

CLAIMS

1. A fusion protein, comprising:

(a) a TACI polypeptide and an anti-IFNAR1 antibody or an antigen-binding fragment thereof, or

(b) a TACI polypeptide, a BCMA polypeptide, and an anti-IFNAR1 antibody or an antigen-binding fragment thereof,

wherein the TACI polypeptide comprises a CRD1 and/or a CRD2 of a TACI extracellular region;

preferably, the BCMA polypeptide comprises a CRD1 of a BCMA extracellular region.

2. The fusion protein according to claim 1, wherein:

the TACI polypeptide comprises a polypeptide selected from any one of (1)-(6) below:

(1) the amino acid residues at positions 68-105 of SEQ ID NO: 1, or a variant thereof;

(2) SEQ ID NO: 1 or a polypeptide having at least 95% sequence identity thereto;

(3) the amino acid residues at positions 33-67 of SEQ ID NO: 1;

(4) the amino acid residues at positions 70-104 of SEQ ID NO: 1, or a variant thereof;

(5) the amino acid residues at positions 30-110, 69-111, 69-112, 13-118, or 33-104 of SEQ ID NO: 1, or a variant thereof; and

(6) the amino acid residues at positions 68-106, 68-107, or 68-108 of SEQ ID NO: 1, or a variant thereof;

preferably, the variant has one or more amino acid mutations selected from positions 69, 72, 73, 77, 85, 102, and 103;

more preferably, the variant has one or more amino acid replacements selected from 69T or 69R, 72S, 73E or 73Q, 77E, 85T or 85A, 102A or 102R, and 103Y;

most preferably, the variant has an amino acid replacement or a combination of amino acid replacements selected from any one of the following:

69T; 72S; 73E; 73Q; 77E; 69R and 85T; 69R and 85A; 102A; 69R, 85T, and 102R; 73E and 77E; 72S, 73E, and 77E; 69T and 102A; 69T and 103Y; 69T, 102A, and 103Y; and 69T, 73E, 77E, and 102A;

amino acid residues are numbered in natural order according to the sequence set forth in SEQ ID NO: 1.

3. The fusion protein according to any one of claims 1-2, wherein the TACI polypeptide comprises an amino acid sequence selected from any one of SEQ ID NOs: 1, 2, and 6-29.

4. The fusion protein according to any one of claims 1-3, wherein the anti-IFNAR1 antibody or the antigen-binding fragment thereof comprises a heavy chain variable region and a light chain variable region, wherein:

the heavy chain variable region comprises a HCDR1, a HCDR2, and a HCDR3, and the

- amino acid sequences of the HCDR1, the HCDR2, and the HCDR3 are set forth in SEQ ID NOs: 45-47, respectively;
the light chain variable region comprises a LCDR1, a LCDR2, and a LCDR3, and the amino acid sequences of the HCDR1, the HCDR2, and the HCDR3 are set forth in SEQ ID NOs: 48-50, respectively.
5. The fusion protein according to claim 4, wherein:
the heavy chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 43 or having at least 90% sequence identity thereto;
the light chain variable region comprises an amino acid sequence set forth in SEQ ID NO: 44 or having at least 90% sequence identity thereto.
6. The fusion protein according to any one of the preceding claims, comprising an Fc region of an immunoglobulin, preferably an Fc region of IgG1, and more preferably an Fc region set forth in SEQ ID NO: 3.
7. The fusion protein according to claim 6, wherein the Fc region comprises one or more amino acid mutations capable of reducing binding of the Fc to an FcR; preferably, the one or more amino acid mutations are capable of reducing binding of the Fc to an FcγR; more preferably, the one or more amino acid mutations are any one of the following amino acid mutations or combinations of amino acid mutations: 234A; 235A; 234F; 235E; 234F and 235E; 234A and 235A; and 234F, 235E, and 331S; mutation sites are defined according to the EU numbering scheme.
8. The fusion protein according to any one of claims 1-7, wherein the anti-IFNAR1 antibody comprises a heavy chain and a light chain; the heavy chain comprises an amino acid sequence set forth in SEQ ID NO: 55 or 61 or having at least 90% sequence identity thereto, and the light chain comprises an amino acid sequence set forth in SEQ ID NO: 54 or having at least 90% sequence identity thereto.
9. The fusion protein according to any one of the preceding claims, comprising polypeptide chains set forth in any one of (I)-(VIII) below:
(I) a first polypeptide chain that is, from the N-terminus to the C-terminus, [TACI polypeptide]-[linker 1]a-[antibody heavy chain], and a second polypeptide chain that is an antibody light chain;
(II) a first polypeptide chain that is, from the N-terminus to the C-terminus, [antibody heavy chain]-[linker 2]b-[TACI polypeptide], and a second polypeptide chain that is an antibody light chain;
(III) a first polypeptide chain that is an antibody heavy chain, and a second polypeptide chain that is, from the N-terminus to the C-terminus, [TACI polypeptide]-[linker 3]c-[antibody light chain];

