CLAIMS

1. An hIL-2/anti-IL-2 antibody fusion protein, comprising: (1) the wild-type hIL-2 as set forth in SEQ ID NO: 1, or a mutein thereof; (2) an anti-IL-2 antibody or an antigen-binding fragment thereof; and (3) disulfide linkage(s) comprised at the antigen-antibody binding interface of the hIL-2 or a mutein thereof and the anti-IL-2 antibody or the antigen-binding fragment thereof;

wherein the anti-IL-2 antibody or the antigen-binding fragment thereof is capable of specifically binding to hIL-2 or a mutein thereof, and competitively blocking the hIL-2 or a mutein thereof from binding with IL2Rα or an IL-2 receptor complex comprising IL2Rα (i.e., IL2Rα/β or IL2Rα/β/γ); and

the disulfide linkage(s) is/are formed by introducing at least one cysteine mutation in the hIL-2 or a mutein thereof at the antigen-antibody binding interface and at least one cysteine mutation in the anti-IL-2 antibody or the antigen-binding fragment thereof at the antigen-antibody binding interface; and

the hIL-2/anti-IL-2 antibody fusion protein is unable to bind to IL2Rα, or the αβ heterodimer (i.e., IL2Rα/β), or the αβγ heterotrimer (i.e., IL2Rα/β/γ), but retains binding and functional activity to the dimeric receptor consisting of IL2Rβ and γ (i.e., IL2Rβ/γ).

2. The hIL-2/anti-IL-2 antibody fusion protein of claim 1, comprising at least one of the following characteristics:

(1) the antigen-antibody binding interface of the hIL-2 or a mutein thereof and the anti-IL-2 antibody or the antigen-binding fragment thereof encompasses or partially overlaps with the binding interface of hIL-2 or a mutein thereof to IL2Rα;

alternatively, the antigen-antibody binding interface of the hIL-2 or a mutein thereof and the anti-IL-2 antibody or the antigen-binding fragment thereof is located in AB loop, B helix, C helix, BC loop and/or CD loop of the hIL-2 or a mutein thereof; the IL2Rα binding interface of the hIL-2 or a mutein thereof is located in AB loop and B helix of the hIL-2 or a mutein thereof;

alternatively, the antigen-antibody binding interface of the hIL-2 or a mutein thereof and the anti-IL-2 antibody or the antigen-binding fragment thereof is located at the position 30-45 or their adjacent amino acid residues, the position 57-77 or their adjacent amino acid residues, and/or the position 90-111 or their adjacent amino acid residues of the hIL-2 or a mutein thereof;

(2) the anti-IL-2 antibody or the antigen-binding fragment thereof is selected from the group consisting of an anti-mouse IL-2 (mIL-2) antibody and a humanized antibody thereof, wherein the anti-mIL-2 antibody is able to specifically recognize the binding site of mIL-2 to mouse IL2Rα (mIL2Rα), and cross-react with the hIL-2 mutein; the anti-IL-2 antibody is also selected from the group consisting of other anti-IL-2 humanized antibody or an antigen-binding fragment thereof which is capable of specifically recognizing the IL2Rα-binding site of hIL-2;

(3) a first cysteine residue and a second cysteine residue are introduced into the antigen-antibody binding interface of the hIL-2/anti-IL-2 antibody fusion protein by amino acid mutation, wherein the site for introducing the first cysteine residue in the hIL-2 or a mutein thereof of the said fusion protein, and the site for introducing the second cysteine residue in the anti-IL-2 antibody or the antigen-binding fragment thereof of the said fusion protein are able to be paired correctly, and the spatial distance between the pair of the first cysteine residue and the second cysteine residue is less than 5 angstroms.

3. The hIL-2/anti-IL-2 antibody fusion protein of claim 1 or 2, wherein the amino acid mutation of the hIL-2 mutein is located in the binding interface between the hIL-2 mutein and the anti-IL-2 antibody or the antigen-binding fragment thereof; wherein, relative to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1, the hIL-2 mutein comprises at least one of the following mutations: (1) K is mutated to G, S, T, C, Y, N or Q at the position 64 corresponding to the wild-type hIL-2 as set forth in SEQ ID NO: 1; (2) N is mutated to R, K or H at the position 90 corresponding to the wild-type hIL-2 as set forth in SEQ ID NO: 1; or (3) M is mutated to E or D at the position 104 corresponding to the wild-type hIL-2 as set forth in SEQ ID NO: 1;

optionally, wherein the hIL-2 mutein comprises one or more of the following amino acid mutations

relative to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1: (1) an amino acid mutation K64G at the position 64 corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1; (2) an amino acid mutation N90R at the position 90 corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1; and (3) an amino acid mutation M104E at the position 104 corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1.

4. The hIL-2/anti-IL-2 antibody fusion protein of claim 3, wherein the hIL-2 mutein further comprises the following one or more amino acid mutations: (1) a deletion of the first three or five amino acids at the N-terminus corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1; (2) an amino acid mutation at the third amino acid residue at the N-terminus corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1; and/or (3) an amino acid mutation C125A, C125L, C125S, C125Q, or C125V at the position 125 corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1;

optionally, the hIL-2 mutein comprises the following amino acid mutations: a deletion of the first three N-terminal amino acids, and/or an amino acid mutation of C125A, C125L, C125S, C125Q, or C125V at the position 125 corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1.

