

CLAIMS

1. A polypeptide that comprises at least three immunoglobulin single variable domains (ISVDs), wherein each of said ISVDs comprises three complementarity determining regions (CDRs), CDR1 to CDR3, respectively, and wherein:

a) a first ISVD specifically binds to the constant domain of a T cell receptor (TCR) on a T cell and comprises:

- i. a CDR1 comprising the amino acid sequence of SEQ ID NO: 6;
- ii. a CDR2 comprising the amino acid sequence of SEQ ID NO: 10; and
- iii. a CDR3 comprising the amino acid sequence of SEQ ID NO: 14;

b) a second ISVD specifically binds to Glypican-3 (GPC3) and comprises:

- iv. a CDR1 comprising the amino acid sequence of SEQ ID NO: 7;
- v. a CDR2 comprising the amino acid sequence of SEQ ID NO: 11; and
- vi. a CDR3 comprising the amino acid sequence of SEQ ID NO: 15; and

c) a third ISVD specifically binds to GPC3 and comprises:

- vii. a CDR1 comprising the amino acid sequence of SEQ ID NO: 8;
- viii. a CDR2 comprising the amino acid sequence of SEQ ID NO: 12; and
- ix. a CDR3 comprising the amino acid sequence of SEQ ID NO: 16,

wherein the order of the ISVDs indicates their relative position to each other considered from the N-terminus to the C-terminus of said polypeptide.

2. The polypeptide according to claim 1, wherein:

a) said first ISVD comprises a CDR1 consisting of the amino acid sequence of SEQ ID NO:

6, a CDR2 consisting of the amino acid sequence of SEQ ID NO: 10 and a CDR3 consisting of the amino acid sequence of SEQ ID NO: 14;

b) said second ISVD comprises a CDR1 consisting of the amino acid sequence of SEQ ID NO: 7, a CDR2 consisting of the amino acid sequence of SEQ ID NO: 11 and a CDR3 consisting of the amino acid sequence of SEQ ID NO: 15; and

c) said third ISVD comprises a CDR1 consisting of the amino acid sequence of SEQ ID NO: 8, a CDR2 consisting of the amino acid sequence of SEQ ID NO: 12 and a CDR3 consisting of the amino acid sequence of SEQ ID NO: 16.

3. The polypeptide according to claim 1, wherein:

- a) said first ISVD comprises the amino acid sequence of SEQ ID NO: 2;
- b) said second ISVD comprises the amino acid sequence of SEQ ID NO: 3; and
- c) said third ISVD comprises the amino acid sequence of SEQ ID NO: 4.

4. The polypeptide according to claim 1, wherein:

- a) said first ISVD consists of the amino acid sequence of SEQ ID NO: 2;
- b) said second ISVD consists of the amino acid sequence of SEQ ID NO: 3; and
- c) said third ISVD consists of the amino acid sequence of SEQ ID NO: 4.

5. The polypeptide according to claim 1, wherein the first ISVD and the second ISVD are linked to each other via a linker consisting of less than 10 amino acids, a linker consisting of less than 6 amino acids, or a 5GS linker.

6. The polypeptide according to claim 1, wherein said polypeptide further comprises one or more other groups, residues, moieties or binding units, in which said one or more other groups, residues, moieties or binding units provide the polypeptide with increased half-life, compared to the corresponding polypeptide without said one or more other groups, residues, moieties or binding units.

7. The polypeptide according to claim 6, in which said one or more other groups, residues, moieties or binding units that provide the polypeptide with increased half-life is chosen from the group consisting of a polyethylene glycol molecule, serum proteins or fragments thereof, binding units that can bind to serum proteins, an Fc portion, and small proteins or peptides that can bind to serum proteins.

8. The polypeptide according to claim 7, in which said one or more other groups, residues, moieties or binding units that provide the polypeptide with increased half-life comprise an ISVD that binds to human serum albumin.

9. The polypeptide according to claim 8, wherein the ISVD binding to human serum albumin comprises a CDR1 consisting of the amino acid sequence of SEQ ID NO: 9, a CDR2 consisting of the amino acid sequence of SEQ ID NO: 13 and a CDR3 consisting of the amino acid sequence of SEQ ID NO: 17.

10. The polypeptide according to claim 8, wherein said ISVD binding to human serum albumin consists of the amino acid sequence of SEQ ID NO: 5.

