nucleic acid molecule as described herein, into an immune effector cell, preferably wherein said immune effector cell is a T-cell or an NK cell.

In another aspect, the present disclosure refers to use of the immune effector cell as described herein in the manufacture of a medicament for the treatment of cancer, wherein said cancer expresses HLA-A2 and a mutated TGFβRII protein which comprises SEQ ID NO: 1, and wherein said immune effector cell is a CD4+ or CD8+ T cell.

Accordingly, the invention firstly provides a nucleic acid molecule encoding a TCR molecule directed against a mutated TGFβRII protein which comprises the sequence of SEQ ID NO: 1, wherein said TCR molecule is capable of binding a peptide of SEQ ID NO: 1 when said peptide is presented by a Class I MHC, and wherein said TCR molecule comprises an α-chain domain and/or a β-chain domain, each chain domain comprising three CDR sequences, wherein

a) CDRs 1, 2 and 3 of the α-chain domain have the sequences of SEQ ID NOs: 2, 3 and 4 respectively; and

b) CDRs 1, 2 and 3 of the β-chain domain have the sequences of SEQ ID NOs: 5, 6 and 7 respectively, and

wherein one or more of said CDR sequences, and in a more particular embodiment one or more of said CDR1 or CDR2 sequences, may optionally be modified by substitution, addition or deletion of 1 or 2 amino acids.

The amino acid sequences of CDR1 and CDR2 of the Radium-1 α-chain are presented in SEQ ID NO: 2 and SEQ ID NO: 3 respectively, and the previously disclosed sequence of CDR3 of the Radium-1 α-chain in SEQ ID NO: 4. The amino acid sequences of CDR1 and CDR2 of the Radium-1 β-chain are presented in SEQ ID NO: 5 and SEQ ID NO: 6 respectively, and the previously disclosed sequence of CDR3 of the Radium-1 β-chain in SEQ ID NO: 7.

CLAIMS

1. A nucleic acid molecule encoding a T-cell receptor (TCR) molecule directed against a mutated TGFβRII protein which comprises the sequence of SEQ ID NO: 1, wherein said TCR molecule is capable of binding a peptide of SEQ ID NO: 1 when said peptide is presented by a Class I Major Histocompatibility Complex (MHC) comprising HLA-A2, and wherein said TCR molecule comprises an α-chain domain and a β-chain domain, each chain domain comprising three CDR sequences, wherein

a) CDRs 1, 2 and 3 of the α-chain domain have the sequences of SEQ ID NOs: 2, 3 and 4 respectively; and

b) CDRs 1, 2 and 3 of the β-chain domain have the sequences of SEQ ID NOs: 5, 6 and 7 respectively; and

wherein said α-chain domain comprises:

i) a variable region comprising the amino acid sequence set forth in SEQ ID NO: 72; or an amino acid sequence with at least 95 % sequence identity thereto; and

ii) a constant region comprising the amino acid sequence set forth in SEQ ID NO: 9, or a modified version thereof comprising one or more amino acid substitutions or insertions relative to SEQ ID NO: 9 and having at least 95 % sequence identity to SEQ ID NO: 9, or a murinised version of SEQ ID NO: 9; and

said β-chain domain comprises:

i) a variable region comprising the amino acid sequence set forth in SEQ ID NO: 75; or an amino acid sequence with at least 95 % sequence identity thereto; and

ii) a constant region comprising the amino acid sequence set forth in SEQ ID NO: 14, or an amino acid sequence with at least 95 % sequence identity to SEQ ID NO: 14, or a murinised version of SEQ ID NO: 14.

2. The nucleic acid molecule of claim 1 , wherein the α-chain domain and/or the β-chain domain comprises a double Myc-tag with the amino acid sequence of SEQ ID NO: 19.

3. The nucleic acid molecule of claim 1 or 2, wherein the constant region of said α-chain domain is modified by insertion of or substitution for a cysteine residue; and

the constant region of said β-chain domain is modified by insertion of or substitution for a cysteine residue.

4. The nucleic acid molecule of claim 1, wherein the α-chain domain comprises the amino acid sequence of SEQ ID NO: 11 and the β-chain domain comprises the amino acid sequence of SEQ ID NO: 16.

5. The nucleic acid molecule of claim 1, wherein the α-chain domain comprises the amino acid sequence of SEQ ID NO: 25 and the β-chain domain comprises the amino acid sequence of SEQ ID NO: 31.

6. The nucleic acid molecule of claim 3, wherein the α-chain domain comprises the amino acid sequence of SEQ ID NO: 12 and the β-chain domain comprises the amino acid sequence of SEQ ID NO: 17.

7. The nucleic acid molecule of claim 3, wherein the α-chain domain comprises the amino acid sequence of SEQ ID NO: 26 and the β-chain domain comprises the amino acid sequence of SEQ ID NO: 32.