- (IV) a first polypeptide chain that is an antibody heavy chain, and a second polypeptide chain that is, from the N-terminus to the C-terminus, [antibody light chain]-[linker 4]d-[TACI polypeptide];
- (V) a first polypeptide chain that is, from the N-terminus to the C-terminus, [TACI polypeptide 1]-[linker 1]a-[antibody heavy chain], and a second polypeptide chain that is, from the N-terminus to the C-terminus, [antibody light chain]-[linker 4]d-[TACI polypeptide 2];
- (VI) a first polypeptide chain that is, from the N-terminus to the C-terminus, [antibody heavy chain]-[linker 2]b-[TACI polypeptide 1], and a second polypeptide chain that is, from the N-terminus to the C-terminus, [TACI polypeptide 2]-[linker 3]c-[antibody light chain];
- (VII) a first polypeptide chain that is, from the N-terminus to the C-terminus, [TACI polypeptide 1]-[linker 1]a-[antibody heavy chain]-[linker 2]b-[TACI polypeptide 2], and a second polypeptide chain that is an antibody light chain; and
- (VIII) a first polypeptide chain that is an antibody heavy chain, and a second polypeptide chain that is, from the N-terminus to the C-terminus, [TACI polypeptide 1]-[linker 3]c-[antibody light chain]-[linker 4]d-[TACI polypeptide 2];
- wherein:
- represents a peptide bond;
 - linker 1, linker 2, linker 3, and linker 4 may be identical or different;
 - the TACI polypeptide, the TACI polypeptide 1, and the TACI polypeptide 2 are each independently selected from the TACI polypeptide defined in any one of claims 1-3, and TACI polypeptide 1 and TACI polypeptide 2 may be identical or different;
 - a, b, c, and d are each independently 0 or 1;
 - the antibody is the anti-IFNAR1 antibody defined in any one of claims 4-5;
 - preferably, the linker 1, linker 2, linker 3, and linker 4 are each independently $(GxS)_y$, wherein x is an integer of 1-5, and y is an integer of 1-6;
 - more preferably, the amino acid sequences of the linker 1, linker 2, linker 3, and linker 4 are each independently set forth in any one of SEQ ID NOs: 39-41.
10. The fusion protein according to any one of the preceding claims, comprising:
- two identical first polypeptide chains set forth in any one of SEQ ID NOs: 51-53 and 62 and two identical second polypeptide chains set forth in SEQ ID NO: 54; or
 - two identical first polypeptide chains set forth in SEQ ID NO: 55 and two identical second polypeptide chains set forth in any one of SEQ ID NOs: 56-60; or
 - two identical first polypeptide chains set forth in SEQ ID NO: 61 and two identical second polypeptide chains set forth in any one of SEQ ID NOs: 56-60.
11. The fusion protein according to claim 1, wherein the BCMA polypeptide comprises the amino acid residues at positions 7-41 of SEQ ID NO: 30;
- preferably, the amino acid sequence of the BCMA polypeptide comprises a sequence

selected from any one of SEQ ID NOs: 30, 67, and 68.

