

Claims

1. An isolated antigen binding protein (ABP) that specifically binds human GITR (hGITR; SEQ ID NO: 1), comprising the following six CDR sequences:
 - (a) a CDR-H3 having the sequence $X_1X_2X_3X_4X_5$ RGYGDYGGHHAFDI, wherein X_1 is A or V, X_2 is H, D, L, or R, X_3 is E or D, X_4 is R, N, S, or A, and X_5 is V, D or G (SEQ ID NO:141);
 - (b) a CDR-H2 having the sequence $X_1IX_2X_3SGX_4$ TTYNPSLKS, wherein X_1 is G, L, or S, X_2 is Y, A, or V, X_3 is E, Y or H, and X_4 is S or K (SEQ ID NO:142);
 - (c) a CDR-H1 having the sequence $X_1SISSX_2X_3X_4X_5WX_6$, wherein X_1 is Y or G, X_2 is G, S, or E, X_3 is L, G, S, Y, or A, X_4 is G, A, Y, M, or G, X_5 is V, A, or is absent, and X_6 is S or G (SEQ ID NO:143);
 - (d) a CDR-L3 having the sequence QQEYX₁TPPX₂, wherein X_1 is A or N and X_2 is T or S (SEQ ID NO:144);
 - (e) a CDR-L2 having the sequence $X_1AX_2SLX_3X_4$, wherein X_1 is A or S, X_2 is D or S, X_3 is Q, D, K, or E, and X_4 is S or Y (SEQ ID NO:145); and
 - (f) a CDR-L1 having the sequence- $X_1AS X_2SI X_3X_4YLN$, wherein X_1 is G or R, X_2 is Q or K, X_3 is S, D, or N, and X_4 is S or T (SEQ ID NO:146),
wherein the ABP agonizes GITR expressed on the surface of a target cell.
2. The ABP of claim 1, wherein the ABP comprises:
 - a) a CDR-H3 of SEQ ID NO:13, a CDR-H2 of SEQ ID NO:12, a CDR-H1 of SEQ ID NO:11, a CDR-L3 of SEQ ID NO:16, a CDR-L2 of SEQ ID NO:15, and a CDR-L1 of SEQ ID NO:14;
 - b) a CDR-H3 of SEQ ID NO:23, a CDR-H2 of SEQ ID NO:22, a CDR-H1 of SEQ ID NO:21, a CDR-L3 of SEQ ID NO:17, a CDR-L2 of SEQ ID NO:15, and a CDR-L1 of SEQ ID NO:14;
 - c) a CDR-H3 of SEQ ID NO:30, a CDR-H2 of SEQ ID NO:29, a CDR-H1 of SEQ ID NO:28, a CDR-L3 of SEQ ID NO:17, a CDR-L2 of SEQ ID NO:31, and a CDR-L1 of SEQ ID NO:14;
 - d) a CDR-H3 of SEQ ID NO:30, a CDR-H2 of SEQ ID NO:29, a CDR-H1 of SEQ ID NO:28, a CDR-L3 of SEQ ID NO:17, a CDR-L2 of SEQ ID NO:15, and a CDR-L1 of SEQ ID NO:36;

