A Codon-Optimized Lentiviral Vector For Stem Cell Reprogramming

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SUMMARY

UCLA researchers in the Department of Medicine and the Department of Surgery have developed a novel lentiviral vector that expresses a codon-optimized sequence of a T cell receptor (TCR) specific for the cancer-testis antigen NY-ESO-1 as well as a positron emission tomography (PET) reporter and suicide gene HSV1-sr39tk for use in adoptive T cell therapy for cancer treatment.

BACKGROUND

The adaptive immune system is composed of highly specialized lymphocytes that are capable of creating immunological memory after an initial response to a specific pathogen, and leads to an enhanced response to subsequent encounters with that pathogen. The adaptive system includes both humoral and cell-mediated immune responses, carried out by B cells and T cells, respectively. Both B cells and T cells are derived from the same multipotent hematopoietic stem cells (HSCs), and are morphologically indistinguishable until after they are activated. While cell-mediated immunity involves the activation of phagocytes, antigen-specific cytotoxic T lymphocytes, and the release of various cytokines in response to an antigen, humoral immunity is mediated by macromolecules, such as antibodies, complement proteins and certain antimicrobial peptides found in extracellular fluids.

Adoptive T cell therapy involves the isolation andex vivoexpansion of tumor specific T cells to achieve greater number of T cells than what could be obtained by vaccination alone. The tumor specific T cells are then infused into patients with cancer in an attempt to give their immune system the ability to overwhelm remaining tumorviaT cells. There are many forms of adoptive T cell therapy being used for cancer treatment, such as culturing tumor infiltrating lymphocytes, isolating and expanding one particular T cell or clone, and using T cells that have been engineered to potently recognize and attack tumors.

Cancer-testis antigens are a unique family of antigens, which have restricted expression to testicular germ cells in a normal adult but are aberrantly expressed on a variety of solid tumors. Cancer-testis antigens are highly immunogenic and can elicit spontaneous T-cell and/or humoral responses upon exposure. Among the known cancer-testis antigens, NY-ESO-1 is considered the most immunogenic and has become an attractive target for cancer vaccine development, which would utilize the immune system to selectively target and eliminate the cancer-testis antigen-expressing tumor cells.

INNOVATION

Researchers at UCLA have developed a novel lentiviral vector that expresses a codon-optimized sequence of a TCR specific for the cancer-testis antigen NY-ESO-1 to genetically modify G-CSF-mobilized peripheral blood stem cells (PBSC). These genetically modified cells can be used in a hematopoietic stem cell (HSC) transplantation to treat patients with NY-ESO-1 positive cancers. The described lentiviral vector also expresses HSV1-sr39tk, which serves as both a PET reporter gene to study hematopoietic and immune reconstitution, and a suicide gene to deplete transduced cells if they become toxic.

APPLICATIONS

Adoptive T cell therapy: genetically engineer PBSC from patients with NY-ESO-1 positive cancers with the described lentiviral vector and administer the modified cells back to patients after receiving a myelodepleting conditioning chemotherapy regimen.

ADVANTAGES

- The codon-optimized sequence allows more efficient production of the TCR α and β chains in human cells

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OTHER INFORMATION

KEYWORDS

Immunotherapy, gene therapy, adoptive T cell therapy, T cell receptor, TCR, cancer-testis antigens, lentivirus, hematopoietic stem cells, HSCs, transplantation, tumor immunity, codon-optimization, PET reporter gene, suicide gene, stem cell reprogramming

CATEGORIZED AS

- **Biotechnology**
  - Genomics
  - Health
- **Medical**
  - Disease: Cancer
  - Gene Therapy
  - Stem Cell
  - Therapeutics
- **Research Tools**
  - Vectors

RELATED CASES

2014-014-0

- The use of G-CSF-mobilized PBSC instead of HSCs makes this approach more broadly applicable
- The inclusion of HSV1-sr39tk in the lentiviral vector allows it to serve as both a PET reporter gene to study hematopoietic and immune reconstitution, and a suicide gene to deplete transduced cells if they become toxic

STATE OF DEVELOPMENT

Tested in mouse models:

- The TCR transgenic adoptive cell transfer results in high initial antitumor regressions
- Tumors relapse as TCR transgenic cells decrease in frequency and function in blood
- Inserting TCR genes into HSCs results in continuous production of fully functional TCR transgenic lymphocytes

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	10,201,597	02/12/2019	2014-014

RELATED MATERIALS

- Gschweng, E.H., McCracken, M.N., Kaufman, M.L., Ho, M., Hollis, R.P., Wang, X., Saini, N., Koya, R.C., Chodon, T., Ribas, A. and Witte, O.N., HSV-sr39TK positron emission tomography and suicide gene elimination of human hematopoietic stem cells and their progeny in humanized mice, Cancer research, 2014.
- Ribas, A. and Koya, R.C., Adoptive cell transfer of T-cell receptor-engineered lymphocytes: lessons from recent modeling, Future Oncology, 2010.

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Genetic Mechanisms Of Resistance To Anti-Pd-1/L1

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