

bispecific molecules that do not require lymphocyte preconditioning or co-stimulation in order to elicit efficient lysis of target cells. Several bispecific antibody formats have been developed and their suitability for T cell mediated immunotherapy investigated. These include BiTE (bispecific T cell engager) molecules (Nagorsen and Bäuerle, Exp Cell Res 317, 1255-1260 (2011)),
5 diabodies (Holliger et al., Prot Eng 9, 299-305 (1996)) and derivatives thereof, such as tandem diabodies (Kipriyanov et al., J Mol Biol 293, 41-66 (1999)), DART (dual affinity retargeting) molecules, (Moore et al., Blood 117, 4542-51 (2011)), and triomabs (Seimetz et al., Cancer Treat Rev 36, 458-467 (2010)).

The task of generating bispecific molecules suitable for treatment provides several technical
10 challenges related to efficacy, toxicity, applicability and produceability that have to be met. In instances where the bispecific molecule targets an antigen on a target cell, e.g., a cancer cell, that is also expressed in non-target tissue, toxicity can occur. There is thus a need for efficacious T cell activating bispecific molecules that unleash full T cell activation in the presence of target cells but not in the presence of normal cells or tissue.

SUMMARY

The disclosure generally relates to T cell activating bispecific molecules that are activated selectively in the presence of a target cell.

In one aspect, provided is a protease-activatable T cell activating bispecific molecule comprising
20 (a) a first antigen binding moiety capable of binding to CD3, wherein the first antigen binding moiety comprises

(i) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 2, a HCDR 2 of SEQ ID NO: 4, and a HCDR 3 of SEQ ID NO: 10, and

(ii) a light chain variable region (VL) comprising a light chain complementarity
25 determining region (LCDR) 1 of SEQ ID NO: 20, a LCDR 2 of SEQ ID NO: 21 and a LCDR 3 of SEQ ID NO: 22;

(b) a second antigen binding moiety capable of binding to a target cell antigen; and

(c) a masking moiety covalently attached to the T cell bispecific binding molecule through a protease-cleavable linker, wherein the masking moiety is capable of binding to the idiotype of
30 the first antigen binding moiety thereby reversibly concealing the first or the second antigen binding moiety.

In one example, the VH comprises an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 16, and/or the VL comprises an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 23.

- 5 In one example, the masking moiety is covalently attached to the first antigen binding moiety and reversibly conceals the first antigen binding moiety.

In one example, the masking moiety is covalently attached to the heavy chain variable region of the first antigen binding moiety.

In one example, the masking moiety is an anti-idiotypic scFv.

- 10 In one example, the second antigen binding moiety is a crossover Fab molecule wherein either the variable or the constant regions of the Fab light chain and the Fab heavy chain are exchanged. In one example, the first antigen binding moiety is a conventional Fab molecule.

In one example, provided is the protease-activatable T cell activating bispecific molecule as herein above described, comprising not more than one antigen binding moiety capable of binding
15 to CD3.

In one example, provided is the protease-activatable T cell activating bispecific molecule as herein above described, comprising, comprising a third antigen binding moiety which is a Fab molecule capable of binding to a target cell antigen.

- In one example, the third antigen binding moiety is identical to the second antigen binding
20 moiety.

In one example, the second antigen binding moiety is capable of binding to a target cell antigen selected from the group consisting of FolR1 and TYRP1.

In one example, the first and the second antigen binding moiety are fused to each other, optionally via a peptide linker.

- 25 In one example, the second antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding moiety.

In one example, the first antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the second antigen binding moiety.

- In one example, provided is the protease-activatable T cell activating bispecific molecule as
30 herein above described, additionally comprising an Fc domain composed of a first and a second subunit capable of stable association.

In one example, the Fc domain is an IgG, specifically an IgG1 or IgG4, Fc domain.

In one example, the Fc domain exhibits reduced binding affinity to an Fc receptor and/or reduced effector function, as compared to a native IgG1 Fc domain.

In one example, the masking moiety comprises a heavy chain variable region comprising:

- (a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of DYSMN (SEQ ID NO:58);
- (b) a CDR H2 amino acid sequence selected from the group consisting of WINTETGEPRYTDDFKG (SEQ ID NO:59), WINTETGEPRYTDDFTG (SEQ ID NO:84) and WINTETGEPRYTQGFKG (SEQ ID NO:86);
- (c) a CDR H3 amino acid sequence of EGDYDVFDY (SEQ ID NO:60); and a light chain variable region comprising:
- (d) a light chain (CDR L)1 amino acid sequence selected from the group consisting of RASKSVSTSSYSYMH (SEQ ID NO:62) and KSSKSVSTSSYSYMH (SEQ ID NO:82);
- (e) a CDR L2 amino acid sequence of YVSYLES (SEQ ID NO:63); and
- (f) a CDR L3 amino acid sequence selected from the group consisting of QHSREFPYT (SEQ ID NO:64) and QQSREFPYT (SEQ ID NO:88).