8. A nucleic acid molecule encoding a soluble T-cell receptor (TCR) molecule directed against a mutated TGFβRII protein which comprises the sequence of SEQ ID NO: 1, wherein said TCR molecule is capable of binding a peptide of SEQ ID NO: 1 when said peptide is presented by a Class I Major Histocompatibility Complex (MHC) comprising HLA-A2, and wherein said soluble TCR molecule comprises an α-chain domain and a β-chain domain, each chain domain comprising three CDR sequences, wherein

a) CDRs 1, 2 and 3 of the α-chain domain have the sequences of SEQ ID NOs: 2, 3 and 4 respectively; and

b) CDRs 1, 2 and 3 of the β-chain domain have the sequences of SEQ ID NOs: 5, 6 and 7 respectively; and

wherein said α-chain domain comprises:

i) a variable region comprising the amino acid sequence set forth in SEQ ID NO: 72, or an amino acid sequence with at least 95 % sequence identity thereto; and

ii) a constant region comprising the amino acid sequence set forth in SEQ ID NO: 60, or an amino acid sequence with at least 95 % sequence identity thereto; and

said β-chain domain comprises:

i) a variable region comprising the amino acid sequence set forth in SEQ ID NO: 75, or an amino acid sequence with at least 95 % sequence identity thereto; and

ii) a constant region comprising the amino acid sequence set forth in SEQ ID NO: 62, or an amino acid sequence with at least 95 % sequence identity thereto.

9. The nucleic acid molecule of claim 8, wherein the constant region of said α-chain domain is modified by insertion of or substitution for a cysteine residue; and the constant

region of said β-chain domain is modified by insertion of or substitution for a cysteine residue.

10. The nucleic acid molecule of claim 8, wherein said α-chain domain comprises the amino acid sequence set forth in SEQ ID NO: 73 and said β-chain domain comprises the amino acid sequence set forth in SEQ ID NO: 76.

11. The nucleic acid molecule of claim 9, wherein said α-chain domain comprises the amino acid sequence set forth in SEQ ID NO: 74, and said β-chain domain comprises the amino acid sequence set forth in SEQ ID NO: 77.

12. The nucleic acid molecule of any one of claims 1 to 11, wherein the TCR molecule is encoded as a single-chain TCR (scTCR) comprising an α-chain domain joined to a β-chain domain by a self-splicing linker.

13. The nucleic acid molecule of claim 12, wherein said linker is a 2A peptide and comprises the amino acid sequence of SEQ ID NO: 18, or an amino acid sequence having at least 40 % sequence identity thereto.

14. The nucleic acid molecule of claim 13, wherein the scTCR comprises the amino acid sequence of any one of SEQ ID NOs: 33 to 40.

15. The nucleic acid molecule of any one of claims 1 to 14, wherein the nucleic acid is RNA.

16. A vector comprising the nucleic acid molecule of any one of claims 1 to 15.

17. The vector of claim 16, wherein said vector is:
i) an expression vector, optionally an mRNA expression vector, or a cloning vector; and/or
ii) a viral vector, optionally a retroviral vector or a lentiviral vector.

18. A soluble TCR molecule as defined in any one of claims 8 to 11.

19. A host cell comprising the nucleic acid molecule of any one of claims 1 to 15 or the vector of claim 16 or 17.

20. The host cell of claim 19, wherein said host cell is an immune effector cell, said nucleic acid molecule being as defined in any one of claims 1 to 7 or said vector comprising a nucleic acid molecule as defined in any one of claims 1 to 7; preferably wherein said immune effector cell is a T-cell or an NK cell.

21. The host cell of claim 19, wherein said host cell is a production host cell, said nucleic acid molecule being as defined in any one of claims 8 to 11 or said vector comprising a nucleic acid molecule as defined in any one of claims 8 to 11; preferably wherein said production host cell is a human cell.

22. A composition comprising the TCR molecule of claim 18 or the immune effector cell of claim 20, and at least one physiologically acceptable carrier or excipient.

23. A method of generating a TGFβRII frameshift mutant-specific immune effector cell, said method comprising introducing a nucleic acid molecule as defined in any one of claims 1 to 7 or a vector as defined in claim 16 or 17, said vector comprising a nucleic acid molecule as defined in any one of claims 1 to 7, into an immune effector cell, preferably wherein said immune effector cell is a T-cell or an NK cell.

24. The method of claim 23, wherein said method further comprises stimulating the cells and inducing them to proliferate before and/or after introducing the nucleic acid molecule or vector.

25. Use of the immune effector cell of claim 20 in the manufacture of a medicament for the treatment of cancer, wherein said cancer expresses HLA-A2 and a mutated TGFβRII protein which comprises SEQ ID NO: 1, and wherein said immune effector cell is a CD4+ or CD8+ T cell.

26. The use of claim 25, wherein said cancer is colorectal cancer and/or said cancer is in a subject with Lynch Syndrome.