11. The polypeptide according to claim 1, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 1.

12. The polypeptide according to claim 1, wherein the polypeptide consists of the amino acid sequence of SEQ ID NO: 1.

13. A polypeptide that comprises at least one immunoglobulin single variable domain (ISVD) that specifically binds Glypican-3 (GPC3), wherein said ISVD comprises three complementarity determining regions (CDRs, CDR1 to CDR3, respectively, and wherein the at least one ISVD comprises:

- a) a CDR1 consisting of the amino acid sequence of SEQ ID NO: 7;
- a CDR2 consisting of the amino acid sequence of SEQ ID NO: 11; and
- a CDR3 consisting of the amino acid sequence of SEQ ID NO: 15; or
- b) a CDR1 consisting of the amino acid sequence of SEQ ID NO: 8;
- a CDR2 consisting of the amino acid sequence of SEQ ID NO: 12; and
- a CDR3 consisting of the amino acid sequence of SEQ ID NO: 16.

14. A polypeptide that comprises at least two immunoglobulin single variable domains (ISVDs), wherein each of said ISVDs comprises three complementarity determining regions (CDRs), CDR1 to CDR3, respectively, and wherein:

a) each of a first and a second ISVD specifically binds to Glypican-3 (GPC3) and comprises:

- i. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 7;
- ii. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 11; and
- iii. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 15;

b) each of a first and a second ISVD specifically binds to GPC3 and comprises:

- i. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 8;
- ii. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 12; and
- iii. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 16;

c) a first ISVD specifically binds to GPC3 and comprises:

- i. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 7;
- ii. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 11; and
- iii. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 15; and

a second ISVD specifically binds to GPC3 and comprises:

- iv. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 8;
- v. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 12; and

- vi. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 16;
- d) a first ISVD specifically binds to GPC3 and comprises:
- i. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 8;
 - ii. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 12; and
 - iii. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 16; and
- a second ISVD specifically binds to GPC3 and comprises:
- iv. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 7;
 - v. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 11; and
 - vi. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 15;
- e) a first ISVD specifically binds to the constant domain of a T cell receptor (TCR) on a T cell and comprises:
- i. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 6;
 - ii. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 10; and
 - iii. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 14; and
- a second ISVD specifically binds to GPC3 and comprises:
- iv. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 7;
 - v. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 11; and
 - vi. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 15;
- f) a first ISVD specifically binds to GPC3 and comprises:
- i. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 7;
 - ii. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 11; and
 - iii. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 15; and
- a second ISVD specifically binds to the constant domain of a TCR on a T cell and comprises:
- iv. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 6;
 - v. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 10; and
 - vi. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 14;

g) a first ISVD specifically binds to the constant domain of a TCR on a T cell and comprises:

- i. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 6;
- ii. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 10; and
- iii. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 14; and

a second ISVD specifically binds to GPC3 and comprises:

- iv. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 8;
- v. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 12; and
- vi. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 16; or

h) a first ISVD specifically binds to GPC3 and comprises:

- i. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 8;
- ii. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 12; and
- iii. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 16; and

a second ISVD specifically binds to the constant domain of a TCR on a T cell and comprises:

- iv. a CDR1 consisting of the amino acid sequence of SEQ ID NO: 6;
- v. a CDR2 consisting of the amino acid sequence of SEQ ID NO: 10; and
- vi. a CDR3 consisting of the amino acid sequence of SEQ ID NO: 14

wherein the order of the ISVDs indicates their relative position to each other considered from the N-terminus to the C-terminus of said polypeptide.

15. A nucleic acid comprising a nucleotide sequence that encodes a polypeptide according to claim 1.

16. A host or host cell comprising a nucleic acid according to claim 15.

17. A method for producing a polypeptide comprising:

expressing, in a suitable host cell or host organism or in another suitable expression system, a nucleic acid according to claim 15.

18. A composition comprising at least one polypeptide according to claim 1.

19. The composition according to claim 18, which is a pharmaceutical composition which further comprises at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant.

20. Use of a pharmaceutically active amount of a polypeptide according to claim 1 in the manufacture of a medicament for treating liver cancer or lung cancer in a subject in need thereof.
21. The polypeptide according to claim 1, wherein the at least three ISVDs are linked via one or more peptidic linkers.
22. The polypeptide according to claim 1, wherein the first ISVD is located at the N-terminus of said polypeptide.
23. The polypeptide according to claim 6, wherein the one or more other groups, residues, moieties or binding units are linked via one or more peptidic linkers.
24. The polypeptide according to claim 7, wherein said one or more other groups, residues, moieties or binding units that provide the polypeptide with increased half-life comprise a binding units that can bind to serum albumin or a serum immunoglobulin.
25. The polypeptide according to claim 14, wherein the at least two ISVDs are linked via one or more peptidic linkers.
26. The method according to claim 17, further comprising:

isolating and/or purifying the polypeptide encoded by the nucleic acid.
27. The composition according to claim 19, wherein the composition comprises one or more further pharmaceutically active polypeptides and/or compounds.
28. The use according to claim 20, wherein the liver cancer is hepatocellular carcinoma.