

Claims

1.- An antigen recognizing construct comprising a first domain and a second domain, each domain comprising three complementary determining regions (CDRs) comprising, wherein the first domain comprises the amino acid sequences according to SEQ ID NOs: 5 (CDRa1), 6 (CDRa2), and 7 (CDRa3), and at the second domain comprising three complementary determining regions (CDRs) comprising comprises the amino acid sequences according to SEQ ID NOs: 13 (CDRb1), 14 (CDRb2), and 15 (CDRb3), wherein

at least one of said complementary determining regions a) the CDRa1 of the first domain is replaced with at least one amino acid sequence as set forth in SEQ ID NO: 5 and the CDRb1 of the second domain is selected from the group of:

- a) SEQ ID NO: 26 (CDRa1 mutant 1) and one of the amino acid sequences according to SEQ ID NOs: 37 to 49 (CDRb1 mut1 to CDRb1 mut13), and 44, or
- b) a mutated sequence comprising at least one amino acid sequence selected from the group consisting of SEQ ID NO: 26 and SEQ ID NOs: 37 to 49, wherein the at least one amino acid sequence contains one, two, or three amino acid substitutions.

b) the CDRa1 of the first domain is as set forth in SEQ ID NO: 26 and the CDRb1 of the second domain is selected from one of the amino acid sequences according to SEQ ID NOs: 13 and 37 to 49, wherein the antigen recognizing construct is a T cell receptor (TCR) or derivative or fragment thereof, wherein the derivative or fragment retains the antigen binding and/or recognizing ability of the parent molecule to specifically and/or selectively bind to a COL6A3 antigenic polypeptide.

2.- The antigen recognizing construct according to claim 1, wherein said antigen recognizing construct is stable, and capable of specifically and/or selectively binding to a COL6A3 antigenic peptide comprising the amino acid sequence according to SEQ ID NO: 1, in particular in the context with MHC.

3.- The antigen recognizing construct according to claim 1 or 2, wherein the antigen recognizing construct is an antibody, or derivative such as a bispecific molecule or fragment thereof, or a T cell receptor (TCR), or a derivative such as a bispecific molecule or fragment thereof.

~~4.~~ _____ The antigen recognizing construct according to any one of claims 1 to ~~3~~2, wherein said first domain is part of a TCR α or γ chain; and/or wherein said second domain is part of a TCR β or δ chain.

4. _____ The antigen recognizing construct according to any one of claims 1 to 3, wherein the antigen recognizing construct is a single chain antigen recognizing construct, preferably wherein the single chain antigen recognizing construct is a single chain TCR.

5.- _____ The antigen recognizing construct according to any one of claims 1 to 4, wherein the antigen recognizing construct is a soluble TCR.

6. _____ A nucleic acid encoding for an antigen recognizing construct according to any one of claims 1 to 4, ~~or a~~5.

7. _____ A nucleic acid vector comprising ~~said~~the nucleic acid of claim 6.

~~6-8.~~ _____ A recombinant host cell comprising an antigen recognizing construct according to any one of claims 1 to 4, ~~or a~~5, the nucleic acid of claim 6 or ~~a~~the vector according to claim ~~5~~7, wherein said host cell preferably is a) ~~a lymphocyte, such as a T lymphocyte or T lymphocyte progenitor mammalian cell, for example a CD4 or CD8 positive T more preferably a human cell~~ or b) ~~a non-lymphocyte, such as a Chinese Hamster Ovary (CHO) cell.~~

~~7-9.~~ _____ The host cell according to claim 8, wherein said host cell is

a) a lymphocyte, preferably a T lymphocyte or T lymphocyte progenitor cell, more preferably a CD4 or CD8 positive T cell, or

b) a non-lymphocyte.

10. _____ A pharmaceutical composition comprising the antigen recognizing construct according to any one of claims 1 to ~~4~~5, the nucleic acid ~~or according to claim 6~~, the vector according to claim ~~5~~7, or the host cell according to claim ~~6~~8 or 9, and a pharmaceutically acceptable carrier, diluent stabilizer and/or excipient.