5. The hIL-2/anti-IL-2 antibody fusion protein of any one of claims 1 to 4, wherein the antigen-antibody binding interface of the hIL-2 mutein and the anti-IL-2 antibody or the antigen-binding fragment thereof of the IL-2/anti-IL-2 antibody fusion protein is located at the position 41-45 or their adjacent amino acid residues, the position 57-68 or their adjacent amino acid residues, and/or the position 90-107 or their adjacent amino acid residues of the hIL-2 mutein, relative to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1; optionally the first cysteine residue is introduced by one or more cysteine mutations in the hIL-2 mutein at the said antigen-antibody binding interface;

the anti-IL-2 antibody or the antigen-binding fragment thereof is selected from the group consisting of an anti-mouse IL-2 (mIL-2) antibody and a humanized antibody thereof, optionally wherein the anti-IL-2 antibody or the antigen-binding fragment thereof comprises the following HCDR1, HCDR2 and HCDR3 of the heavy chain variable region, and LCDR1, LCDR2 and LCDR3 of the light chain variable region: (1) HCDR1 having an amino acid sequence of X_1YYX_2H (wherein X_1=A or D; X_2=L or M); (2) HCDR2 having an amino acid sequence of $RIDPZ_1DDSTKYAENFKX_3$ (wherein Z_1=E or D; X_3=N, S or G, as set forth in SEQ ID NO: 230); (3) HCDR3 having an amino acid sequence of $Z_2TFZ_3YZ_4RELRWFAY$ (wherein Z_2=V, I, R or T; Z_3=Y, L, H or W; Z_4=S, T, A, R, N, D, Q, E, H, I, L, K, F, P, W, Y or V, as set forth in SEQ ID NO: 231); (4) LCDR1 having an amino acid sequence of $QASQZ_5IZ_6NYLS$ (wherein Z_5=D, Y, N, H, I, L or F; Z_6=G, S, A, R, N, Q, I, L, T or D; as set forth in SEQ ID NO: 232); (5) LCDR2 having an amino acid sequence of $Z_7AZ_8SLAX_4$ (wherein Z_7=S, Q, R, T, W or Y; Z_8=T or G; X_4=D, S or T; as set forth in SEQ ID NO: 233); and (6) LCDR3 having an amino acid sequence of LQHYSTPYT (as set forth in SEQ ID NO: 12); optionally wherein the second cysteine residue is introduced by one or more amino acid mutations in the anti-IL-2 antibody or the antigen-binding fragment thereof at the said antigen-antibody binding interface.

6. The hIL-2/anti-IL-2 antibody fusion protein of claim 5, wherein the anti-IL-2 antibody or the antigen-binding fragment thereof comprises the following HCDR1, HCDR2 and HCDR3 of the heavy chain variable region, and LCDR1, LCDR2 and LCDR3 of the light chain variable region: (1) HCDR1 having an amino acid sequence of X_1YYX_2H (wherein X_1=A; X_2=L or M); (2) HCDR2 having an amino acid sequence of $RIDPZ_1DDSTKYAENFKX_3$ (wherein Z_1=E or D; X_3=N, S or G); (3) HCDR3 having an amino acid sequence of $Z_2TFZ_3YZ_4RELRWFAY$ (wherein Z_2=V or I; Z_3=Y or L; Z_4=S or T); (4) LCDR1 having an amino acid sequence of $QASQZ_5IZ_6NYLS$ (wherein Z_5=D or Y; Z_6=G or S); (5) LCDR2 having an amino acid sequence of $Z_7AZ_8SLAX_4$ (wherein Z_7=S or Q; Z_8=T; X_4=D, S or T); and (6) LCDR3 having an amino acid sequence of LQHYSTPYT.

7. The hIL-2/anti-IL-2 antibody fusion protein of claim 6, wherein the anti-IL-2 antibody or the antigen-binding fragment thereof comprises the following HCDR1, HCDR2 and HCDR3 of the heavy chain variable region, and LCDR1, LCDR2 and LCDR3 of the light chain variable region:

(1) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 7, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 8, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 9, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 10, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 11, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; or

(2) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 8, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 9, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 10, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 11, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; or

(3) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 7, HCDR2 having an amino acid sequence as set forth in SEQ ID NOs: 15 or 16, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 9, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 10, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 11, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; or

(4) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 7, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 8, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 9, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 10, LCDR2 having an amino acid sequence as set forth in SEQ ID Nos: 17 or 18, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; or

(5) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 15, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 9, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 10, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 17, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; or

(6) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 15, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 9, LCDR1 having an amino acid sequence as set forth in SEQ ID NOs: 26 or 27, LCDR2 having an amino acid sequence as set forth in SEQ ID NOs: 17 or 28, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; or

(7) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 15, HCDR3 having an amino acid sequence as set forth in SEQ ID NOs: 20, 21, 22, 23, 24 or 25, LCDR1 having an amino acid sequence as set forth in SEQ ID NOs: 26 or 27, LCDR2 having an amino acid sequence as set forth in SEQ ID NOs: 17 or 28, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; or

(8) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 19, HCDR3 having an amino acid sequence as set forth in SEQ ID NOs: 9, 20, 23, 24 or 25, LCDR1 having an amino acid sequence as set forth in SEQ ID NOs: 26 or 27, LCDR2 having an amino acid sequence as set forth in SEQ ID Nos: 17 or 28, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12;

alternatively, the anti-IL-2 antibody or the antigen-binding fragment thereof comprises the following HCDR1, HCDR2 and HCDR3 of the heavy chain variable region, and LCDR1, LCDR2 and LCDR3 of the light chain variable region:

(1) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 15, HCDR3 having an amino acid sequence as set forth in SEQ ID NOs: 24 or 25, LCDR1 having an amino acid sequence as set forth in SEQ ID NOs: 26 or 27, LCDR2 having an amino acid sequence as set forth in SEQ ID NOs: 17 or 28, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; or

(2) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 19, HCDR3 having an amino acid sequence as set forth in SEQ ID NOs: 23, 24 or 25, LCDR1 having an amino acid sequence as set forth in SEQ ID NOs: 26 or 27, LCDR2 having an amino acid sequence as set forth in SEQ ID NOs: 17 or 28, and LCDR3 having an amino acid

sequence as set forth in SEQ ID NO: 12; or

(3) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 15, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 9, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 10, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 17, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12.

8. The hIL-2/anti-IL-2 antibody fusion protein of claim 6 or 7, wherein the anti-IL-2 antibody or the antigen-binding fragment thereof comprises: heavy chain variable region VH having the HCDR1, HCDR2 and HCDR3, which has at least 85% identity to a sequence as set forth in SEQ ID NOs: 49, 51, 54, 55, 56, 57, 58, 63, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, or 75; and light chain variable region VL having the LCDR1, LCDR2 and LCDR3, which has at least 85% identity to a sequence as set forth in SEQ ID NOs: 48, 50, 59, 60, 62, 64, 76, 77, 78, or 79;

alternatively, the anti-IL-2 antibody or the antigen-binding fragment thereof comprises the following heavy chain variable region and light chain variable region: amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH as set forth in any of SEQ ID NOs: 63 and 65-75, and the VL as set forth in any of SEQ ID NOs: 64 and 76-79.