- e) a CDR-H3 of SEQ ID NO:30, a CDR-H2 of SEQ ID NO:29, a CDR-H1 of SEQ ID NO:28, a CDR-L3 of SEQ ID NO:17, a CDR-L2 of SEQ ID NO:41, and a CDR-L1 of SEQ ID NO:14;
- f) a CDR-H3 of SEQ ID NO:48, a CDR-H2 of SEQ ID NO:47, a CDR-H1 of SEQ ID NO:46, a CDR-L3 of SEQ ID NO:17, a CDR-L2 of SEQ ID NO:50, and a CDR-L1 of SEQ ID NO:49;
- g) a CDR-H3 of SEQ ID NO:48, a CDR-H2 of SEQ ID NO:47, a CDR-H1 of SEQ ID NO:46, a CDR-L3 of SEQ ID NO:56, a CDR-L2 of SEQ ID NO:55, and a CDR-L1 of SEQ ID NO:54;
- h) a CDR-H3 of SEQ ID NO:61, a CDR-H2 of SEQ ID NO:60, a CDR-H1 of SEQ ID NO:59, a CDR-L3 of SEQ ID NO:16, a CDR-L2 of SEQ ID NO:15, and a CDR-L1 of SEQ ID NO:14;
- i) a CDR-H3 of SEQ ID NO:61, a CDR-H2 of SEQ ID NO:47, a CDR-H1 of SEQ ID NO:46, a CDR-L3 of SEQ ID NO:16, a CDR-L2 of SEQ ID NO:15, and a CDR-L1 of SEQ ID NO:14; or
- j) a CDR-H3 of SEQ ID NO:103, a CDR-H2 of SEQ ID NO:22, a CDR-H1 of SEQ ID NO:21, a CDR-L3 of SEQ ID NO:16, a CDR-L2 of SEQ ID NO:15, and a CDR-L1 of SEQ ID NO:14.

3. The ABP of claim 2, wherein:

- a) the ABP of claim 2 a) comprises a V_H sequence of SEQ ID NO:9 and a V_L sequence of SEQ ID NO:10;
- b) the ABP of claim 2 b) comprises a V_H sequence of SEQ ID NO:19 and a V_L sequence of SEQ ID NO:20;
- c) the ABP of claim 2 b) comprises a V_H sequence of SEQ ID NO:26 and a V_L sequence of SEQ ID NO:27;
- d) the ABP of claim 2 d) comprises a V_H sequence of SEQ ID NO:26 or SEQ ID NO:34 and a V_L sequence of SEQ ID NO:35;
- e) the ABP of claim 2 e) comprises a V_H sequence of SEQ ID NO:26 and a V_L sequence of SEQ ID NO:40;
- f) the ABP of claim 2 f) comprises a V_H sequence of SEQ ID NO:44 and a V_L sequence of SEQ ID NO:45;

- g) the ABP of claim 2 g) comprises a V_H sequence of SEQ ID NO:44 and a V_L sequence of SEQ ID NO:53;
- h) the ABP of claim 2 h) comprises a V_H sequence of SEQ ID NO:58 and a V_L sequence of SEQ ID NO:10;
- i) the ABP of claim 2 i) comprises a V_H sequence of SEQ ID NO:104 and a V_L sequence of SEQ ID NO:10; and
- j) the ABP of claim 2 j) comprises a V_H sequence of SEQ ID NO:105 and a V_L sequence of SEQ ID NO:10.

4. The ABP of claim 3, wherein:

- a) the ABP of claim 3 a) comprises a heavy chain of SEQ ID NO:7 and a light chain of SEQ ID NO:8;
- b) the ABP of claim 3 b) comprises a heavy chain of SEQ ID NO:221 and a light chain of SEQ ID NO:18;
- c) the ABP of claim 3 c) comprises a heavy chain of SEQ ID NO:24 and a light chain of SEQ ID NO:25;
- d) the ABP of claim 3 d) comprises (i) a heavy chain of SEQ ID NO:32 and a light chain of SEQ ID NO:33, or (ii) a heavy chain of SEQ ID NO:37 and a light chain of SEQ ID NO:33;
- e) the ABP of claim 3 e) comprises (i) a heavy chain of SEQ ID NO:38 and a light chain of SEQ ID NO:39;
- f) the ABP of claim 3 f) comprises (i) a heavy chain of SEQ ID NO:42 and a light chain of SEQ ID NO:43;
- g) the ABP of claim 3 g) comprises (i) a heavy chain of SEQ ID NO:51 and a light chain of SEQ ID NO:52;
- h) the ABP of claim 3 h) comprises (i) a heavy chain of SEQ ID NO:57 and a light chain of SEQ ID NO:8, or (ii) a heavy chain of SEQ ID NO:220 and a light chain of SEQ ID NO:8;
- i) the ABP of claim 3 i) comprises (i) a heavy chain of SEQ ID NO:114 and a light chain of SEQ ID NO:8, or (ii) a heavy chain of SEQ ID NO:120 and a light chain of SEQ ID NO:8; or (iii) a heavy chain of SEQ ID NO:122 and a light chain of SEQ ID NO:8; or

j) the ABP of claim 3 j) comprises (i) a heavy chain of SEQ ID NO:115 and a light chain of SEQ ID NO:8, or (ii) a heavy chain of SEQ ID NO:121 and a light chain of SEQ ID NO:8; or (iii) a heavy chain of SEQ ID NO:123 and a light chain of SEQ ID NO:8.

