

NEOANTIGENS AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims priority to U.S. Provisional Application Nos. 62/687,188, filed on June 19, 2018 and 62/800,735, filed on February 4, 2019; which are incorporated herein by reference in their entirety.

BACKGROUND

[0002] Cancer immunotherapy is the use of the immune system to treat cancer. Immunotherapies exploit the fact that cancer cells often have molecules on their surface that can be detected by the immune system, known as tumor antigens, which are often proteins or other macromolecules (*e.g.* carbohydrates). Active immunotherapy directs the immune system to attack tumor cells by targeting tumor antigens. Passive immunotherapies enhance existing anti-tumor responses and include the use of monoclonal antibodies, lymphocytes and cytokines. Tumor vaccines are typically composed of tumor antigens and immunostimulatory molecules (*e.g.*, adjuvants, cytokines or TLR ligands) that work together to induce antigen-specific cytotoxic T cells (CTLs) that recognize and lyse tumor cells. One of the critical barriers to developing curative and tumor-specific immunotherapy is the identification and selection of highly specific and restricted tumor antigens to avoid autoimmunity.

[0003] Tumor neoantigens, which arise as a result of genetic change (*e.g.*, inversions, translocations, deletions, missense mutations, splice site mutations, etc.) within malignant cells, represent the most tumor-specific class of antigens and can be patient-specific or shared. Tumor neoantigens are unique to the tumor cell as the mutation and its corresponding protein are present only in the tumor. They also avoid central tolerance and are therefore more likely to be immunogenic. Therefore, tumor neoantigens provide an excellent target for immune recognition including by both humoral and cellular immunity. However, tumor neoantigens have rarely been used in cancer vaccine or immunogenic compositions due to technical difficulties in identifying them, selecting optimized antigens, and producing neoantigens for use in a vaccine or immunogenic composition. Accordingly, there is still a need for developing additional cancer therapeutics.

INCORPORATION BY REFERENCE

[0004] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

SUMMARY

[0004a] In one aspect, provided herein is a composition comprising T cells specific to an HLA-peptide complex comprising at least one mutant RAS peptide consisting of an amino acid sequence GAVGVGKSA.

[0004b] In one aspect, provided herein is a method of preparing the T cells of the composition as described herein, comprising priming T cells with antigen presenting cells (APCs) comprising (i) at least one

polypeptide comprising the amino acid sequence of the at least one mutant RAS peptide of claim 1 or (ii) at least one polynucleotide encoding the at least one polypeptide of (i).

[0004c] In one aspect, provided herein is a method of preparing T cells specific to an HLA-peptide complex comprising at least one mutant RAS peptide sequence comprising priming T cells with antigen presenting cells (APCs) comprising the at least one polypeptide, or at least one polynucleotide encoding the at least one polypeptide as described herein.

[0004d] In one aspect, provided herein is a pharmaceutical composition comprising (i) the composition as described herein; and (ii) a pharmaceutically acceptable excipient.

[0004e] In one aspect, provided herein is a pharmaceutical composition comprising T cells primed with antigen presenting cells (APCs) comprising (i) the at least one polypeptide, or at least one polynucleotide encoding the at least one polypeptide as described herein; and (ii) a pharmaceutically acceptable excipient.

[0005] In some aspects, provided herein is a composition comprising at least one polypeptide comprising two or more mutant RAS peptide sequences selected from the group consisting of KLVVVGADGV, KLVVVGACGV, KLVVVGAVGV, LVVVGADGV, LVVVGACGV, LVVVGAVGV; GADGVGKSAL, GACGVGKSAL, GAVGVGKSAL, GADGVGKSA, GACGVGKSA, GAVGVGKSA; and/or VVGADGVGK, VVGACGVGK, VVGAVGVGK,

CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising T cells specific to an HLA-peptide complex comprising at least one mutant RAS peptide consisting of an amino acid sequence GAVGVGKSA.
2. The composition of claim 1, wherein the HLA-peptide complex comprises:
a protein encoded by an HLA-C03:03 or HLA-C03:04 allele.
3. A method of preparing the T cells of the composition of claim 1 or 2, comprising priming T cells with antigen presenting cells (APCs) comprising (i) at least one polypeptide comprising the amino acid sequence of the at least one mutant RAS peptide of claim 1 or (ii) at least one polynucleotide encoding the at least one polypeptide of (i).
4. The method of claim 3, wherein
 - (a) the at least one polypeptide has a formula

$$(Xaa_N)_N-(Xaa_{RAS})_P-(Xaa_C)_C$$

wherein

P is an integer greater than 7;

$(Xaa_{RAS})_P$ is a mutant RAS peptide sequence comprising at least 8 contiguous amino acids of a mutant RAS protein;

the at least 8 contiguous amino acids comprising at least 8 contiguous amino acids of the sequence

Lys₁ Leu₂ Val₃ Val₄ Val₅ Gly₆ Ala₇ Xaa₈ Gly₉ Val₁₀ Gly₁₁ Lys₁₂ Ser₁₃ Ala₁₄ Leu₁₅;

N is (i) 0 or (ii) an integer greater than 2;

$(Xaa_N)_N$ is any amino acid sequence heterologous to the mutant RAS protein;

C is (i) 0 or (ii) an integer greater than 2;

$(Xaa_C)_C$ is any amino acid sequence heterologous to the mutant RAS protein;

Xaa₈ is selected from the group consisting of Asp, Val, Cys, Ala, Arg and Ser;

the polypeptide is not KLVVVGAVGVGKSALTIQL; and

wherein if N is 0 C is not 0 and if C is 0 N is not 0; or

- (b) at least one polynucleotide encoding the at least one polypeptide.

5. The method of claim 4, wherein C is 0.
6. The method of claim 4 or 5, wherein N is a polylysine sequence.
7. The method of any one of claims 4-6, wherein N is an integer less than 50.
8. The method of claim 7, wherein N is 2, 3, 4, 5, or 6.
9. The method of any one of claims 4-8, wherein Xaa₈ is selected from the group consisting of Asp, Val, Cys and Arg.
10. The method of any one of claims 3-9, wherein the at least one polypeptide comprises an amino acid sequence of TEY.

11. The method of any one of claims 3-10, wherein the at least one polypeptide comprises an amino acid sequence of GKSALTIQL or GKSALTI.
12. A method of preparing T cells specific to an HLA-peptide complex comprising at least one mutant RAS peptide sequence comprising priming T cells with antigen presenting cells (APCs) comprising the at least one polypeptide, or at least one polynucleotide encoding the at least one polypeptide of any one of claims 4-11.
13. A pharmaceutical composition comprising (i) the composition of claim 1 or 2; and (ii) a pharmaceutically acceptable excipient.
14. A pharmaceutical composition comprising T cells primed with antigen presenting cells (APCs) comprising (i) the at least one polypeptide, or at least one polynucleotide encoding the at least one polypeptide of any one of claims 4-12; and (ii) a pharmaceutically acceptable excipient.
15. The method of any one of claim 3 -14, wherein the at least one polynucleotide encoding the at least one polypeptide is RNA.
16. The method of any one of claims 3-14, wherein the T cells are from a human subject with a cancer that expresses the at least one mutant RAS peptide sequence, and wherein the human subject's genome comprises an HLA-allele encoding the HLA of the HLA-peptide complex.
17. The method of claim 12, wherein the APCs express a protein encoded by an HLA-C03:03 allele, or an HLA-C03:04 allele.