~~8-11.~~ _____ A method of producing the COL6A3-specific antigen recognizing construct according to any one of claims 1 to ~~4~~5, comprising

a. _____ providing a suitable host cell,

- b. providing a genetic construct comprising a coding sequence encoding the antigen recognizing construct according to any of claims 1 to 45,
- c. introducing said genetic construct into said suitable host cell, and
 - a. ~~—~~ d. expressing said genetic construct by said suitable host cell-

~~9. The, the~~ method according to claim 8, preferably further comprising isolating and purifying the antigen recognizing construct from the suitable host cell and, optionally, reconstituting the antigen recognizing construct in a T-cell.

~~10-12.~~ The antigen recognizing construct according to any one of claims 1 to 45, the nucleic acid or according to claim 6, the vector according to claim 57, the host cell according to claim 68 or 9, or the pharmaceutical composition according to claim 710, for use in medicine as a medicament.

~~11. The~~ 13. Use of the antigen recognizing construct according to any one of claims 1 to 45, the nucleic acid ~~or according to claim 6, the~~ vector according to claim 57, the host cell according to claim 68 or 9, or the pharmaceutical composition according to claim 710 for ~~use in the the~~ manufacture of a medicament for the diagnosis, prevention, and/or treatment of a proliferative disease, such as cancer-

~~12. The, wherein said cancer is selected from a cancer where COL6A3 is overexpressed, mutated, and/or a COL6A3-derived tumor-associated antigen recognizing construct according to any one of claims 1 to 4, the nucleic acid or vector according to claim 5, the host cell according to claim 6 or the pharmaceutical composition according to claim 7 for use according to claim 11 is presented.~~

14. An in vitro method for treating cancer or COL6A3-positive premalignancy, wherein said cancer is selected from a cancer where COL6A3 is overexpressed, mutated, and/or a COL6A3-derived tumor-associated antigen is presented, such as, for example, colorectal cancer, colon cancer, liver cancer, ovarian cancer, and gastric cancer, the method comprising:

- a) transforming a cell obtained from a subject in need of a cancer treatment with at least one vector according to claim 7 to produce a transformed cell; and
- b) expanding the transformed cell to produce a plurality of transformed cells.

15.
~~13. The~~ An in vitro method for detecting cancer in a biological sample comprising:

- a) contacting the biological sample with the antigen recognizing construct according to any one of claims 1 —4, wherein the mutated sequence is a combination of a first and a second amino acid sequence, such that the mutated sequence is provided by replacing one, two or three amino acids in the first sequence with to 5;
- b) detecting binding of the corresponding one, two or three amino acids of the second sequence-antigen recognizing construct to the biological sample,

~~14. The antigen recognizing construct according to claim 13, wherein the mutated sequence is a combination of a first and a second amino acid sequence, such that the mutated sequence is provided by replacing one, two or three consecutive amino acids in the first sequence with the corresponding one, two or three consecutive amino acids of the second sequence.~~

wherein said cancer is selected from a cancer where COL6A3 is overexpressed, mutated, and/or a COL6A3-derived tumor-associated antigen is presented.

~~15. The antigen recognizing construct according to any one of claims 1 —4 and 13 —14, wherein the mutated sequence of (b) contains at least one conservative amino acid substitution compared to the at least one amino acid sequence of (a).~~

~~16. The antigen recognizing construct according to any one of claims 1 —4, wherein said at least one of said complementary determining regions is replaced with SEQ ID NO: 40 and wherein SEQ ID NO: 40 contains one, two, or three amino acid substitutions.~~

~~17. The antigen recognizing construct according to any one of claims 1 —4, wherein said at least one of said complementary determining regions is replaced with SEQ ID NO: 40.~~

~~18. The antigen recognizing construct according to any one of claims 1 to 4, comprising a variant selected from the group consisting of 75-1 —75-25 of Table 2 and C-1 —C-18 of Table 5.~~