12. The fusion protein according to any one of claims 1-11, comprising polypeptide chains set forth in any one of (i)-(viii) below:

- 5 (i) a first polypeptide chain that is, from the N-terminus to the C-terminus, [TACI polypeptide and BCMA polypeptide domain]-[linker 1]a-[antibody heavy chain], and a second polypeptide chain that is an antibody light chain;
- (ii) a first polypeptide chain that is, from the N-terminus to the C-terminus, [antibody heavy chain]-[linker 2]b-[TACI polypeptide and BCMA polypeptide domain], and a
10 second polypeptide chain that is an antibody light chain;
- (iii) a first polypeptide chain that is an antibody heavy chain, and a second polypeptide chain that is, from the N-terminus to the C-terminus, [TACI polypeptide and BCMA polypeptide domain]-[linker 3]c-[antibody light chain];
- (iv) a first polypeptide chain that is an antibody heavy chain, and a second polypeptide
15 chain that is, from the N-terminus to the C-terminus, [antibody light chain]-[linker 4]d-[TACI polypeptide and BCMA polypeptide domain];
- (v) a first polypeptide chain that is, from the N-terminus to the C-terminus, [TACI polypeptide and BCMA polypeptide domain 1]-[linker 1]a-[antibody heavy chain], and a second polypeptide chain that is, from the N-terminus to the C-terminus, [antibody
20 light chain]-[linker 4]d-[TACI polypeptide and BCMA polypeptide domain 2];
- (vi) a first polypeptide chain that is, from the N-terminus to the C-terminus, [antibody heavy chain]-[linker 2]b-[TACI polypeptide and BCMA polypeptide domain 1], and a second polypeptide chain that is, from the N-terminus to the C-terminus, [TACI polypeptide and BCMA polypeptide domain 2]-[linker 3]c-[antibody light chain];
- 25 (vii) a first polypeptide chain that is, from the N-terminus to the C-terminus, [TACI polypeptide and BCMA polypeptide domain 1]-[linker 1]a-[antibody heavy chain]-[linker 2]b-[TACI polypeptide and BCMA polypeptide domain 2], and a second polypeptide chain that is an antibody light chain; and
- (viii) a first polypeptide chain that is an antibody heavy chain, and a second polypeptide
30 chain that is, from the N-terminus to the C-terminus, [TACI polypeptide and BCMA polypeptide domain 1]-[linker 3]c-[antibody light chain]-[linker 4]d-[TACI polypeptide and BCMA polypeptide domain 2];

wherein:

- the [TACI polypeptide and BCMA polypeptide domain], the [TACI polypeptide and
35 BCMA polypeptide domain 1], and the [TACI polypeptide and BCMA polypeptide domain 2] are, from the N-terminus to the C-terminus: [TACI polypeptide]-[linker 5]e-[BCMA polypeptide] or [BCMA polypeptide]-[linker 5]e-[TACI polypeptide];
- the [TACI polypeptide and BCMA polypeptide domain 1] and the [TACI polypeptide and BCMA polypeptide domain 2] may be identical or different, and the BCMA
40 polypeptide domain 1 and the BCMA polypeptide domain 2 may be identical or different;