In one example, the masking moiety comprises a heavy chain variable region comprising:

- (a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of DYSMN (SEQ ID NO:58);
- (b) a CDR H2 amino acid sequence of WINTETGEPRYTDDFKG (SEQ ID NO:59);
- (c) a CDR H3 amino acid sequence of EGDYDVFDY (SEQ ID NO:60); and a light chain variable region comprising:
- (d) a light chain (CDR L)1 amino acid sequence of RASKSVSTSSYSYMH (SEQ ID NO:62);
- (e) a CDR L2 amino acid sequence of YVSYLES (SEQ ID NO:63); and
- (f) a CDR L3 amino acid sequence of QHSREFPYT (SEQ ID NO:64).

In one example, the masking moiety comprises a heavy chain variable region comprising:

- (a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of SYGVS (SEQ ID NO:58);
- (b) a CDR H2 amino acid sequence of IIWGDGSTNYHSALIS (SEQ ID NO:59);
- (c) a CDR H3 amino acid sequence of GITTVDYDYAMDY (SEQ ID NO:60); and a light chain variable region comprising:
- (d) a light chain (CDR L)1 amino acid sequence of KSSKSVSTSSYSYMH (SEQ ID NO:82);
- (e) a CDR L2 amino acid sequence of AATFLAD (SEQ ID NO:63); and

(f) a CDR L3 amino acid sequence of QHYYSTPYT (SEQ ID NO:64).

In one example, the masking moiety comprises a heavy chain variable region comprising:

(a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of SYGVS (SEQ ID NO:58);

5 (b) a CDR H2 amino acid sequence of WINTETGEPRYTDDFTG (SEQ ID NO:84);

(c) a CDR H3 amino acid sequence of GITTIVDDYYAMDY (SEQ ID NO:60); and a light chain variable region comprising:

(d) a light chain (CDR L)1 amino acid sequence of KSSKSVSTSSYSYMH (SEQ ID NO:82);

10 (e) a CDR L2 amino acid sequence of AATFLAD (SEQ ID NO:63); and

(f) a CDR L3 amino acid sequence of QHYYSTPYT (SEQ ID NO:64).

In one example, the masking moiety comprises a heavy chain variable region comprising:

(a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of SYGVS (SEQ ID NO:58);

15 (b) a CDR H2 amino acid sequence of WINTETGEPRYTQGFKG (SEQ ID NO:86);

(c) a CDR H3 amino acid sequence of GITTIVDDYYAMDY (SEQ ID NO:60); and a light chain variable region comprising:

(d) a light chain (CDR L)1 amino acid sequence of KSSKSVSTSSYSYMH (SEQ ID NO:82);

20 (e) a CDR L2 amino acid sequence of AATFLAD (SEQ ID NO:63); and

(f) a CDR L3 amino acid sequence of QHYYSTPYT (SEQ ID NO:64).

In one example, the protease cleavable linker comprises at least one protease recognition sequence.

In one example, the protease recognition sequence is selected from the group consisting of:

25 (a) RQARVVNG (SEQ ID NO:100);

(b) VHMP LGFLGPGRSRGSFP (SEQ ID NO:101);

(c) RQARVVNGXXXXXVPLSLYSG (SEQ ID NO:102);

(d) RQARVVNGVPLSLYSG (SEQ ID NO:103);

(e) PLGLWSQ (SEQ ID NO:104);

30 (f) VHMP LGFLGP RQARVVNG (SEQ ID NO:105);

(g) FVGGTG (SEQ ID NO:106);

(h) KKAAPVNG (SEQ ID NO:107);

(i) PMAKKVNG (SEQ ID NO:108);

(j) QARAKVNG (SEQ ID NO:109);

- (k) VHMP LGFLGP (SEQ ID NO:110);
- (l) QARAK (SEQ ID NO:111);
- (m) VHMP LGFLGPPMAKK (SEQ ID NO:112);
- (n) KKAAP (SEQ ID NO:113); and
- 5 (o) PMAKK (SEQ ID NO:114), wherein X is any amino acid.

In one example, the protease cleavable linker comprises the protease recognition sequence PMAKK (SEQ ID NO:114).

