

CLAIMS

What is claimed is:

1. An isolated anti-TNFR2 (tumor necrosis factor receptor 2) antibody comprising a set of three complementarity determining regions (CDRs) on a heavy chain (HCDR1, HCDR2, and HCDR3) and a set of three CDRs on a light chain (LCDR1, LCDR2, and LCDR3), wherein said CDRs have the amino acid sequences of
 - a. SEQ ID NO: 187, SEQ ID NO:345, and SEQ ID NO: 356 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 371, SEQ ID NO: 377, and SEQ ID NO: 395 (LCDR1, LCDR2, and LCDR3, respectively);
 - b. SEQ ID NO: 402, SEQ ID NO:345, and SEQ ID NO: 413 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 371, SEQ ID NO: 418, and SEQ ID NO: 427 (LCDR1, LCDR2, and LCDR3, respectively);
 - c. SEQ ID NO: 398, SEQ ID NO:346, and SEQ ID NO: 407 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 371, SEQ ID NO: 377, and SEQ ID NO: 419 (LCDR1, LCDR2, and LCDR3, respectively);
 - d. SEQ ID NO: 187, SEQ ID NO:346, and SEQ ID NO: 408 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 371, SEQ ID NO: 377, and SEQ ID NO: 420 (LCDR1, LCDR2, and LCDR3, respectively);
 - e. SEQ ID NO: 189, SEQ ID NO:406, and SEQ ID NO: 409 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 371, SEQ ID NO: 377, and SEQ ID NO: 421 (LCDR1, LCDR2, and LCDR3, respectively);
 - f. SEQ ID NO: 187, SEQ ID NO:345, and SEQ ID NO: 410 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 371, SEQ ID NO: 418, and SEQ ID NO: 422 (LCDR1, LCDR2, and LCDR3, respectively);
 - g. SEQ ID NO: 399, SEQ ID NO:346, and SEQ ID NO: 411 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 371, SEQ ID NO: 418, and SEQ ID NO: 423 (LCDR1, LCDR2, and LCDR3, respectively);
 - h. SEQ ID NO: 400, SEQ ID NO:346, and SEQ ID NO: 412 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 417, SEQ ID NO: 377, and SEQ ID NO: 424 (LCDR1, LCDR2, and LCDR3, respectively);
 - i. SEQ ID NO: 401, SEQ ID NO:346, and SEQ ID NO: 413 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 417, SEQ ID NO: 418, and SEQ ID NO: 425

- (LCDR1, LCDR2, and LCDR3, respectively);
- 5 j. SEQ ID NO: 401, SEQ ID NO:346, and SEQ ID NO: 414 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 417, SEQ ID NO: 418, and SEQ ID NO: 426 (LCDR1, LCDR2, and LCDR3, respectively);
- k. SEQ ID NO: 398, SEQ ID NO:346, and SEQ ID NO: 415 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 417, SEQ ID NO: 377, and SEQ ID NO: 428 (LCDR1, LCDR2, and LCDR3, respectively);
- 10 l. SEQ ID NO: 403, SEQ ID NO:346, and SEQ ID NO: 412 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 371, SEQ ID NO: 418, and SEQ ID NO: 429 (LCDR1, LCDR2, and LCDR3, respectively);
- m. SEQ ID NO: 404, SEQ ID NO:346, and SEQ ID NO: 412 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 371, SEQ ID NO: 418, and SEQ ID NO: 425 (LCDR1, LCDR2, and LCDR3, respectively);
- 15 n. SEQ ID NO: 401, SEQ ID NO:346, and SEQ ID NO: 414 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 417, SEQ ID NO: 418, and SEQ ID NO: 430 (LCDR1, LCDR2, and LCDR3, respectively);
- o. SEQ ID NO: 405, SEQ ID NO:406, and SEQ ID NO: 416 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 371, SEQ ID NO: 377, and SEQ ID NO: 431 (LCDR1, LCDR2, and LCDR3, respectively);
- 20 p. SEQ ID NO: 185, SEQ ID NO:190, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 359, SEQ ID NO: 372, and SEQ ID NO: 378 (LCDR1, LCDR2, and LCDR3, respectively);
- q. SEQ ID NO: 185, SEQ ID NO:190, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 359, SEQ ID NO: 372, and SEQ ID NO: 378 (LCDR1, LCDR2, and LCDR3, respectively);
- 25 r. SEQ ID NO: 185, SEQ ID NO:334, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 360, SEQ ID NO: 372, and SEQ ID NO: 379 (LCDR1, LCDR2, and LCDR3, respectively);
- s. SEQ ID NO: 185, SEQ ID NO:190, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 359, SEQ ID NO: 372, and SEQ ID NO: 380 (LCDR1, LCDR2, and LCDR3, respectively);
- 30 t. SEQ ID NO: 185, SEQ ID NO:190, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 359, SEQ ID NO: 372, and SEQ ID NO: 381