- the TACI polypeptide is selected from the TACI polypeptide defined in any one of claims 1-3, the BCMA polypeptide is selected from the BCMA polypeptide defined in claim 1 or 11, and the antibody is selected from the anti-IFNAR1 antibody defined in any one of claims 4-8;
- 5 wherein:
- represents a peptide bond;
 - the linker 1, linker 2, linker 3, linker 4, and linker 5 may be identical or different; a, b, c, d, and e are each independently 0 or 1;
 - preferably, the linker 1, linker 2, linker 3, linker 4, and linker 5 are each independently
 - 10 $(GxS)_y$, wherein x is an integer of 1-5, and y is an integer of 1-6;
 - more preferably, the amino acid sequences of the linker 1, linker 2, linker 3, linker 4, and linker 5 are each independently set forth in any one of SEQ ID NOs: 39-41.
13. The fusion protein according to any one of claims 1-12, comprising: two identical
- 15 first polypeptide chains set forth in SEQ ID NO: 55 and two identical second polypeptide chains set forth in any one of SEQ ID NOs: 63-66, 71, and 72;
- two identical first polypeptide chains set forth in SEQ ID NO: 61 and two identical second polypeptide chains set forth in any one of SEQ ID NOs: 63-66, 71, and 72; or
- two identical first polypeptide chains set forth in SEQ ID NO: 73 or 74 and two
- 20 identical second polypeptide chains set forth in any one of SEQ ID NO: 54.
14. A fusion protein, comprising a TACI polypeptide and a BCMA polypeptide, wherein:
- the TACI polypeptide comprises a CRD1 and/or a CRD2 of a TACI extracellular
- 25 domain;
- the BCMA polypeptide comprises a CRD1 of a BCMA extracellular domain;
- preferably, the TACI polypeptide and the BCMA polypeptide are linked directly or by a linker.
- 30 15. The fusion protein according to claim 14, wherein the TACI polypeptide comprises a polypeptide selected from any one of (1)-(6) below:
- (1) the amino acid residues at positions 68-105 of SEQ ID NO: 1, or a variant thereof;
 - (2) SEQ ID NO: 1 or a polypeptide having at least 95% sequence identity thereto;
 - (3) the amino acid residues at positions 33-67 of SEQ ID NO: 1;
 - 35 (4) the amino acid residues at positions 70-104 of SEQ ID NO: 1, or a variant thereof;
 - (5) the amino acid residues at positions 30-110, 69-111, 69-112, 13-118, or 33-104 of SEQ ID NO: 1, or a variant thereof; and
 - (6) the amino acid residues at positions 68-106, 68-107, or 68-108 of SEQ ID NO: 1, or a variant thereof;
 - 40 preferably, the variant has one or more amino acid mutations selected from positions 69, 72, 73, 77, 85, 102, and 103;

more preferably, the variant has one or more amino acid replacements selected from 69T or 69R, 72S, 73E or 73Q, 77E, 85T or 85A, 102A or 102R, and 103Y;

most preferably, the variant has an amino acid replacement or a combination of amino acid replacements selected from any one of the following: 69T; 72S; 73E; 73Q; 77E; 69R and 85T; 69R and 85A; 102A; 69R, 85T, and 102R; 73E and 77E; 72S, 73E, and 77E; 69T and 102A; 69T and 103Y; 69T, 102A, and 103Y; and 69T, 73E, 77E, and 102A;

amino acid residues are numbered in natural order according to the sequence set forth in SEQ ID NO: 1.

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16. The fusion protein according to claim 14 or 15, wherein the TACI polypeptide comprises an amino acid sequence selected from any one of SEQ ID NOs: 1, 2, and 6-29.

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17. The fusion protein according to any one of claims 14-16, wherein the BCMA polypeptide comprises the amino acid residues at positions 7-41 of SEQ ID NO: 30.

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18. The fusion protein according to claim 17, wherein the amino acid sequence of the BCMA polypeptide comprises a sequence selected from any one of SEQ ID NOs: 30, 67, and 68.

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19. The fusion protein according to any one of claims 14-18, further comprising an Fc region of an immunoglobulin, preferably an Fc region of IgG1, and more preferably an Fc region set forth in SEQ ID NO: 3.

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20. The fusion protein according to claim 19, wherein the Fc region comprises one or more amino acid mutations capable of reducing binding of the Fc to an FcR; preferably, the one or more amino acid mutations are capable of reducing binding of the Fc to an FcγR; more preferably, the one or more amino acid mutations are any one of the following amino acid mutations or combinations of amino acid mutations: 234A; 235A; 234F; 235E; 234F and 235E; 234A and 235A; and 234F, 235E, and 331S; mutation sites are defined according to the EU numbering scheme.