In one example, the second antigen binding moiety is capable of binding to FolR1 and comprises a heavy chain variable region comprising:

- 10 a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of NAWMS (SEQ ID NO:54);
- b) a CDR H2 amino acid sequence of RIKSKTDGGTTDYAAPVKG (SEQ ID NO:55); and
- c) a CDR H3 amino acid sequence of PWEWSWYDY (SEQ ID NO:56); and a light
- 15 chain variable region comprising:
 - d) a light chain (CDR L)1 amino acid sequence of GSSTGAVTTSNYAN (SEQ ID NO:20);
 - e) a CDR L2 amino acid sequence of GTNKRAP (SEQ ID NO:21); and
 - f) a CDR L3 amino acid sequence of ALWYSNLWV (SEQ ID NO:22).

20 In one example, the second antigen binding moiety is capable of binding to TYRP1 and comprises a heavy chain variable region comprising:

- a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of DYFLH (SEQ ID NO:24);
- b) a CDR H2 amino acid sequence of WINPDNGNTVYAQKFQG (SEQ ID NO:25);
- 25 and
- c) a CDR H3 amino acid sequence of RDYTYEKAALDY (SEQ ID NO:26); and a light chain variable region comprising:
 - d) a light chain (CDR L)1 amino acid sequence of RASGNIYNYLA (SEQ ID NO:28);
 - 30 e) a CDR L2 amino acid sequence of DAKTLAD (SEQ ID NO:29); and
 - f) a CDR L3 amino acid sequence of QHFWSLPFT (SEQ ID NO:30).

The present disclosure provides an idiotype-specific polypeptide for reversibly concealing an anti-CD3 antigen binding site of a molecule, wherein the idiotype-specific polypeptide comprises a heavy chain variable region comprising:

(a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of DYSMN (SEQ ID NO:58);

(b) a CDR H2 amino acid sequence selected from the group consisting of WINTETGEPRYTDDFKG (SEQ ID NO:59), WINTETGEPRYTDDFTG (SEQ ID NO:84) and WINTETGEPRYTQGFKG (SEQ ID NO:86);

(c) a CDR H3 amino acid sequence of EGDYDVFDY (SEQ ID NO:60); and a light chain variable region comprising:

(d) a light chain (CDR L)1 amino acid sequence selected from the group consisting of RASKSVSTSSYSYMH (SEQ ID NO:62) and KSSKSVSTSSYSYMH (SEQ ID NO:82);

(e) a CDR L2 amino acid sequence of YVSYLES (SEQ ID NO:63); and

(f) a CDR L3 amino acid sequence selected from the group consisting of QHSREFPYT (SEQ ID NO:64) and QQSREFPYT (SEQ ID NO:88).

In another aspect, the present disclosure provides a idiotype-specific polypeptide capable of reversibly concealing an anti-CD3 antigen binding site of a molecule, wherein the idiotype-specific polypeptide comprises a heavy chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 79, SEQ ID NO:83 and SEQ ID NO:85, and a light chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 80 and SEQ ID NO:81.

In one example, the idiotype-specific polypeptide comprises a heavy chain variable region comprising:

(a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of DYSMN (SEQ ID NO:58);

(b) a CDR H2 amino acid sequence of WINTETGEPRYTDDFKG (SEQ ID NO:59);

(c) a CDR H3 amino acid sequence of EGDYDVFDY (SEQ ID NO:60); and a light chain variable region comprising:

(d) a light chain (CDR L)1 amino acid sequence of RASKSVSTSSYSYMH (SEQ ID NO:62);

(e) a CDR L2 amino acid sequence of YVSYLES (SEQ ID NO:63); and

(f) a CDR L3 amino acid sequence of QHSREFPYT (SEQ ID NO:64).

5 In one example, the idiotype-specific polypeptide comprises a heavy chain variable region comprising:

(a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of SYGVS (SEQ ID NO:58);

(b) a CDR H2 amino acid sequence of IIWGDGSTNYHSALIS (SEQ ID NO:59);

10 (c) a CDR H3 amino acid sequence of GITTVVDDYYAMDY (SEQ ID NO:60); and
a light chain variable region comprising:

(d) a light chain (CDR L)1 amino acid sequence of KSSKSVSTSSYSYMH (SEQ ID NO:82);

(e) a CDR L2 amino acid sequence of AATFLAD (SEQ ID NO:63); and

(f) a CDR L3 amino acid sequence of QHYYSTPYT (SEQ ID NO:64).

