CLAIMS

1. A polypeptide that redirects T cells for killing of CD123 expressing cells, comprising one immunoglobulin single variable domain (ISV) that specifically binds T cell receptor (TCR) and one or more ISV that specifically bind CD123, wherein the ISV that specifically binds TCR essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:

   i) CDR1 is chosen from the group consisting of:

      a) SEQ ID NOs: 181-191; or

      b) amino acid sequences that have 4, 3, 2 or 1 amino acid(s) difference with the amino acid sequence of one of SEQ ID NOs: 181-191; provided that the ISV comprising the CDR1 with 4, 3, 2 or 1 amino acid(s) difference binds TCR with about the same or a higher affinity compared to the binding by the ISV comprising the CDR1 without the 4, 3, 2 or 1 amino acid(s) difference, said affinity as measured by surface plasmon resonance;

   and

   ii) CDR2 is chosen from the group consisting of:

      c) SEQ ID NOs: 192-217; or

      d) amino acid sequences that have 4, 3, 2 or 1 amino acid(s) difference with the amino acid sequence of one of SEQ ID NOs: 192-217; provided that the ISV comprising the CDR2 with 4, 3, 2 or 1 amino acid(s) difference binds TCR with about the same or a higher affinity compared to the binding by the ISV comprising the CDR2 without the 4, 3, 2 or 1 amino acid(s) difference, said affinity as measured by surface plasmon resonance;

   and

   iii) CDR3 is chosen from the group consisting of:

      e) SEQ ID NOs: 218-225; or

      f) amino acid sequences that have 4, 3, 2 or 1 amino acid(s) difference with the amino acid sequence of one of SEQ ID NOs: 218-225; provided that the ISV comprising the CDR3 with 4, 3, 2 or 1 amino acid(s) difference binds TCR with about the same or a higher affinity compared to the binding by the ISV comprising the CDR3 without the 4, 3, 2 or 1 amino acid(s) difference, said affinity as measured by surface plasmon resonance;

and wherein the one or more ISV that specifically bind CD123 essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:

i) CDR1 is chosen from the group consisting of:

a) SEQ ID NOs: 11-16; or

b) amino acid sequences that have 4, 3, 2 or 1 amino acid(s) difference with the amino acid sequence of one of SEQ ID NOs: 11-16; provided that the ISV comprising the CDR1 with 4, 3, 2 or 1 amino acid(s) difference binds CD123 with about the same or a higher affinity compared to the binding by the ISV comprising the CDR1 without the 4, 3, 2 or 1 amino acid(s) difference, said affinity as measured by surface plasmon resonance;

and

ii) CDR2 is chosen from the group consisting of:

c) SEQ ID NOs: 17-20; or

d) amino acid sequences that have 4, 3, 2 or 1 amino acid(s) difference with the amino acid sequence of one of SEQ ID NOs: 17-20; provided that the ISV comprising the CDR2 with 4, 3, 2 or 1 amino acid(s) difference binds CD123 with about the same or a higher affinity compared to the binding by the ISV comprising the CDR2 without the 4, 3, 2 or 1 amino acid(s) difference, said affinity as measured by surface plasmon resonance;

and

iii) CDR3 is chosen from the group consisting of:

e) SEQ ID NOs: 21-25; or

f) amino acid sequences that have 4, 3, 2 or 1 amino acid(s) difference with the amino acid sequence of one of SEQ ID NOs: 21-25; provided that the ISV comprising the CDR3 with 4, 3, 2 or 1 amino acid(s) difference binds CD123 with about the same or a higher affinity compared to the binding by the ISV comprising the CDR3 without the 4, 3, 2 or 1 amino acid(s) difference, said affinity as measured by surface plasmon resonance.

2. The polypeptide according to claim 1, wherein the ISV that specifically binds TCR essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:

i) CDR1 is chosen from the group consisting of:

a) SEQ ID NOs: 181-191; or

b) amino acid sequences that have 4, 3, 2 or 1 amino acid(s) difference with the amino acid sequence of one of SEQ ID NOs: 181-191, wherein the 4, 3, 2 or 1 amino acid(s) difference are present at position 2, 4, 5, 6, 8 and/or 10 of the CDR1 (position 27, 29, 30, 31, 33 and/or 35 according to Kabat numbering); provided that the ISV comprising the CDR1 with 4, 3, 2 or 1 amino acid(s) difference binds TCR with about the same or a higher affinity compared to the binding by the ISV comprising the CDR1 without the 4, 3, 2 or 1 amino acid(s) difference, said affinity as measured by surface plasmon resonance;