- (LCDR1, LCDR2, and LCDR3, respectively);
- 5 u. SEQ ID NO: 185, SEQ ID NO:190, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 361, SEQ ID NO: 372, and SEQ ID NO: 381 (LCDR1, LCDR2, and LCDR3, respectively);
- v. SEQ ID NO: 185, SEQ ID NO:190, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 362, SEQ ID NO: 372, and SEQ ID NO: 382 (LCDR1, LCDR2, and LCDR3, respectively);
- 10 w. SEQ ID NO: 185, SEQ ID NO:335, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 363, SEQ ID NO: 372, and SEQ ID NO: 383 (LCDR1, LCDR2, and LCDR3, respectively);
- x. SEQ ID NO: 185, SEQ ID NO:190, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 364, SEQ ID NO: 372, and SEQ ID NO: 384 (LCDR1, LCDR2, and LCDR3, respectively);
- 15 y. SEQ ID NO: 185, SEQ ID NO:336, and SEQ ID NO: 348 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 365, SEQ ID NO: 372, and SEQ ID NO: 378 (LCDR1, LCDR2, and LCDR3, respectively);
- z. SEQ ID NO: 185, SEQ ID NO:337, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 359, SEQ ID NO: 373, and SEQ ID NO: 385 (LCDR1, LCDR2, and LCDR3, respectively);
- 20 aa. SEQ ID NO: 185, SEQ ID NO:338, and SEQ ID NO: 348 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 359, SEQ ID NO: 372, and SEQ ID NO: 386 (LCDR1, LCDR2, and LCDR3, respectively);
- bb. SEQ ID NO: 185, SEQ ID NO:339, and SEQ ID NO: 349 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 359, SEQ ID NO: 372, and SEQ ID NO: 378 (LCDR1, LCDR2, and LCDR3, respectively);
- 25 cc. SEQ ID NO: 185, SEQ ID NO:190, and SEQ ID NO: 350 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 366, SEQ ID NO: 372, and SEQ ID NO: 387 (LCDR1, LCDR2, and LCDR3, respectively);
- dd. SEQ ID NO: 185, SEQ ID NO:190, and SEQ ID NO: 351 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 359, SEQ ID NO: 372, and SEQ ID NO: 378 (LCDR1, LCDR2, and LCDR3, respectively);
- 30 ee. SEQ ID NO: 185, SEQ ID NO:334, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 360, SEQ ID NO: 372, and SEQ ID NO: 388