5 In one example, the idiotype-specific polypeptide comprises a heavy chain variable region comprising:

(a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of SYGVS (SEQ ID NO:58);

(b) a CDR H2 amino acid sequence of WINTETGEPRYTDDFTG (SEQ ID NO:84);

10 (c) a CDR H3 amino acid sequence of GITTVVDDYYAMDY (SEQ ID NO:60); and a light chain variable region comprising:

(d) a light chain (CDR L)1 amino acid sequence of KSSKSVSTSSYSYMH (SEQ ID NO:82);

(e) a CDR L2 amino acid sequence of AATFLAD (SEQ ID NO:63); and

15 (f) a CDR L3 amino acid sequence of QHYYSTPYT (SEQ ID NO:64).

In one example, the idiotype-specific polypeptide comprises a heavy chain variable region comprising:

(a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of SYGVS (SEQ ID NO:58);

20 (b) a CDR H2 amino acid sequence of WINTETGEPRYTQGFKG (SEQ ID NO:86);

(c) a CDR H3 amino acid sequence of GITTVVDDYYAMDY (SEQ ID NO:60); and a light chain variable region comprising:

(d) a light chain (CDR L)1 amino acid sequence of KSSKSVSTSSYSYMH (SEQ ID NO:82);

25 (e) a CDR L2 amino acid sequence of AATFLAD (SEQ ID NO:63); and

(f) a CDR L3 amino acid sequence of QHYYSTPYT (SEQ ID NO:64).

In one example, the idiotype-specific polypeptide is an anti-idiotype scFv.

In one example, the idiotype-specific polypeptide is covalently attached to the molecule through a linker.

30 In one example, the linker is a peptide linker.

In one example, the linker is a protease-cleavable linker.

In one example, the peptide linker comprises at least one protease recognition site.

In one example, the protease recognition sequence is selected from the group consisting of:

- (a) RQARVVNG (SEQ ID NO:100);
- (b) VHMPLGFLGPGRSRGSFP (SEQ ID NO:101);
- (c) RQARVVNGXXXXXVPLSLYSG (SEQ ID NO:102);
- (d) RQARVVNGVPLSLYSG (SEQ ID NO:103);
- 5 (e) PLGLWSQ (SEQ ID NO:104);
- (f) VHMPLGFLGPQRQARVVNG (SEQ ID NO:105);
- (g) FVGGTG (SEQ ID NO:106);
- (h) KKAAPVNG (SEQ ID NO:107);
- (i) PMAKKVNG (SEQ ID NO:108);
- 10 (j) QARAKVNG (SEQ ID NO:109);
- (k) VHMPLGFLGP (SEQ ID NO:110);
- (l) QARAK (SEQ ID NO:111);
- (m) VHMPLGFLGPPMAKK (SEQ ID NO:112);
- (n) KKAAP (SEQ ID NO:113); and
- 15 (o) PMAKK (SEQ ID NO:114), wherein X is any amino acid.

In one example, the protease cleavable linker comprises the protease recognition sequence PMAKK (SEQ ID NO:114).

In one example, the idotype-specific polypeptide is part of a T-cell activating bispecific molecule.

- 20 In another aspect, provided is a pharmaceutical composition comprising the protease-activatable T cell activating bispecific molecule as hereinbefore described or the idotype-specific polypeptide as hereinbefore described and a pharmaceutically acceptable carrier.

- In another aspect, provided is an isolated polynucleotide encoding the protease-activatable T cell activating bispecific antigen binding molecule as hereinbefore described or the idotype-specific
25 polypeptide as hereinbefore described.

In another aspect, provided is a vector, particularly an expression vector, comprising the polynucleotide as hereinbefore described.

In another aspect, provided is a host cell comprising the polynucleotide as hereinbefore described or the vector as hereinbefore described.

- 30 In another aspect, provided is a method of producing a protease-activatable T cell activating bispecific molecule, comprising the steps of a) culturing the host cell as hereinbefore described under conditions suitable for the expression of the protease-activatable T cell activating bispecific molecule and b) recovering the protease-activatable T cell activating bispecific molecule.

In another aspect, provided is a protease-activatable T cell activating bispecific molecule as hereinbefore described, the idiotype-specific polypeptide as hereinbefore described or the pharmaceutical composition as hereinbefore described for use as a medicament.

In one example, the medicament is for treating or delaying progression of cancer, treating or
5 delaying progression of an immune related disease, or enhancing or stimulating an immune response or function in an individual.

In another aspect, provided is the use of the protease-activatable T cell activating bispecific molecule as hereinbefore described or the idiotype-specific polypeptide as hereinbefore described in the manufacture of a medicament for the treatment of a disease.