and

ii) CDR2 is chosen from the group consisting of:

c) SEQ ID NOs: 192-217; or

d) amino acid sequences that have 4, 3, 2 or 1 amino acid(s) difference with the amino acid sequence of one of SEQ ID NOs: 192-217, wherein the 4, 3, 2 or 1 amino acid(s) difference are present at position 1, 3, 5, 7, 8 and/or 9 of the CDR2 (position 50, 52, 54, 56, 57 and/or 58 according to Kabat numbering); provided that the ISV comprising the CDR2 with 4, 3, 2 or 1 amino acid(s) difference binds TCR with about the same or a higher affinity compared to the binding by the ISV comprising the CDR2 without the 4, 3, 2 or 1 amino acid(s) difference, said affinity as measured by surface plasmon resonance;

and

iii) CDR3 is chosen from the group consisting of:

e) SEQ ID NOs: 218-225; or

f) amino acid sequences that have 4, 3, 2 or 1 amino acid(s) difference with the amino acid sequence of one of SEQ ID NOs: 218-225, wherein the 4, 3, 2 or 1 amino acid(s) difference are present at position 1, 4, 5 and/or 8 of the CDR3 (position 95, 98, 99 and/or 101 according to Kabat numbering); provided that the ISV comprising the CDR3 with 4, 3, 2 or 1 amino acid(s) difference binds TCR with about the same or a higher affinity compared to the binding by the ISV comprising the CDR3 without the 4, 3, 2 or 1 amino acid(s) difference, said affinity as measured by surface plasmon resonance.

3. The polypeptide according to any of claims 1 or 2, wherein the ISV that specifically binds TCR essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity

determining regions (CDR1 to CDR3, respectively), in which CDR1 is SEQ ID NO: 181, CDR2 is SEQ ID NO: 192, and CDR3 is SEQ ID NO: 218.

4. The polypeptide according to any of claims 1 to 3, wherein the ISV that specifically binds TCR is chosen from the group consisting of SEQ ID NOs: 42 and 78-180 or from ISVs that have a sequence identity of more than 80%, more than 85%, more than 90%, more than 95%, or even more than 99% with one of SEQ ID NOs: 42 and 78-180.

5. The polypeptide according to any of claims 1 to 4, wherein the one or more ISV that specifically bind CD123 essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which:

i) CDR1 is chosen from the group consisting of:

a) SEQ ID NOs: 11-16; or

b) amino acid sequences that have 4, 3, 2 or 1 amino acid(s) difference with the amino acid sequence of one of SEQ ID NOs: 11-16, wherein the 4, 3, 2 or 1 amino acid(s) difference are present at position 3, 6, 7 and/or 8 of the CDR1 (position 28, 31, 32 and/or 33 according to Kabat numbering); provided that the ISV comprising the CDR1 with 4, 3, 2 or 1 amino acid(s) difference binds CD123 with about the same or a higher affinity compared to the binding by the ISV comprising the CDR1 without the 4, 3, 2 or 1 amino acid(s) difference, said affinity as measured by surface plasmon resonance;

and

ii) CDR2 is chosen from the group consisting of:

c) SEQ ID NOs: 17-20; or

d) amino acid sequences that have 3, 2 or 1 amino acid(s) difference with the amino acid sequence of one of SEQ ID NOs: 17-20, wherein the 3, 2 or 1 amino acid(s) difference are present at position 3, 6 and/or 10 of the CDR2 (position 52, 54 and/or 58 according to Kabat numbering); provided that the ISV comprising the CDR2 with 3, 2 or 1 amino acid(s) difference binds CD123 with about the same or a higher affinity compared to the binding by the ISV comprising the CDR2 without the 3, 2 or 1 amino acid(s) difference, said affinity as measured by surface plasmon resonance;

and

iii) CDR3 is chosen from the group consisting of:

e) SEQ ID NOs: 21-25; or

f) amino acid sequences that have 3, 2 or 1 amino acid(s) difference with the amino acid sequence of one of SEQ ID NOs: 21-25, wherein the 3, 2 or 1 amino acid(s) difference are present at position 3, 4 and/or 5 of the CDR3 (position 97, 98 and/or 99 according to Kabat numbering); provided that the ISV comprising the CDR3 with 3, 2 or 1 amino acid(s) difference binds CD123 with about the same or a higher affinity compared to the binding by the ISV comprising the CDR3 without the 3, 2 or 1 amino acid(s) difference, said affinity as measured by surface plasmon resonance.

