CLAIMS

1) A multi-chain Chimeric Antigen Receptor (CAR) comprising at least:

   - one transmembrane polypeptide comprising at least one extracellular ligand-binding domain, wherein the at least one extracellular ligand-binding domain interacts with a cell surface molecule; and
   - one transmembrane polypeptide comprising at least one signal-transducing domain;

   wherein the signal transducing domain(s) of the multi-chain Chimeric Antigen Receptor is present on a polypeptide distinct from that carrying the extracellular ligand-binding domain(s).

2) The multi-chain Chimeric Antigen Receptor of claim 1 wherein at least one transmembrane polypeptide comprises a part of Fc receptor.

3) The multi-chain Chimeric Antigen Receptor of claim 2 wherein said part of Fc receptor is selected from the group consisting of: (a) FcεRI alpha chain, (b) FcεRI beta chain and (c) FcεRI gamma chain.

4) The multi-chain Chimeric Antigen Receptor of claim 3 wherein said part of Fc receptor is a part of FcεRI alpha chain.

5) The multi-chain Chimeric Antigen Receptor according to claim 3 or 4 comprising a part of FcεRI alpha chain and a part of FcεRI beta chain such that said FcεRI chains dimerize together to form a dimeric Chimeric Antigen Receptor.

6) The multi-chain Chimeric Antigen Receptor according to claim 3 or 4 comprising a part of FcεRI alpha chain and a part of FcεRI gamma chain such that said FcεRI chains trimerize together to form a trimeric Chimeric Antigen Receptor.

7) The multi-chain Chimeric Antigen Receptor according to claim 3 or 4 comprising a part of FcεRI alpha chain, a part of FcεRI beta chain and a part of FcεRI gamma chain such that said FcεRI chains tetramerize together to form a tetrameric Chimeric Antigen Receptor.

8) The multi-chain Chimeric Antigen Receptor according to any one of claims 1 to 7, wherein the extracellular ligand-binding domain recognizes a ligand that acts as a cell surface marker on target cells associated with a particular disease state.

9) The multi-chain Chimeric Antigen Receptor according to any one of claims 1 to 8 wherein said extracellular ligand-binding domain is a single chain antibody fragment (scFv).

10) The multi-chain Chimeric Antigen Receptor according to any one of claims 1 to 9 wherein said transmembrane polypeptide further comprises a stalk region.

11) The multi-chain Chimeric Antigen Receptor according to any one of claims 1 to 10 wherein said signal transducing domain is selected from the group consisting of: TCR zeta chain, FCεRβ chain, FcεRIγ chain, immunoreceptor tyrosine-based activation motif (ITAM).

12) The multi-chain Chimeric Antigen Receptor according to any one of claims 1 to 11 wherein said CAR comprises a co-stimulatory domain.

13) The multi-chain Chimeric Antigen Receptor according to any one of claims 1 to 11 further comprising a co-stimulatory molecule selected from the group consisting of: CD28, OX40, ICOS, CD137 and CD8.

14) The multi-chain Chimeric Antigen Receptor according to any one of claims 1 to 13 comprising polypeptides selected from the group consisting of SEQ ID NO: 202 to SEQ ID NO: 204 and SEQ ID NO: 206 to SEQ ID NO: 213.

15) A polynucleotide comprising two or more nucleic acid sequences encoding the transmembrane polypeptides composing the multi-chain CAR according to any one of claims 1 to 14.

16) A vector comprising a polynucleotide of claim 15.

17) A method of engineering an immune cell comprising:

(a) Providing an immune cell;

(b) Expressing at the surface of said cells at least one multi-chain Chimeric Antigen Receptor according to any one of the claims 1 to 14.

18) The method of engineering an immune cell of claim 17 comprising:

(a) Providing an immune cell;

(b) Introducing into said cell at least one polynucleotide encoding polypeptides composing at least one multi-chain Chimeric Antigen Receptor according to any one of claims 1 to 14;

(c) Expressing said polynucleotides into said cell.

19) The method of engineering an immune cell of claim 17 comprising:

(a) Providing an immune cell;

(b) Expressing at the surface of said cell a population of multi-chain Chimeric Antigen Receptors according to any one of the claims 1 to 14 each one comprising different extracellular ligand-binding domains.

20) The method of engineering an immune cell of claim 18 comprising:

(a) Providing an immune cell;

(b) Introducing into said cell at least one polynucleotide encoding polypeptides composing a population of multi-chain Chimeric Antigen Receptors according to any one of claims 1 to 14 each one comprising different extracellular ligand binding domains.

(c) Expressing said polynucleotides into said cell.

21) The method of engineering an immune cell of any one of claims 17 to 20 further comprising the step of d) inactivating in said immune cell at least one gene selected from the group consisting of TCR alpha, TCR beta, CD52, GR and immune checkpoints.

22) An isolated immune cell obtainable from the method according to any one of claims 17 to 21.

23) An isolated immune cell comprising at least one multi-chain Chimeric Antigen Receptor according to any one of claims 1 to 14.

24) An isolated cell according to claim 22 or 23 derived from inflammatory T-lymphocytes, cytotoxic T-lymphocytes, regulatory T-lymphocytes or helper T-lymphocytes.

25) An isolated immune cell according to any one of claims 22 to 24 for its use as a medicament.