10 In one example, the disease is a cancer.

The present disclosure provides a method of treating a disease in an individual, comprising administering to said individual a therapeutically effective amount of a composition comprising the protease-activatable T cell activating bispecific molecule as hereinbefore described.

In one example, the method is for treating or delaying progression of cancer, treating or delaying
15 progression of an immune related disease, or enhancing or stimulating an immune response or function in an individual.

SHORT DESCRIPTION OF THE FIGURES

Figure 1. Exemplary configurations of the (multispecific) antibodies of the invention. (A, D) Illustration of the “1+1 CrossMab” molecule. (B, E) Illustration of the “2+1 IgG Crossfab”
20 molecule with alternative order of Crossfab and Fab components (“inverted”). (C, F) Illustration of the “2+1 IgG Crossfab” molecule. (G, K) Illustration of the “1+1 IgG Crossfab” molecule with alternative order of Crossfab and Fab components (“inverted”). (H, L) Illustration of the “1+1 IgG Crossfab” molecule. (I, M) Illustration of the “2+1 IgG Crossfab” molecule with two CrossFabs. (J, N) Illustration of the “2+1 IgG Crossfab” molecule with two CrossFabs and
25 alternative order of Crossfab and Fab components (“inverted”). (O, S) Illustration of the “Fab-Crossfab” molecule. (P, T) Illustration of the “Crossfab-Fab” molecule. (Q, U) Illustration of the “(Fab)₂-Crossfab” molecule. (R, V) Illustration of the “Crossfab-(Fab)₂” molecule. (W, Y) Illustration of the “Fab-(Crossfab)₂” molecule. (X, Z) Illustration of the “(Crossfab)₂-Fab” molecule. Black dot: optional modification in the Fc domain promoting heterodimerization. ++, -
30 -: amino acids of opposite charges optionally introduced in the CH1 and CL domains. Crossfab molecules are depicted as comprising an exchange of VH and VL regions, but may – in aspects

Claims

1. A protease-activatable T cell activating bispecific molecule comprising
 - (a) a first antigen binding moiety capable of binding to CD3, wherein the first antigen binding moiety comprises
 - 5 (i) a heavy chain variable region (VH) comprising a heavy chain complementary determining region (HCDR) 1 of SEQ ID NO: 2, a HCDR 2 of SEQ ID NO: 4, and a HCDR 3 of SEQ ID NO: 10, and
 - (ii) a light chain variable region (VL) comprising a light chain complementarity determining region (LCDR) 1 of SEQ ID NO: 20, a LCDR 2 of SEQ ID NO: 21 and a
 - 10 LCDR 3 of SEQ ID NO: 22;
 - (b) a second antigen binding moiety capable of binding to a target cell antigen; and
 - (c) a masking moiety covalently attached to the T cell bispecific binding molecule through a protease-cleavable linker, wherein the masking moiety is capable of binding to the idiotype of the first antigen binding moiety thereby reversibly concealing the first antigen binding moiety.
- 15 2. The protease-activatable T cell activating bispecific molecule of claim 1, wherein the VH comprises an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 16, and/or the VL comprises an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO: 23.
- 20 3. The protease-activatable T cell activating bispecific molecule of claim 1 or 2, wherein the masking moiety is covalently attached to the first antigen binding moiety and reversibly conceals the first antigen binding moiety.
4. The protease-activatable T cell activating bispecific molecule of any one of claims 1-3, wherein the masking moiety is covalently attached to the heavy chain variable region of the first
- 25 antigen binding moiety.
5. The protease-activatable T cell activating bispecific molecule of any one of claims 1-4, wherein the masking moiety is an scFv.
6. The protease-activatable T cell activating bispecific molecule of any one of claims 1-5, wherein the second antigen binding moiety is a crossover Fab molecule wherein either the
- 30 variable or the constant regions of the Fab light chain and the Fab heavy chain are exchanged.
7. The protease-activatable T cell activating bispecific molecule of any one of claims 1-6, wherein the first antigen binding moiety is a conventional Fab molecule.

8. The protease-activatable T cell activating bispecific molecule of any one of claims 1-7, comprising not more than one antigen binding moiety capable of binding to CD3.

9. The protease-activatable T cell activating bispecific molecule of any one of claims 1-8, comprising a third antigen binding moiety which is a Fab molecule capable of binding to a target
5 cell antigen.

10. The protease-activatable T cell activating bispecific molecule of claim 9, wherein the third antigen binding moiety is identical to the second antigen binding moiety.