6. The polypeptide according to any of claims 1 to 5, wherein the one or more ISV that specifically bind CD123 essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3, respectively), in which
CDR1 is SEQ ID NO: 11, CDR2 is SEQ ID NO: 17, and CDR3 is SEQ ID NO: 21; or
CDR1 is SEQ ID NO: 16, CDR2 is SEQ ID NO: 18, and CDR3 is SEQ ID NO: 23.

7. The polypeptide according to any of claims 1 to 6, wherein the one or more ISV that specifically bind CD123 is chosen from the group consisting of SEQ ID NOs: 1-10 or from ISVs that have a sequence identity of more than 80%, more than 85%, more than 90%, more than 95%, or even more than 99% with one of SEQ ID NOs: 1-10.

8. The polypeptide according to any of claims 1 to 7, comprising two or more ISVs that specifically bind CD123 wherein the two or more ISVs that specifically bind CD123 are biparatopic, comprising a first ISV and a second ISV, wherein the first ISV binds to an epitope on CD123 that is different from the epitope on CD123 bound by the second ISV.

9. The polypeptide according to claim 8, wherein the first ISV is selected from the ISVs according to claim 12 and wherein the second ISV is selected from the ISVs according to claim 13.

10. The polypeptide according to any of claims 1 to 9, wherein the ISV that specifically binds TCR and the one or more ISV that specifically bind CD123 essentially consist of a single domain antibody, a dAb, a Nanobody, a VHH, a humanized VHH, a camelized VH or a VHH which has been obtained by affinity maturation.

11. The polypeptide according to any of claims 1 to 10, wherein said polypeptide is chosen from the group consisting of SEQ ID NOs: 47, 49, 52, 53, 55, 56 and 58-61 or from polypeptides that

have a sequence identity of more than 80%, more than 85%, more than 90%, more than 95%, or even more than 99% with one of SEQ ID NOs: 47, 49, 52, 53, 55, 56 and 58-61.

12. A polypeptide that is an ISV that specifically binds CD123, wherein the polypeptide is chosen from the group consisting of SEQ ID NOs: 1-6 or from polypeptides that have a sequence identity of more than 80%, more than 85%, more than 90%, more than 95%, or even more than 99% with one of SEQ ID NOs: 1-6.

13. A polypeptide that is an ISV that specifically binds CD123, wherein the polypeptide is chosen from the group consisting of SEQ ID NOs: 7-10 or from polypeptides that have a sequence identity of more than 80%, more than 85%, more than 90%, more than 95%, or even more than 99% with one of SEQ ID NOs: 7-10.

14. A construct comprising a polypeptide according to any of claims 1 to 13, and further comprising one or more other groups, residues, moieties or binding units, optionally linked via one or more peptidic linkers, in which said one or more other groups, residues, moieties or binding units provide the construct with increased half-life, compared to the corresponding polypeptide according to any of claims 1 to 13.

15. The construct according to claim 14, in which said one or more other binding units that provide the construct with increased half-life is chosen from the group consisting of binding units that can bind to serum albumin (such as human serum albumin) or a serum immunoglobulin (such as IgG).

16. A nucleic acid encoding the polypeptide according to any of claims 1 to 13 or the construct according to claims 14 or 15 that is such that it can be obtained by expression of a nucleic acid encoding the same, optionally in the form of a genetic construct.

17. A host or host cell comprising the nucleic acid or the genetic construct according to claim 16, or an expression vector comprising the nucleic acid and/or the genetic construct according to claim 16.

18. A method for the production of the polypeptide according to any of claims 1 to 13 or the construct according to claims 14 or 15 that is such that it can be obtained by expression of a nucleic acid encoding the same, said method at least comprising the steps of:

a) expressing, in a suitable host cell or host organism or in another suitable expression system, the nucleic acid according to claim 16; optionally followed by

b) isolating and/or purifying the polypeptide according to any of claims 1 to 13 or the construct according to claims 14 or 15.

19. A composition comprising at least one polypeptide according to any of claims 1 to 13, or a construct according to claims 14 or 15, or a nucleic acid according to claim 16.

20. The polypeptide according to any of claims 1 to 13, the construct according to claims 14 or 15, or the composition according to claim 19, for use as a medicament.

21. The polypeptide according to any of claims 1 to 13, the construct according to claims 14 or 15, or the composition according to claim 19, for use in the prevention, treatment and/or amelioration of a CD123 associated disease or condition.