5. The ABP of claim 1, wherein the ABP competes for binding to GITR with an antibody having a V_H/V_L pair comprising amino acid sequences selected from the group consisting of SEQ ID NOs: 9/10, 19/20, 26/27, 34/35, 26/35, 26/40, 44/45, 44/53, 58/10, 62/63, 70/63, 71/72, 79/80, 87/80, 88/80, 89/90, 95/90, 97/63, 98/72, 99/80, 101/90, 104/10, 105/10, 97/63, 98/72, 99/80, 101/90, 104/10, 105/10, 126/128, and 127/128.

6. The ABP of claim 1, wherein the ABP blocks the binding of GITRL to GITR.

7. The ABP of claim 1, wherein the ABP is capable of binding to one or more of GITR (SEQ ID NO:1) residues from the group consisting of R56, C58, R59, D60, Y61, P62, E64, E65, C66, and C67.

8. The ABP of claim 1, wherein the ABP (a) specifically binds cynomolgus monkey GITR (cGITR; SEQ ID NO: 3); (b) binds murine GITR (mGITR; SEQ ID NO: 4) with an affinity lower (as indicated by higher K_D) than the affinity of the ABP for hGITR, or does not bind mGITR; or (c) is capable of any combination of (a) - (b).

9. The ABP of claim 1, wherein the ABP multimerizes GITR expressed on the surface of a target cell, wherein the ABP multimerizes 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 GITR molecules.

10. A pharmaceutical composition comprising an ABP of claim 1 and a pharmaceutically acceptable excipient, wherein the amount of the ABP in the pharmaceutical composition is sufficient to (a) reduce the suppression of effector T cells by regulatory T cells; (b) activate effector T cells; (c) reduce the number of regulatory T cells in a tissue or systemically; (d) induce or enhance proliferation of effector T cells; (e) inhibit the rate of tumor growth; (f) induce tumor regression; or (g) combinations thereof, in a subject.

11. The ABP of claim 1, wherein
- (a) the CDR-H3 has a sequence selected from the group consisting of SEQ ID NOs: 13, 23, 30, 48, 61 and 103;
 - (b) the CDR-H2 has a sequence selected from the group consisting of SEQ ID NOs: 12, 22, 29, 47, and 60;
 - (c) the CDR-H1 has a sequence selected from the group consisting of SEQ ID NOs: 11, 21, 28, 46, and 59;
 - (d) the CDR-L3 has a sequence selected from the group consisting of SEQ ID NOs: 16, 17, and 56;
 - (e) the CDR-L2 has a sequence selected from the group consisting of SEQ ID NOs: 15, 31, 41, 50, and 55; and
 - (f) the CDR-L1 has a sequence selected from the group consisting of SEQ ID NOs: 14, 36, 49, and 54.
12. An isolated antigen binding protein (ABP) that specifically binds human GITR (hGITR; SEQ ID NO: 1), comprising: a CDR-H3 of SEQ ID NO:13, a CDR-H2 of SEQ ID NO:12, a CDR-H1 of SEQ ID NO:11, a CDR-L3 of SEQ ID NO:16, a CDR-L2 of SEQ ID NO:15, and a CDR-L1 of SEQ ID NO:14.
13. An isolated antigen binding protein (ABP) that specifically binds human GITR (hGITR; SEQ ID NO: 1), comprising a V_H sequence of SEQ ID NO:9 and a V_L sequence of SEQ ID NO:10.
14. A pharmaceutical composition comprising the ABP of claim 12 and a pharmaceutically acceptable carrier.
15. A pharmaceutical composition comprising the ABP of claim 13 and a pharmaceutically acceptable carrier.