11. The protease-activatable T cell activating bispecific molecule of any one of claims 1-10, wherein the second antigen binding moiety is capable of binding to a target cell antigen selected
10 from the group consisting of FolR1 and TYRP1.

12. The protease-activatable T cell activating bispecific molecule of any one of claims 1-11, wherein the first and the second antigen binding moiety are fused to each other, optionally via a peptide linker.

13. The protease-activatable T cell activating bispecific molecule of any one of claims 1-12,
15 wherein the second antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the first antigen binding moiety.

14. The protease-activatable T cell activating bispecific molecule of any one of claims 1 to 1-13, wherein the first antigen binding moiety is fused at the C-terminus of the Fab heavy chain to the N-terminus of the Fab heavy chain of the second antigen binding moiety.

20 15. The protease-activatable T cell activating bispecific molecule of any one of claims 1-14, additionally comprising an Fc domain composed of a first and a second subunit capable of stable association.

16. The protease-activatable T cell activating bispecific molecule of claim 15, wherein the Fc domain is an IgG, specifically an IgG1 or IgG4, Fc domain.

25 17. The protease-activatable T cell activating bispecific molecule of claim 15 or 16, wherein the Fc domain exhibits reduced binding affinity to an Fc receptor and/or reduced effector function, as compared to a native IgG1 Fc domain.

18. The protease-activatable T cell activating bispecific molecule of any one of claims 1-17, wherein the masking moiety comprises a heavy chain variable region comprising:

30 (a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of DYSMN (SEQ ID NO:58);

(b) a CDR H2 amino acid sequence selected from the group consisting of WINTETGEPRYTDDFKG (SEQ ID NO:59), WINTETGEPRYTDDFTG (SEQ ID NO:84) and WINTETGEPRYTQGFKG (SEQ ID NO:86);

(c) a CDR H3 amino acid sequence of EGDYDVFDY (SEQ ID NO:60); and a light chain variable region comprising:

(d) a light chain (CDR L)1 amino acid sequence selected from the group consisting of RASKSVSTSSYSYMH (SEQ ID NO:62) and KSSKSVSTSSYSYMH (SEQ ID NO:82);

(e) a CDR L2 amino acid sequence of YVSYLES (SEQ ID NO:63); and

(f) a CDR L3 amino acid sequence selected from the group consisting of QHSREFPYT (SEQ ID NO:64) and QQSREFPYT (SEQ ID NO:88).

19. The protease-activatable T cell activating bispecific molecule of any one of claims 1-17, wherein the masking moiety comprises a heavy chain variable region comprising:

(a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of DYSMN (SEQ ID NO:58);

(b) a CDR H2 amino acid sequence of WINTETGEPRYTDDFKG (SEQ ID NO:59);

(c) a CDR H3 amino acid sequence of EGDYDVFDY (SEQ ID NO:60); and a light chain variable region comprising:

(d) a light chain (CDR L)1 amino acid sequence of RASKSVSTSSYSYMH (SEQ ID NO:62);

(e) a CDR L2 amino acid sequence of YVSYLES (SEQ ID NO:63); and

(f) a CDR L3 amino acid sequence of QHSREFPYT (SEQ ID NO:64).

20. The protease-activatable T cell activating bispecific molecule of any one of claims 1-17, wherein the masking moiety comprises a heavy chain variable region comprising:

(a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of SYGVS (SEQ ID NO:58);

(b) a CDR H2 amino acid sequence of IIWGDGSTNYHSALIS (SEQ ID NO:59);

(c) a CDR H3 amino acid sequence of GITTVVDDYYAMDY (SEQ ID NO:60); and a light chain variable region comprising:

(d) a light chain (CDR L)1 amino acid sequence of KSSKSVSTSSYSYMH (SEQ ID NO:82);

(e) a CDR L2 amino acid sequence of AATFLAD (SEQ ID NO:63); and

(f) a CDR L3 amino acid sequence of QHYYSTPYT (SEQ ID NO:64).

21. The protease-activatable T cell activating bispecific molecule of any one of claims 1-17, wherein the masking moiety comprises a heavy chain variable region comprising:

(a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of SYGVS (SEQ ID NO:58);

5 (b) a CDR H2 amino acid sequence of WINTETGEPRYTDDFTG (SEQ ID NO:84);

(c) a CDR H3 amino acid sequence of GITTVVDDYYAMDY (SEQ ID NO:60); and a light chain variable region comprising:

(d) a light chain (CDR L)1 amino acid sequence of KSSKSVSTSSYSYMH (SEQ ID NO:82);

10 (e) a CDR L2 amino acid sequence of AATFLAD (SEQ ID NO:63); and

(f) a CDR L3 amino acid sequence of QHYYSTPYT (SEQ ID NO:64).