9. The hIL-2/anti-IL-2 antibody fusion protein of claim 8, wherein the anti-IL-2 antibody or the antigen-binding fragment thereof comprises the following heavy chain variable region and light chain variable region:

(1) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH amino acid sequence as set forth in SEQ ID NO: 49, and the VL as set forth in SEQ ID NOs: 48 or 50, respectively; or

(2) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH as set forth in SEQ ID Nos: 54, 55, 56, 57 or 58, and the VL as set forth in SEQ ID NO: 48, respectively; or

(3) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH amino acid sequence as set forth in SEQ ID NO: 49, and the VL as set forth in SEQ ID NOs: 59, 60 or 62, respectively; or

(4) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH as set forth in SEQ ID NO: 63, and the VL as set forth in SEQ ID NO: 64, respectively; or

(5) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH as set forth in any of SEQ ID NOs: 63 and 65-75, and the VL as set forth in SEQ ID NO: 76, respectively; or

(6) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH as set forth in any of SEQ ID NOs: 63 and 65-75, and the VL as set forth in SEQ ID NO: 77, respectively; or

(7) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH as set forth in any of SEQ ID NOs: 63 and 65-75, and the VL as set forth in SEQ ID NO: 78, respectively; or

(8) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH as set forth in any of SEQ ID NOs: 63 and 65-75, and the VL as set forth in SEQ ID NO: 79, respectively;

alternatively, the anti-IL-2 antibody or the antigen-binding fragment thereof comprises the following heavy chain variable region and light chain variable region:

(1) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH as set forth in SEQ ID NO: 63, and the VL as set

forth in SEQ ID NO: 64, respectively; or

(2) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93% 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH as set forth in any of SEQ ID NOs: 71-75, and the VL as set forth in SEQ ID NO: 76, respectively; or

(3) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH as set forth in any of SEQ ID NOs: 72-75, and the VL as set forth in SEQ ID NOs: 77, respectively; or

(4) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH as set forth in SEQ ID NO: 74, and the VL as set forth in SEQ ID NO: 78, respectively; or

(5) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VH as set forth in SEQ ID NO: 75, and the VL as set forth in SEQ ID NO: 79, respectively.

10. The hIL-2/anti-IL-2 antibody fusion protein of claim 5, wherein the antigen-antibody binding interface of the hIL-2 mutein and the anti-IL-2 antibody or the antigen-binding fragment thereof of the said fusion protein comprises two or more introduced cysteine mutations to form the said disulfide linkage(s),

wherein the hIL-2 mutein has one or more cysteine mutations at the positions 42, 60, 61, 64, 65, 102, and 104 corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1, to introduce the first cysteine residue;

wherein the anti-IL-2 antibody or the antigen-binding fragment thereof comprises: (1) HCDR1 having an amino acid sequence of X_1YYX_2H (wherein X_1=A; X_2=M; as set forth in SEQ ID NO: 14); (2) HCDR2 having an amino acid sequence of RIDPZ_1DDSTKYAENFKX_3 (wherein Z_1=E or D; X_3=G); (3) HCDR3 having an amino acid sequence of Z_2TFZ_3YZ_4RELRWFAY (wherein Z_2=V or I; Z_3=Y or L; Z_4=S or T); (4) LCDR1 having an amino acid sequence of QASQZ_5IZ_6NYLS (wherein Z_5=D or Y; Z_6=G or S); (5) LCDR2 having an amino acid sequence of Z_7AZ_8SLAX_4 (wherein Z_7=S or Q; Z_8=T; X_4=S), and (6) LCDR3 having an amino acid sequence of LQHYSTPYT (as set forth in SEQ ID NO: 12), and the anti-IL-2 antibody or the antigen-binding fragment thereof has one or more cysteine mutations at the position 3 of HCDR3, at the positions 7, 8 and/or 9 of LCDR1, at the positions 1 and 3 of LCDR2, at position 4 of LCDR3, and/or at the positions 67 and/or 68 of the light chain variable region, to introduce the second cysteine residue.

11. The hIL-2/anti-IL-2 antibody fusion protein of claim 10, wherein the pair of the first cysteine residue and the second cysteine residue for forming disulfide linkage at the antigen-antibody binding interface of the hIL-2 mutein and the anti-IL-2 antibody or the antigen-binding fragment thereof of the said fusion protein is selected from one or more of the following paired amino acid mutations:

(1) the first cysteine residue is introduced by a mutation F42C at the position 42, a mutation of K64C at the position 64, or a mutation of P65C at the position 65 of the hIL-2 mutein corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1; and the second cysteine residue is introduced by a mutation of F3C at the position 3 of HCDR3 in the anti-IL-2 antibody or the antigen-binding fragment thereof;

(2) the first cysteine residue is introduced by a mutation of E60C at the position 60 of the hIL-2 mutein corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1; and the second cysteine residue is introduced by a mutation of G7C or S7C at the position 7 of LCDR1 in the anti-IL-2 antibody or the antigen-binding fragment thereof;

(3) the first cysteine residue is introduced by a mutation of E61C at the position 61 of the hIL-2 mutein corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1; and the second cysteine residue is introduced by a mutation of G7C or S7C at the position 7 of LCDR1, or a mutation of N8C at the position 8 of LCDR1, or a mutation of S1C or Q1C at the position 1 of LCDR2 in the anti-IL-2 antibody or the antigen-binding fragment thereof;

(4) the first cysteine residue is introduced by a mutation of M104C at the position 104 of the hIL-2

mutein corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1; and the second cysteine residue is introduced by a mutation of T3C at the position 3 of LCDR2 of the anti-IL-2 antibody or the antigen-binding fragment thereof;

