Switchable Chimeric Antigen Receptor-Engineered Human Natural Killer Cells

Tech ID: 31628 / UC Case 2019-288-0

BACKGROUND

The existing CAR-engineered T cell-based (CAR-T) therapy represents one of the most successful immunotherapy approaches developed in recent years. Most CAR-T cell therapy has been used clinically to treat hematological malignancies by targeting the B cell-specific antigen, CD19. However, this approach is not without limitations due to toxicities such as by neurotoxicity or cytokine release syndrome. Additionally, CAR-T cells function only as autologous cells due to graft-versus-host disease that would develop if cells were obtained from another person. Therefore, CAR-T cells must be produced on a patient-specific basis. NK cells, on the other hand, function as allogenic cytotoxic effector cells that do not have to be utilized on a patient-specific basis and are proven to be less toxic since they do not cause cytokine release syndrome, neurotoxicity, or graft-versus-host disease. For these reasons, CAR-engineered NK (CAR-NK) cells have increasingly attracted interest as an alternative CAR-cell therapy. However, there exist other unmet challenges. Targeting CAR-based therapies against solid tumors has been challenging due to the lack of truly tumor-specific antigens as most targets are shared by non-malignant cells and can cause toxicity due to “on-target, off-tumor” effects.” A fine-tunable CAR therapy is useful to better identify and target tumors while limiting this toxicity.

TECHNOLOGY DESCRIPTION

Researchers at UC San Diego have an invention that describes the engineering of natural killer (NK) cells with a switchable chimeric antigen receptor (sCAR) that is designed to create a targeted, NK cell-based therapeutic modality, referred to as sCAR-NK cells, to more effectively treat refractory cancers: both hematologic malignancies and solid tumors. Specifically, by equipping NK cell with the sCAR, the NK cells are able to target tumors in a tightly titratable manner, as well as target multiple tumor antigens simultaneously or sequentially. Therefore, this system mediates improved anti-tumor killing, prevents development of tumor antigen loss as a means of tumor escape from immune-mediated killing, and minimizes toxicity to the patient.

APPLICATIONS

The invention may be applied commercially as: (1) A therapeutic modality for cancer; (2) A therapeutic modality for infectious disease (by targeting virally infected antigens such as gp120 on HIV-infected cells) [Although the descriptions and the antigens of choice in our proof-of-concept studies are based on cancers, the utility of the invention can be easily transferred to infectious diseases, especially viral infections, as the mechanisms of NK cells to kill cancerous cells and virally infected cells are similar.]; (3) A tool for research on antigen discovery and validation (as the future success of CAR-based cancer immunotherapy depends heavily on discovery of reliable cancer-specific antigens).

ADVANTAGES

The use of sCAR-NK iPSC-derived natural killer (NK) cells combined with soluble switches that recognize defined tumor antigens will enable anti-cancer cell-based therapies to be produced and function more like standard drugs.

To overcome the difficultly of scaling up CAR-cell manufacturing rate to meet patient need, we combine different technologies in a unique way to first make NK cell-specific sCAR, and then genetically engineer NK cells with NK-sCAR to create the unique sCAR-NK cells as a potential therapeutic cell product.

STATE OF DEVELOPMENT

The inventors have re-engineered the sCAR to include the CAR4 NK cell signaling domains that mediate activation of NK cell intracellular signaling pathways and improved NK-CAR anti-tumor activity compared to CAR-T cell constructs expressed in NK cells. We demonstrate efficacy of both an anti-CD19 switch and anti-FZD7 switch to mediate specific killing of either CD19+ Raji B cell lymphoblastic leukemia (hematological malignancy model) or the FZD7+ MA148 ovarian cancer cell line (solid tumor model).

INTELLECTUAL PROPERTY INFO

The invention is patent-pending and is available for licensing and collaborations.

PATENT STATUS

Patent Pending

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OTHER INFORMATION

KEYWORDS

NK cells, CAR-engineered T cell-based (CAR-T) therapy, cancer, solid tumors, natural killer cells, switchable chimeric antigen receptor, therapeutic, iPSC-derived cells

CATEGORIZED AS

- Medical
  - Disease: Blood and Lymphatic System
  - Disease: Cancer
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  - Other

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