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21. The fusion protein according to any one of claims 14-20, comprising a polypeptide chain set forth in any one of (I)-(VIII) below:

(I) [TACI polypeptide]-[linker 1]a-[BCMA polypeptide]-[linker 2]b-[Fc region]e;

(II) [BCMA polypeptide]-[linker 1]a-[TACI polypeptide]-[linker 2]b-[Fc region]e;

(III) [Fc region]e-[linker 3]c-[TACI polypeptide]-[linker 4]d-[BCMA polypeptide];

(IV) [Fc region]e-[linker 3]c-[BCMA polypeptide]-[linker 4]d-[TACI polypeptide];

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(V) [TACI polypeptide 1]-[linker 1]a-[BCMA polypeptide 1]-[linker 2]b-[Fc region]e-[linker 3]c-[TACI polypeptide 2]-[linker 4]d-[BCMA polypeptide 2];

- (VI) [BCMA polypeptide 1]-[linker 1]a-[TACI polypeptide 1]-[linker 2]b-[Fc region]e-[linker 3]c-[BCMA polypeptide 2]-[linker 4]d-[TACI polypeptide 2];
- (VII) [TACI polypeptide 1]-[linker 1]a-[BCMA polypeptide 1]-[linker 2]b-[Fc region]e-[linker 3]c-[BCMA polypeptide 2]-[linker 4]d-[TACI polypeptide 2]; and
- 5 (VIII) [BCMA polypeptide 1]-[linker 1]a-[TACI polypeptide 1]-[linker 2]b-[Fc region]e-[linker 3]c-[TACI polypeptide 2]-[linker 4]d-[BCMA polypeptide 2];
- wherein:
- represents a peptide bond, and the linker 1, linker 2, linker 3, and linker 4 may be identical or different;
- 10 the TACI polypeptide 1 and the TACI polypeptide 2 are selected from the TACI polypeptide defined in any one of claims 14-16, and the TACI polypeptide 1 and the TACI polypeptide 2 may be identical or different;
- the BCMA polypeptide 1 and the BCMA polypeptide 2 are selected from the BCMA polypeptide defined in any one of claims 14-18, and the BCMA polypeptide 1 and the
- 15 BCMA polypeptide 2 may be identical or different;
- a, b, c, d, and e are each independently 0 or 1;
- preferably, the linker 1, linker 2, linker 3, and linker 4 are each independently (GxS)_y, wherein x is an integer of 1-5, and y is an integer of 1-6;
- more preferably, the amino acid sequences of the linker 1, linker 2, linker 3, linker 4,
- 20 and linker 5 are each independently set forth in any one of SEQ ID NOs: 39-41.
22. The fusion protein according to any one of claims 14-21, comprising the amino acid sequence set forth in any one of SEQ ID NOs: 31-38, 69, and 70.
- 25 23. The fusion protein according to any one of claims 14-22, wherein the fusion protein is a dimer.
24. A complex, comprising:
- the TACI polypeptide defined in any one of claims 1-3, the anti-IFNAR1 antibody
- 30 defined in any one of claims 4-8, and the BCMA polypeptide defined in claim 1 or 11;
- or
- the TACI polypeptide defined in any one of claims 14-23 and the BCMA polypeptide defined in any one of claims 14-23.
- 35 25. A pharmaceutical composition, comprising:
- the fusion protein according to any one of claims 1-23 or the complex according to claim 24, and
- one or more pharmaceutically acceptable carriers, diluents, or excipients.
- 40 26. A polynucleotide, wherein the polynucleotide encodes:
- the fusion protein according to any one of claims 1-23, or

the complex according to claim 24.

27. A host cell, comprising or expressing the polynucleotide according to claim 26.

5 28. Use of the fusion protein according to any one of claims 1-23, the complex according to claim 24, the pharmaceutical composition according to claim 25, or the polynucleotide according to claim 26, in the manufacture of a medicament in treating or ameliorating a disease or disorder, wherein:

the disease or disorder is a B cell disorder or an autoimmune disease;

10 preferably, the B cell disorder or the autoimmune disease is a disease or disorder associated with TACI and/or BCMA expression;

more preferably, the autoimmune disease is systemic lupus erythematosus.

15 29. A method for preparing the fusion protein according to any one of claims 1-23 or the complex according to claim 24, comprising culturing the host cell according to claim 27 and expressing the fusion protein or complex, wherein optionally, the method comprises isolating or purifying the fusion protein or complex.