(5) the first cysteine residue is introduced by a mutation of T102C at the position 102 of the hIL-2 mutein corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1; and the second cysteine residue is introduced by a mutation S67C at the position 67 of the light chain variable region, or a mutation of G68C at the position 68 of the light chain variable region in the anti-IL-2 antibody or the antigen-binding fragment thereof; and/or

(6) the first cysteine residue is introduced by a mutation of K64C at the position 64 of the hIL-2 mutein corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1; and the second cysteine residue is introduced by a mutation of Y9C at the position 9 of LCDR1, or a mutation of Y4C at the position 4 of LCDR3 in the anti-IL-2 antibody or the antigen-binding fragment thereof;

alternatively, the pair of the first cysteine residue and the second cysteine residue for forming disulfide linkage at the antigen-antibody binding interface of the hIL-2 mutein and the anti-IL-2 antibody or the antigen-binding fragment thereof of the said fusion protein is selected from one or more of the following paired amino acid mutations:

(1) the first cysteine residue is introduced by a mutation of M104C at the position 104 of the hIL-2 mutein corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1, and the second cysteine residue is introduced by a mutation of T3C at the position 3 of LCDR2 in the anti-IL-2 antibody or the antigen-binding fragment thereof, wherein the anti-IL-2 antibody or the antigen-binding fragment thereof comprises HCDR1 having the amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having the amino acid sequence as set forth in SEQ ID NO: 19, HCDR3 having the amino acid sequence as set forth in SEQ ID NO: 24, LCDR1 having the amino acid sequence as set forth in SEQ ID NO: 26, LCDR2 having the amino acid sequence as set forth in SEQ ID NO: 17, and LCDR3 having the amino acid sequence as set forth in SEQ ID NO: 12;

(2) the first cysteine residue is introduced by a mutation of T102C at the position 102 of the hIL-2 mutein corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1, and the second cysteine residue is introduced by a mutation of S67C at the position 67, or a mutation of G68C at the position 68 of the light chain variable region of the anti-IL-2 antibody or the antigen-binding fragment thereof, wherein the anti-IL-2 antibody or the antigen-binding fragment thereof comprises an amino acid sequence which is 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the VL as set forth in SEQ ID NO: 77;

(3) the first cysteine residue is introduced by a mutation of F42C at the position 42, a mutation of K64C at the position 64, or a mutation of P65C at the position 65 of the hIL-2 mutein corresponding to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1; and the second cysteine residue is introduced by a mutation of F3C at the position 3 of HCDR3 in the anti-IL-2 antibody or the antigen-binding fragment thereof, wherein the anti-IL-2 antibody or the antigen-binding fragment thereof comprises HCDR1 having the amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having the amino acid sequence as set forth in SEQ ID NO: 15, HCDR3 having the amino acid sequence as set forth in SEQ ID NO: 9, LCDR1 having the amino acid sequence as set forth in SEQ ID NO: 10, LCDR2 having the amino acid sequence as set forth in SEQ ID NO: 17, and LCDR3 having the amino acid sequence as set forth in SEQ ID NO: 12.

12. The hIL-2/anti-IL-2 antibody fusion protein of claim 5 or 10, wherein the hIL-2/anti-IL-2 antibody fusion protein comprises HCDR1, HCDR2, HCDR3 of the heavy chain variable region and LCDR1, LCDR2, LCDR3 of the light chain variable region, and the HCDR3, LCDR1, LCDR2, LCDR3 and/or the light chain variable region comprise one or more introduced cysteine residue mutations, the HCDR1 HCDR2, and HCDR3, and LCDR1, LCDR2 and LCDR3 comprising: (1) HCDR1 having the amino acid sequence of X_1YYX_2H (wherein X_1=A; X_2=M, as set forth in SEQ ID NO: 14), (2) HCDR2 having the amino acid sequence of $RIDPZ_1DDSTKYAENFKX_3$ (wherein Z_1=E or D; X_3=G), (3) HCDR3 having the amino acid sequence of $Z_2TX_{II}Z_3YZ_4RELRWFAY$ (wherein Z_2=V or I; X_{II}=F or C; Z_3=Y or L; Z_4=S or T), (4) LCDR1 having the amino acid sequence of $QASQZ_5IZ_6X_IX_{IV}LS$ (wherein Z_5=D or Y; Z_6=G, S or C; X_I=N or C; X_{IV}=Y or C), (5) LCDR2 having the amino acid sequence of $Z_7AZ_8SLAX_4$ (wherein Z_7=S, Q or C; Z_8=T or C; X_4=S), and (6) LCDR3 having the amino acid sequence of $LQHX_{III}STPYT$ (wherein X_{III}=Y or C);

alternatively, wherein the hIL-2/anti-IL-2 antibody fusion protein further have an amino acid mutation at the position 1 of the light chain variable region or at the position 4 of LCDR1 in the anti-IL-2 antibody or the antigen-binding fragment thereof, wherein the amino acid mutation comprises D1E at the position 1 of the light chain variable region, or Q4D, Q4E, Q4S, Q4G, Q4K, or Q4R at the position 4 of LCDR1, optionally, the amino acid mutation comprising D1E at the position 1 of the light chain variable region, or Q4D, Q4E, Q4S, or Q4G at the position 4 of LCDR1.

13. The hIL-2/anti-IL-2 antibody fusion protein of claim 12, wherein the hIL-2/anti-IL-2 antibody fusion protein comprises the following HCDR1, HCDR2, HCDR3 of the heavy chain variable region and LCDR1, LCDR2, LCDR3 of the light chain variable region:

(1) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 15, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 9, LCDR1 having an amino acid sequence as set forth in SEQ ID NOs: 30 or 31, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 17, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12;

(2) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 15, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 9, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 10, LCDR2 having an amino acid sequence as set forth in SEQ ID NOs: 17, 32 or 33, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12;

(3) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 15, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 29, LCDR1 having an amino acid sequence as set forth in SEQ ID NOs: 10, 39, 40, 41, 42, 43 or 44, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 17, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12;

(4) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 19, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 24, LCDR1 having an amino acid sequence as set forth in SEQ ID NOs: 35, 36 or 37, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 17, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12;

(5) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 19, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 24, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 26, LCDR2 having an amino acid sequence as set forth in SEQ ID NOs: 17, 32 or 33, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12;

(6) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 19, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 34, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 26, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 17, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; and/or

(7) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 19, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 24, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 26, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 17, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 38;

optionally, the hIL-2/anti-IL-2 antibody fusion protein comprises:

(1) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 15, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 29, LCDR1 having an amino acid sequence as set forth in SEQ ID NOs: 10, 39, 40, 41 or 42, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 17, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12; or

(2) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 14, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 19, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 24, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 26, LCDR2 having an amino acid sequence as set forth in SEQ ID NOs: 17 or 33, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 12.

