T Cell Receptors Targeting p53 Hotspot Mutations and Methods of Isolating the Same

Summary (1024-character limit)
Researchers at the National Cancer Institute (NCI) identified a collection of T Cell Receptors (TCRs) that target specific mutations in the p53 tumor suppressor protein. These TCRs recognize “hotspot” mutations, which frequently occur in a variety of unrelated cancers. These TCRs can be used for a variety of therapeutic, diagnostic and research applications. Researchers at the NCI seek licensing and/or co-development research collaborations for these novel T cell receptors that recognize p53 mutations and methods for identifying p53 mutation-reactive T cell receptors.

NIH Reference Number
E-237-2017

Product Type
• Therapeutics

Keywords
• p53 mutation, T Cell Receptors, TCR, Immunotherapy, Screening, Rosenberg

Collaboration Opportunity
This invention is available for licensing and co-development.

Contact
• John D. Hewes
  NCI - National Cancer Institute

  240-276-5515

  John.Hewes@nih.gov

Description of Technology
Mutations in Tumor Protein P53 (p53) are expressed in a variety of human cancers such as cholangiocarcinoma, melanoma, colon cancer, rectal cancer, ovarian cancer, endometrial cancer, non-small cell lung cancer (NSCLC), glioblastoma, uterine cervical cancer, head and neck cancer, breast cancer, pancreatic cancer, and bladder cancer. The p53 protein is involved in determining whether DNA is repaired or the damaged cell undergoes apoptosis – thus acting as a tumor suppressor by regulating cell division. Mutations in the p53 protein can reduce or eliminate its tumor suppressor function or interfere with wild type p53 in a dominant negative fashion. Furthermore, novel therapeutics are needed that specifically target p53 mutations, as small molecules lack specificity for the mutated sequences.

Researchers at the National Cancer Institute (NCI) identified a collection of novel T-cell receptors (TCRs)
targeting defined “hotspot” mutations in the p53 tumor suppressor. The same p53 mutations frequently occur; ~30% of the p53 missense mutations, at the following residues: R175H, Y220C, G245D, G245S, R248L, R248Q, R248W, R249S, R273C, R273L, R273H and R282W. Therefore, p53 mutations are attractive as targets for TCR gene-engineered T cell therapy. This discovery allows for the specific elimination of tumor cells with p53 mutations present in a diverse group of cancer patients. Furthermore, scientists at the NCI have developed a method of identifying T cells reactive to mutations in the p53 tumor suppressor protein. Peptides containing these mutations are flanked by 12 amino acids of the wild type sequence on each side to make 25 amino acid p53 mutation neoantigens. Incorporation of these peptides into autologous antigen presenting cells and co-culturing with T cells, from either tumor or peripheral blood, allow efficient detection of tumor-responsive T cells. These tumor-responsive T cells with p53 mutation reactive TCR are highly applicable to adoptive cell therapy or as gene therapy.

Potential Commercial Applications

- Extensive commercial opportunities as p53 is the commonly mutated gene in human cancer
- Mutated p53 protein, found in approximately half of all tumors, are expressed by the most significant cancer markets – such as melanoma, breast cancer, colon cancer, and bladder cancer
- A component of immunotherapies, such as adoptive cell therapy (ACT) or TCR gene therapy, aimed at targeting cancers expressing mutated p53 protein
- An in vitro diagnostic tool to screen for T cells reactive to mutated p53
- Use of the TCRs in chimeric proteins for research purposes in cancers with mutated p53

Competitive Advantages

- Mutated p53 protein not expressed by healthy tissues, suggesting efficacy with an acceptable toxicity profile
- T cells can be tested independent of the knowledge of the mutations in a patient’s tumor, which is critical when evaluating terminally ill patients
- A p53 mutation-only screening approach increases the speed and efficiency of identifying p53 mutation-specific TCRs compared to traditional screen approaches and can detect low frequency responses, which may be diluted with a traditional high throughput screening approach

Inventor(s)

Steven A Rosenberg (NCI), Paul F Robbins (NCI), Maria R Parkhurst (NCI), Yong-Chen W Lu (NCI), Anna Pasetto (NCI), Rami Yoseph (NCI), Drew C Deniger, Parisa Malekzeh, Winifred M Lo

Development Stage

- Pre-clinical (in vivo)

Publications

Deniger et al. T-cell responses to TP53 “hotspot” mutations and unique neoantigens expressed by human ovarian cancers. [PMID: 29853601]
Patent Status

- **PCT**: PCT Application Number PCT/US2018/051285, Filed 17 Sep 2018
- **PCT**: PCT Application Number PCT/US2018/051280, Filed 17 Sep 2018
- **U.S. Provisional**: U.S. Provisional Patent Application Number 62/867,619, Filed 27 Jun 2019

Related Technologies

- **E-175-2016** - T Cell Receptors Targeting KRAS Mutants for Cancer Immunotherapy/Adoptive Cell Therapy
- **E-135-2019** - T Cell Receptors (TCRs) Specific for Mutant p53

Therapeutic Area

- Cancer/Neoplasm