22. The protease-activatable T cell activating bispecific molecule of any one of claims 1-17, wherein the masking moiety comprises a heavy chain variable region comprising:

15 (a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of SYGVS (SEQ ID NO:58);

(b) a CDR H2 amino acid sequence of WINTETGEPRYTQGFKG (SEQ ID NO:86);

(c) a CDR H3 amino acid sequence of GITTVVDDYYAMDY (SEQ ID NO:60); and a light chain variable region comprising:

20 (d) a light chain (CDR L)1 amino acid sequence of KSSKSVSTSSYSYMH (SEQ ID NO:82);

(e) a CDR L2 amino acid sequence of AATFLAD (SEQ ID NO:63); and

(f) a CDR L3 amino acid sequence of QHYYSTPYT (SEQ ID NO:64).

23. The protease-activatable T cell activating bispecific molecule of any one of claims 1-22, wherein the protease cleavable linker comprises at least one protease recognition sequence.

25 24. The protease-activatable T cell activating bispecific molecule of any one of claims 1-23, wherein the protease recognition sequence is selected from the group consisting of:

(a) RQARVVNG (SEQ ID NO:100);

(b) VHMLPLGFLGPRSRGSFP (SEQ ID NO:101);

30 (c) RQARVVNGXXXXXVPLSLYSG (SEQ ID NO:102), wherein X is any amino acid;

(d) RQARVVNGVPLSLYSG (SEQ ID NO:103);

(e) PLGLWSQ (SEQ ID NO:104);

(f) VHMLPLGFLGPRQARVVNG (SEQ ID NO:105);

- (g) FVGGTG (SEQ ID NO:106);
- (h) KKAAPVNG (SEQ ID NO:107);
- (i) PMAKKVNG (SEQ ID NO:108);
- (j) QARAKVNG (SEQ ID NO:109);
- 5 (k) VHMP LGFLGP (SEQ ID NO:110);
- (l) QARAK (SEQ ID NO:111);
- (m) VHMP LGFLGPPMAKK (SEQ ID NO:112);
- (n) KKAAP (SEQ ID NO:113); and
- (o) PMAKK (SEQ ID NO:114).

10 25. The protease-activatable T cell activating bispecific molecule of claim 23 or 24, wherein the protease cleavable linker comprises the protease recognition sequence PMAKK (SEQ ID NO:114).

26. The protease-activatable T cell activating bispecific molecule of any one of claims 1 to 25, wherein the second antigen binding moiety is capable of binding to FolR1 and comprises a heavy
15 chain variable region comprising:

- a) a heavy chain complementarity determining region (CDR H) 1 amino acid sequence of NAWMS (SEQ ID NO:54);
- b) a CDR H2 amino acid sequence of RIKSKTDGGTTDYAAPVKG (SEQ ID NO:55); and
- 20 c) a CDR H3 amino acid sequence of PWEWSWYDY (SEQ ID NO:56); and a light chain variable region comprising:
 - d) a light chain (CDR L)1 amino acid sequence of GSSTGAVTTSNYAN (SEQ ID NO:20);
 - e) a CDR L2 amino acid sequence of GTNKRAP (SEQ ID NO:21); and
 - 25 f) a CDR L3 amino acid sequence of ALWYSNLWV (SEQ ID NO:22).

27. The protease-activatable T cell activating bispecific molecule of any one of claims 1 to 21, wherein the second antigen binding moiety is capable of binding to TYRP1 and comprises a heavy chain variable region comprising:

- a) a heavy chain complementarity determining region (CDR H) 1 amino acid
30 sequence of DYFLH (SEQ ID NO:24);
- b) a CDR H2 amino acid sequence of WINPDNGNTVYAQKFQG (SEQ ID NO:25); and

c) a CDR H3 amino acid sequence of RDYTYEKAALDY (SEQ ID NO:26); and a light chain variable region comprising:

d) a light chain (CDR L)1 amino acid sequence of RASGNIYNYLA (SEQ ID NO:28);

5 e) a CDR L2 amino acid sequence of DAKTLAD (SEQ ID NO:29); and

f) a CDR L3 amino acid sequence of QHFWSLPFT (SEQ ID NO:30).

28. A idiotype-specific polypeptide capable of reversibly concealing an anti-CD3 antigen binding site of a molecule, wherein the idiotype-specific polypeptide comprises a heavy chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to
10 an amino acid sequence selected from the group consisting of SEQ ID NO: 79, SEQ ID NO:83 and SEQ ID NO:85, and a light chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to an amino acid sequence selected from the group consisting of SEQ ID NO: 80 and SEQ ID NO:81.