14. The hIL-2/anti-IL-2 antibody fusion protein of any one of claims 10-13, wherein the hIL-2/anti-IL-2 antibody fusion protein comprises a heavy chain variable region having the HCDR1, HCDR2 and HCDR3 and a light chain variable region having the LCDR1, LCDR2 and LCDR3, the heavy chain variable region comprising an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence as set forth in SEQ ID NOs: 63, 86, 74 or 112, respectively, and the light chain variable region comprising an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence as set forth in SEQ ID NOs: 64, 77, 80, 81, 82, 83, 84, 85, 87, 88, 89, 90, 91, 92, 93, 104, 105, 106, 107, 108, 109, 110 or 111, respectively;

optionally, the heavy chain variable region comprises an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence as set forth in SEQ ID NOs: 86 or 74, respectively, and the light chain variable region comprises an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence as set forth in SEQ ID NOs: 64, 87, 88, 89, 90, 91, 107, 108 or 109, respectively;

alternatively, the hIL-2/anti-IL-2 antibody fusion protein comprises the following heavy chain variable region and light chain variable region:

(1) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the heavy chain variable region as set forth in SEQ ID NO: 86, and the light chain variable region as set forth in SEQ ID NOs: 64, 87, 88, 89, 90 or 91, respectively; or

(2) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the heavy chain variable region as set forth in SEQ ID NO: 74, and the light chain variable region as set forth in SEQ ID NOs: 107, 108 or 109, respectively.

15. The hIL-2/anti-IL-2 antibody fusion protein of claim 1 or 2, wherein the hIL-2/anti-IL-2 antibody fusion protein comprises the wild-type hIL-2 and another anti-IL-2 humanized antibody or an antigen-binding fragment thereof which specifically recognizes the IL2Rα-binding site of hIL-2 ; and the antigen-antibody binding interface of the wild-type hIL-2 and the anti-IL-2 humanized antibody or the antigen-binding fragment thereof of the said fusion protein comprises introduced disulfide linkage(s), and the anti-IL-2 humanized antibody is selected from the NARA1 antibody and the TCB2 antibody; wherein

the NARA1 antibody or the antigen-binding fragment thereof comprises HCDR1 having the amino acid sequence as set forth in SEQ ID NO: 142, HCDR2 having the amino acid sequence as set forth in SEQ ID NO: 143, HCDR3 having the amino acid sequence as set forth in SEQ ID NO: 144, LCDR1 having the amino acid sequence as set forth in SEQ ID NO: 145, LCDR2 having the amino acid sequence as set forth in SEQ ID NO: 146, and LCDR3 having the amino acid sequence as set forth in SEQ ID NO: 147;

the TCB2 antibody or the antigen-binding fragment thereof comprises HCDR1 having the amino acid sequence as set forth in SEQ ID NO: 170, HCDR2 having the amino acid sequence as set forth in SEQ ID NO: 171, HCDR3 having the amino acid sequence as set forth in SEQ ID NO: 172, LCDR1 having the amino acid sequence as set forth in SEQ ID NO: 173, LCDR2 having the amino acid sequence as set forth in SEQ ID NO: 174, and LCDR3 having the amino acid sequence as set forth in SEQ ID NO: 175;

wherein the antigen-antibody binding interface of the hIL-2/anti-IL-2 antibody fusion protein comprising the NARA1 antibody or the antigen-binding fragment thereof is located in AB loop, B helix and BC loop of the hIL-2, and optionally, the antigen-antibody binding interface is located at the positions 30-43 or their adjacent amino acid residues and the positions 71-77 or their adjacent amino acid residues in the hIL-2;

wherein the antigen-antibody binding interface of the hIL-2/anti-IL-2 antibody fusion protein comprising the TCB2 antibody or the antigen-binding fragment thereof is located in AB loop, B helix and CD loop of the hIL-2, and optionally, the antigen-antibody binding interface is located at positions 34-45 or their adjacent amino acid residues, positions 62-76 or their adjacent amino acid residues, and the position 111 or the adjacent amino acid residues in the hIL-2.

16. The hIL-2/anti-IL-2 antibody fusion protein of claim 15, wherein the antigen-antibody binding interface of the hIL-2 and the anti-IL-2 antibody or the antigen-binding fragment thereof of the hIL-2/anti-IL-2 antibody fusion protein comprises two or more introduced cysteine residues to form the disulfide linkage(s), wherein

the hIL-2 has one or more cysteine mutations at the position 34, 37, 41, 42, 68, 73, 75, 77 and 111 relative to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1, to introduce the first cysteine residue; the NARA1 antibody or antigen-binding fragment thereof has one or more cysteine mutations at the position 1 of HCDR1, at the position 2, 6 and/or 8 of HCDR2, at the position 3 and/or 8 of HCDR3, at the position 9 of LCDR1, and/or at the position 3, 4, and/or 6 of LCDR3, to introduce the second cysteine residue; or

the hIL-2 has one or more cysteine mutations at positions 34, 36, 37, 38, 42, 68 and 109 relative to the amino acid sequence of the wild-type hIL-2 as set forth in SEQ ID NO: 1, to introduce the first cysteine residue; the TCB2 antibody or antigen-binding fragment thereof has one or more cysteine mutations at the position 6 in HCDR2, at positions 3, 5, 6 and/or 7 in HCDR3, at the position 4 in LCDR1, and/or at positions 4, 5, and/or 6 in LCDR3, to introduce a second cysteine residue.

