FDA-approved small molecule to regulate cytokine signaling
- Can use autologous, allogeneic or stem cell-derived therapeutic cells
- Cysteine residues can be included in the extracellular domain to stabilize the CCRs via disulfide bonds
- Detection tags can be optionally included for cell surface expression

Patents

- Published Application: WO2024044768

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