29. The idiotype-specific polypeptide of claim 28, wherein the idiotype-specific polypeptide
15 comprises a heavy chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 79 and a light chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 80.

30. The idiotype-specific polypeptide of claim 28, wherein the idiotype-specific polypeptide comprises a heavy chain variable region sequence that is at least about 95%, 96%, 97%, 98%,
20 99% or 100% identical to SEQ ID NO: 79 and a light chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 81.

31. The idiotype-specific polypeptide of claim 28, wherein the idiotype-specific polypeptide comprises a heavy chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 83 and a light chain variable region sequence that is at
25 least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 81.

32. The idiotype-specific polypeptide of claim 28, wherein the idiotype-specific polypeptide comprises a heavy chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 85 and a light chain variable region sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to SEQ ID NO: 81.

30 33. The idiotype-specific polypeptide of any one of claims 28-32, wherein the idiotype-specific polypeptide is an scFv.

34. The idiotype-specific polypeptide of any one of claims 28-33, wherein the idiotype-specific polypeptide is covalently attached to the molecule through a linker.

35. The idiotype-specific polypeptide of claim 34, wherein the linker is a peptide linker.

36. The idiotype-specific polypeptide of claim 34 or 35, wherein the linker is a protease-cleavable linker.

37. The idiotype-specific polypeptide of any one of claims 34-36, wherein the peptide linker
5 comprises at least one protease recognition site.

38. The idiotype-specific polypeptide of claim 37, wherein the protease recognition sequence is selected from the group consisting of:

(a) RQARVVNG (SEQ ID NO:100);

(b) VHMP LGFLGPGRSRGSFP (SEQ ID NO:101);

10 (c) RQARVVNGXXXXXVPLSLYSG (SEQ ID NO:102), wherein X is any amino acid;

(d) RQARVVNGVPLSLYSG (SEQ ID NO:103);

(e) PLGLWSQ (SEQ ID NO:104);

(f) VHMP LGFLGP RQARVVNG (SEQ ID NO:105);

15 (g) FVG GTG (SEQ ID NO:106);

(h) KKAAPVNG (SEQ ID NO:107);

(i) PMAKKVNG (SEQ ID NO:108);

(j) QARAKVNG (SEQ ID NO:109);

(k) VHMP LGFLGP (SEQ ID NO:110);

20 (l) QARAK (SEQ ID NO:111);

(m) VHMP LGFLGP PMAKK (SEQ ID NO:112);

(n) KKAAP (SEQ ID NO:113); and

(o) PMAKK (SEQ ID NO:114).

39. The idiotype-specific polypeptide of claim 37, wherein the protease cleavable linker
25 comprises the protease recognition sequence PMAKK (SEQ ID NO:114).

40. The idiotype-specific polypeptide of any one of claims 28-39, wherein the idiotype-specific polypeptide is part of a T-cell activating bispecific molecule.

41. A pharmaceutical composition comprising the protease-activatable T cell activating bispecific molecule of any one of claims 1-27 or the idiotype-specific polypeptide of any one of
30 claims 28-40 and a pharmaceutically acceptable carrier.

42. An isolated polynucleotide encoding the protease-activatable T cell activating bispecific antigen binding molecule of any one of claims 1 to 27 or idiotype-specific polypeptide of any one of claims 28 to 40.

43. A vector, particularly an expression vector, comprising the polynucleotide of claim 42.

44. A host cell comprising the polynucleotide of claim 42 or the vector of claim 43.

45. A method of producing a protease-activatable T cell activating bispecific molecule, comprising the steps of a) culturing the host cell of claim 44 under conditions suitable for the expression of the protease-activatable T cell activating bispecific molecule and b) recovering the protease-activatable T cell activating bispecific molecule.

46. A protease-activatable T cell activating bispecific molecule of any one of claims 1 to 27, the idiotype-specific polypeptide of any one of claims 28-40, or the pharmaceutical composition of claim 41 for use as a medicament.

47. The protease-activatable T cell activating bispecific molecule for use according to claim 46, wherein the medicament is for treating or delaying progression of cancer, treating or delaying progression of an immune related disease, or enhancing or stimulating an immune response or function in an individual.

48. Use of the protease-activatable T cell activating bispecific molecule of any one of claims 1-27 or the idiotype-specific polypeptide of any one of claims 28-40 in the manufacture of a medicament for the treatment of a disease.

49. The use of claim 48, wherein the disease is a cancer.