17. The hIL-2/anti-IL-2 antibody fusion protein of claim 16, wherein the pair of the first cysteine residue and the second cysteine residue for forming the disulfide linkage at the antigen-antibody binding interface of the hIL-2 and the NARA1 antibody or the antigen-binding fragment thereof is selected from one or more of the following paired amino acid mutations:

(1) the first cysteine residue is introduced by a mutation of P34C at the position 34 of the hIL-2, and the second cysteine residue is introduced by a mutation of A8C at the position 8 in HCDR3, or a mutation of S3C or N4C at the position 3 or 4 in LCDR3 in the NARA1 antibody or the antigen-binding fragment thereof;

(2) the first cysteine residue is introduced by a mutation of T37C at the position 37 of the hIL-2, and the second cysteine residue is introduced by a mutation of D6C at the position 6 in LCDR3 of the NARA1 antibody or antigen-binding fragment thereof;

(3) the first cysteine residue is a mutation of T41C at the position 41 of the hIL-2, and the second cysteine residue is introduced by a mutation of I2C at position 2 in HCDR2 of the NARA1 antibody or the antigen-binding fragment thereof;

(4) the first cysteine residue is introduced by a mutation F42C at the position 42 of the hIL-2, and the second cysteine residue is introduced by a mutation G8C at the position 8 in HCDR2 of the NARA1 antibody or antigen-binding fragment thereof;

(5) the first cysteine residue is introduced by a mutation E68C at the position 68 of the hIL-2, and the second cysteine residue is introduced by a mutation of N1C at the position 1 in HCDR1 of the NARA1 antibody or antigen-binding fragment thereof;

(6) the first cysteine residue is introduced by a mutation of A73C at the position 73 of the hIL-2, and the second cysteine residue is introduced by a mutation of G3C at the position 3 in HCDR3 of the NARA1 antibody or antigen-binding fragment thereof;

(7) the first cysteine residue is introduced by a mutation of S75C or N77C at the position 75 or 77 of the hIL-2, and the second cysteine residue is introduced by a mutation D9C at the position 9 in LCDR1 of the NARA1 antibody or antigen-binding fragment thereof; and/or

(8) the first cysteine residue is introduced by a mutation T111C at the position 111 of the hIL-2, and the second cysteine residue is introduced by a mutation of S6C at the position 6 in HCDR2 of the NARA1

antibody or antigen-binding fragment thereof;

alternatively,

wherein the pair of the first cysteine residue and the second cysteine residue for forming the disulfide linkage at the antigen- antibody binding interface of the hIL-2 and the TCB2 antibody or the antigen-binding fragment thereof is selected from one or more of the following paired amino acid mutations:

(1) the first cysteine residue is introduced by a mutation of P34C at the position 34 of the hIL-2, and the second cysteine residue is introduced by a mutation of T4C at the position 4 in LCDR1, or a mutation of D4C or N5C at the position 4 or 5 in LCDR3 of the TCB2 antibody or antigen-binding fragment thereof;

(2) the first cysteine residue is introduced by a mutation L36C at the position 36 of the hIL-2, and the second cysteine residue is introduced by a mutation of N5C at the position 5 in LCDR3 of the TCB2 antibody or antigen-binding fragment thereof;

(3) the first cysteine residue is introduced by a mutation of T37C at the position 37 of the hIL-2, and the second cysteine residue is introduced by a mutation of N5C or L6C at the position 5 or 6 in LCDR3 of the TCB2 antibody or antigen-binding fragment thereof;

(4) the first cysteine residue is introduced by a mutation R38C at the position 38 of the hIL-2, and the second cysteine residue is introduced by a mutation of F7C at the position 7 in HCDR3 of the TCB2 antibody or antigen-binding fragment thereof;

(5) the first cysteine residue is introduced by a mutation of F42C at the position 42 of the hIL-2, and the second cysteine residue is introduced by a mutation of R5C at the position 5 in HCDR3 of the TCB2 antibody or antigen-binding fragment thereof;

(6) the first cysteine residue is introduced by a mutation of E68C at the position 68 of the hIL-2, and the second cysteine residue is introduced by a mutation of A3C or G6C at the position 3 or 6 in HCDR3 of the TCB2 antibody or antigen-binding fragment thereof; and/or

(7) the first cysteine residue is introduced by a mutation of D109C at the position 109 of the hIL-2, and the second cysteine residue is introduced by a mutation D6C at the position 6 in HCDR2 in the TCB2 antibody or antigen-binding fragment thereof.

18. The hIL-2/anti-IL-2 antibody fusion protein of claim 16 or 17, wherein the hIL-2/anti-IL-2 antibody fusion protein comprises the HCDR1, HCDR2, and HCDR3 of the heavy chain variable region and the LCDR1, LCDR2, and LCDR3 of the light chain variable region, and the HCDR1, HCDR2, HCDR3, LCDR1, and/or LCDR3 comprise one or more cysteine mutations, wherein the HCDR1, HCDR2 and HCDR3 of the heavy chain variable region and the LCDR1, LCDR2 and LCDR3 of the light chain variable region comprise:

(1) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 142, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 149, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 144, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 145, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 146, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 147;

(2) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 142, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 143, HCDR3 having an amino acid sequence as set forth in SEQ ID NOs: 152 or 153, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 145, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 146, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 147;

(3) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 142, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 143, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 144, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 154, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 146, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 147;

(4) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 142, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 143, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 144, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 145, LCDR2 having an

amino acid sequence as set forth in SEQ ID NO: 146, and LCDR3 having an amino acid sequence as set forth in SEQ ID NOs: 155, 156 or 157;

(5) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 148, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 143, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 144, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 145, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 146, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 147; or

(6) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 142, HCDR2 having an amino acid sequence as the set forth in SEQ ID NOs: 150 or 151, HCDR3 having an amino acid sequence as the set forth in SEQ ID NO: 144, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 145, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 146, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 147;

alternatively, the hIL-2/anti-IL-2 antibody fusion protein comprises the HCDR1, HCDR2 and HCDR3 of the heavy chain variable region and the LCDR1, LCDR2 and LCDR3 of the light chain variable region, and the HCDR2, HCDR3, LCDR1, and/or LCDR3 comprise one or more cysteine mutations, wherein the HCDR1, HCDR2 and HCDR3 of the heavy chain variable region and the LCDR1, LCDR2 and LCDR3 of the light chain variable region comprise:

(1) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 170, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 171, HCDR3 having an amino acid sequence as set forth in SEQ ID NOs: 177, 178, 179 or 180, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 173, LCDR2 having an amino acid sequence as SEQ ID NO: 174, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 175;

(2) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 170, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 176, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 172, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 173, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 174, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 175;

(3) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 170, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 171, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 172, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 181, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 174, and LCDR3 having an amino acid sequence as set forth in SEQ ID NO: 175; or

(4) HCDR1 having an amino acid sequence as set forth in SEQ ID NO: 170, HCDR2 having an amino acid sequence as set forth in SEQ ID NO: 171, HCDR3 having an amino acid sequence as set forth in SEQ ID NO: 172, LCDR1 having an amino acid sequence as set forth in SEQ ID NO: 173, LCDR2 having an amino acid sequence as set forth in SEQ ID NO: 174, and LCDR3 having an amino acid sequence as set forth in SEQ ID NOs: 182, 183 or 184.

19. The hIL-2/anti-IL-2 antibody fusion protein of any one of claims 16-18, wherein the hIL-2/anti-IL-2 antibody fusion protein comprises a heavy chain variable region having the HCDR1, HCDR2 and HCDR3 and a light chain variable region having the LCDR1, LCDR2 and LCDR3, and the heavy chain variable region comprises an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100 % identical to a sequence as set forth in SEQ ID NOs: 140, 158, 159, 160, 161, 162 or 163, respectively, and the light chain variable region comprises an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence as set forth in SEQ ID NOs: 141, 164, 165, 166 or 167, respectively;

optionally, the hIL-2/anti-IL-2 antibody fusion protein comprises the following heavy chain variable region and light chain variable region: (1) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the heavy chain variable region as set forth in SEQ ID NOs: 158, 159, 160, 161, 162 or 163, and the light chain variable region as set forth in SEQ ID NO: 141, respectively; or (2) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the heavy chain variable

region as set forth in SEQ ID NO: 140, and the light chain variable region as set forth in SEQ ID NOs: 164, 165, 166 or 167, respectively;

alternatively,

wherein the hIL-2/anti-IL-2 antibody fusion protein comprises a heavy chain variable region having the HCDR1, HCDR2 and HCDR3 and a light chain variable region having the LCDR1, LCDR2 and LCDR3, and the heavy chain variable regions comprises an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100 % identical to a sequence as set forth in SEQ ID NOs: 168, 185, 186, 187, 188 or 189, respectively, and the light chain variable region comprises an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100 % identical to a sequence as set forth in SEQ ID NOs: 169, 190, 191, 192 or 193, respectively;

optionally, the hIL-2/anti-IL-2 antibody fusion protein comprises the following heavy chain variable region and light chain variable region: (1) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the heavy chain variable region as set forth in SEQ ID NOs: 185, 186, 187, 188 or 189, and the light chain variable region as set forth in SEQ ID NO: 169, respectively; or (2) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the heavy chain variable region as set forth in SEQ ID NO: 168, and the light chain variable region as set forth in SEQ ID NOs: 190, 191, 192 or 193, respectively;

20. The hIL-2/anti-IL-2 antibody fusion protein of any one of claims 1 to 19, wherein the anti-IL-2 antibody or the antigen-binding fragment thereof is linked to hIL-2 or a mutein thereof by a linker, and optionally, the linker is selected from $(G4S)_4$, $(G4S)_3$, $(GAF)_2$.

21. The hIL-2/anti-IL-2 antibody fusion protein of any one of claims 1 to 20, wherein the IL-2/anti-IL-2 antibody fusion protein comprises a first polypeptide and a second polypeptide, wherein the first polypeptide comprises the hIL-2 or a mutein thereof having a cysteine mutation, a linker and one variable region of the anti-IL-2 antibody or antigen-binding fragment thereof, and another cysteine mutation is placed in one variable region of the anti-IL-2 antibody or antigen-binding fragment thereof in the first polypeptide and/or in the other variable region of the anti-IL-2 antibody or antigen-binding fragment thereof in the second polypeptide, whereby a correctly paired and stable disulfide linkage is formed with the cysteine mutation in the hIL-2 or a mutein thereof, and the said disulfide linkage is located at the antigen-antibody binding interface of the said hIL-2 or a mutein thereof and the said anti-IL-2 antibody or antigen-binding fragment thereof; optionally,

the first polypeptide comprises the hIL-2 mutein with a cysteine mutation, a linker and a heavy chain variable region of the anti-IL-2 antibody or antigen-binding fragment thereof, and the second polypeptide comprises a light chain variable region of the anti-IL-2 antibody or antigen-binding fragment thereof, wherein the first polypeptide comprises an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence as set forth in any of SEQ ID NOs: 95-103, 113-120, or 133-138, and the second polypeptide comprises an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence as set forth in any of SEQ ID NOs: 64, 77, 80-85, 87-93, or 104-111;

the first polypeptide comprises a hIL-2 mutein with a cysteine mutation, a linker and a light chain variable region of the anti-IL-2 antibody or antigen-binding fragment thereof, and the second polypeptide comprises a heavy chain variable region of the anti-IL-2 antibody or antigen-binding fragment thereof, wherein the first polypeptide comprises an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence as set forth in any of SEQ ID NOs: 206-216, and the second polypeptide comprises an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence as set forth in any of SEQ ID NOs: 140 or 158-163; or

the first polypeptide comprises a hIL-2 mutein with a cysteine mutation, a linker and a light chain variable region of the anti-IL-2 antibody or antigen-binding fragment thereof, and the second polypeptide

comprises a heavy chain variable region of the anti-IL-2 antibody or antigen-binding fragment thereof, wherein the first polypeptide comprises an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence as set forth in any of SEQ ID NOs: 217-226, and/or the second polypeptide comprises an amino acid sequence which is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence as set forth in any of SEQ ID NOs: 168 or 185-189.

22. The hIL-2/anti-IL-2 antibody fusion protein of claim 21, wherein the hIL-2/anti-IL-2 antibody fusion protein comprises the following first and second polypeptides:

(1) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 95, and the second polypeptide as set forth in SEQ ID NO: 80, respectively; or

(2) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 96, and the second polypeptide as set forth in SEQ ID NO: 81, respectively; or

(3) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 97, and the second polypeptide as set forth in SEQ ID NO: 82, respectively; or

(4) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 98, and the second polypeptide as set forth in SEQ ID NO: 83, respectively; or

(5) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 99, and the second polypeptide as set forth in SEQ ID NO: 84, respectively; or

(6) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 100, and the second polypeptide as set forth in SEQ ID NO: 85, respectively; or

(7) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in any of SEQ ID NOs: 101, 102, 103 and 133-138, and the second polypeptide as set forth in SEQ ID NO: 64, respectively; or

(8) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 102, and the second polypeptide as set forth in any of SEQ ID NOs: 87-93, respectively; or

(9) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 113, and the second polypeptide as set forth in SEQ ID Nos: 104, 105 or 106, respectively; or

(10) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 114, and the second polypeptide as set forth in SEQ ID NO: 107, respectively; or

(11) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 115, and the second polypeptide as set forth in SEQ ID NO: 108 or 109, respectively; or

(12) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NOs: 116, 117 or 119, and the second polypeptide as set forth in SEQ ID NO: 77, respectively; or

(13) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 118, and the second polypeptide as set forth in SEQ ID NO: 110, respectively; or

(14) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 120, and the second polypeptide as set forth in SEQ ID NO: 104, respectively; or

(15) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 118, and the second polypeptide as set forth in SEQ ID NO: 111, respectively;

alternatively, wherein the hIL-2/anti-IL-2 antibody fusion protein comprises the following first and second polypeptides:

(1) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 206, and the second polypeptide as set forth in SEQ ID NO: 158, respectively; or

(2) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 207, and the second polypeptide as set forth in SEQ ID NO: 159, respectively; or

(3) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 208, and the second polypeptide as set forth in SEQ ID NO: 160, respectively; or

(4) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in any of SEQ ID NOs: 209-213, and the second polypeptide as set forth in SEQ ID NO: 140, respectively; or

(5) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 214, and the second polypeptide as set forth in SEQ ID NO: 161 respectively; or

(6) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 215, and the second polypeptide as set forth in SEQ ID NO: 162, respectively; or

(7) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 216, and the second polypeptide as set forth in SEQ ID NO: 163, respectively;

alternatively, wherein the hIL-2/anti-IL-2 antibody fusion protein comprises the following first and second polypeptides:

(1) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 217, and the second polypeptide as set forth in SEQ ID NO: 185 or 187, respectively; or

(2) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 218, and the second polypeptide as set forth in SEQ ID NO: 186, respectively; or

(3) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 219, and the second polypeptide as set forth in SEQ ID NO: 188, respectively; or

(4) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in SEQ ID NO: 220, and the second polypeptide as set forth in SEQ ID NO: 189, respectively; or

(5) amino acid sequences which are at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to the first polypeptide as set forth in any of SEQ ID Nos: 221-226, and the second polypeptide as set forth in SEQ ID NO: 168, respectively.

23. The hIL-2/anti-IL-2 antibody fusion protein of any one of claims 1 to 22, wherein the hIL-2/anti-IL-2 antibody fusion protein comprises a heavy chain constant region and a light chain constant region of an antibody, wherein the heavy chain constant region includes native and mutant forms of the Fc region of a

human IgG heavy chain constant region, and further includes a truncated form of polypeptide containing a hinge region that facilitates the dimerization, and optionally, the Fc region comprises an engineered human IgG1 Fc region, comprising the following one or more amino acid substitution mutations: (1) L234F/L235E/P331S (EU numbering system); and/or (2) N203D/K274Q/Q419E (EU numbering system),

and optionally, the heavy chain constant region includes amino acid sequences as set forth in SEQ ID NOs: 227 or 228.

24. A pharmaceutical composition comprising the hIL-2/anti-IL-2 antibody fusion protein of any one of claims 1 to 23, and a pharmaceutically acceptable carrier.

25. Use of the hIL-2/anti-IL-2 antibody fusion protein of any one of claims 1 to 23 or the pharmaceutical composition of claim 24 in the preparation of a medicament for treating a disease, condition or disorder by boosting host immune response, or of stimulating the immune system, or of treating, alleviating or preventing a disease condition in which stimulation of the host immune system is beneficial,

wherein the disease, condition, disorder or disease condition includes a proliferative disease, an infectious disease, and an immunodeficiency disease; wherein the proliferative disease includes cancer and other cell proliferative disorders, wherein the cancer is selected from: squamous cell carcinoma, lung cancer, peritoneal cancer, hepatocellular carcinoma, gastric cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, urethra cancer, liver tumor, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine cancer, salivary gland cancer, kidney cancer, prostate cancer, vulvar cancer, thyroid cancer, anal cancer, penile cancer, melanoma, superficial spreading melanoma, lentigo maligna melanoma, acral melanoma, nodular melanoma, multiple myeloma and B-cell lymphoma, Non-Hodgkin Lymphoma, chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), hairy cell leukemia, chronic myeloblastic leukemia, and post-transplant lymphoproliferative disorder (PTLD), as well as abnormal vascular proliferation associated with phakomatoses, edema and Meigs syndrome, brain tumor and brain cancer, and head and neck cancer; and the immunodeficiency disease includes HIV positive, immunosuppressive disease, chronic infection.

26. The use of claim 25, wherein the medicament is in combination with one or more selected from the group consisting of: an immune checkpoint inhibitor, an antigen-specific immunotherapeutic agent, a chemotherapeutic agent, an epigenetic modifier, a cytokine, a growth factor, an inhibitor, an antibody targeting tumor antigen, a tumor vaccine, and other cancer therapy.