	<u>(LCDR1, LCDR2, and LCDR3, respectively);</u>
	<u>ff. SEQ ID NO: 185, SEQ ID NO:334, and SEQ ID NO: 352 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 359, SEQ ID NO: 372, and SEQ ID NO: 378 (LCDR1, LCDR2, and LCDR3, respectively);</u>
5	<u>gg. SEQ ID NO: 185, SEQ ID NO:190, and SEQ ID NO: 352 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 359, SEQ ID NO: 372, and SEQ ID NO: 389 (LCDR1, LCDR2, and LCDR3, respectively);</u>
	<u>hh. SEQ ID NO: 185, SEQ ID NO:334, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 359, SEQ ID NO: 372, and SEQ ID NO: 378 (LCDR1, LCDR2, and LCDR3, respectively);</u>
10	<u>ii. SEQ ID NO: 185, SEQ ID NO:190, and SEQ ID NO: 347 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 365, SEQ ID NO: 372, and SEQ ID NO: 378 (LCDR1, LCDR2, and LCDR3, respectively);</u>
	<u>jj. SEQ ID NO: 185, SEQ ID NO:336, and SEQ ID NO: 352 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 365, SEQ ID NO: 372, and SEQ ID NO: 390 (LCDR1, LCDR2, and LCDR3, respectively);</u>
15	<u>kk. SEQ ID NO: 185, SEQ ID NO:336, and SEQ ID NO: 352 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 365, SEQ ID NO: 374, and SEQ ID NO: 391 (LCDR1, LCDR2, and LCDR3, respectively);</u>
	<u>ll. SEQ ID NO: 186, SEQ ID NO:340, and SEQ ID NO: 353 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 367, SEQ ID NO: 375, and SEQ ID NO: 392 (LCDR1, LCDR2, and LCDR3, respectively);</u>
20	<u>mm. SEQ ID NO: 186, SEQ ID NO:341, and SEQ ID NO: 354 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 367, SEQ ID NO: 375, and SEQ ID NO: 392 (LCDR1, LCDR2, and LCDR3, respectively);</u>
25	<u>nn. SEQ ID NO: 186, SEQ ID NO:341, and SEQ ID NO: 354 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 368, SEQ ID NO: 375, and SEQ ID NO: 392 (LCDR1, LCDR2, and LCDR3, respectively);</u>
	<u>oo. SEQ ID NO: 186, SEQ ID NO:342, and SEQ ID NO: 354 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 367, SEQ ID NO: 375, and SEQ ID NO: 392 (LCDR1, LCDR2, and LCDR3, respectively);</u>
30	<u>pp. SEQ ID NO: 186, SEQ ID NO:343, and SEQ ID NO: 354 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 369, SEQ ID NO: 375, and SEQ ID NO: 393</u>

- (LCDR1, LCDR2, and LCDR3, respectively);
- qq. SEQ ID NO: 186, SEQ ID NO:343, and SEQ ID NO: 355 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 367, SEQ ID NO: 375, and SEQ ID NO: 392 (LCDR1, LCDR2, and LCDR3, respectively);
- 5 rr. SEQ ID NO: 186, SEQ ID NO:341, and SEQ ID NO: 354 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 367, SEQ ID NO: 375, and SEQ ID NO: 392 (LCDR1, LCDR2, and LCDR3, respectively);
- ss. SEQ ID NO: 186, SEQ ID NO:341, and SEQ ID NO: 355 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 367, SEQ ID NO: 376, and SEQ ID NO: 392 (LCDR1, LCDR2, and LCDR3, respectively);
- 10 tt. SEQ ID NO: 186, SEQ ID NO:344, and SEQ ID NO: 354 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 370, SEQ ID NO: 375, and SEQ ID NO: 392 (LCDR1, LCDR2, and LCDR3, respectively);
- uu. SEQ ID NO: 186, SEQ ID NO:341, and SEQ ID NO: 354 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 367, SEQ ID NO: 375, and SEQ ID NO: 394 (LCDR1, LCDR2, and LCDR3, respectively);
- 15 vv. SEQ ID NO: 186, SEQ ID NO:344, and SEQ ID NO: 354 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 367, SEQ ID NO: 375, and SEQ ID NO: 392 (LCDR1, LCDR2, and LCDR3, respectively);
- ww. SEQ ID NO: 186, SEQ ID NO:341, and SEQ ID NO: 354 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 367, SEQ ID NO: 375, and SEQ ID NO: 393 (LCDR1, LCDR2, and LCDR3, respectively);
- 20 xx. SEQ ID NO: 188, SEQ ID NO:345, and SEQ ID NO: 357 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 371, SEQ ID NO: 377, and SEQ ID NO: 396 (LCDR1, LCDR2, and LCDR3, respectively); or
- 25 yy. SEQ ID NO: 189, SEQ ID NO:346, and SEQ ID NO: 358 (HCDR1, HCDR2, and HCDR3, respectively), and SEQ ID NO: 371, SEQ ID NO: 377, and SEQ ID NO: 397 (LCDR1, LCDR2, and LCDR3, respectively).
- 30 (i) ~~the set of HCDR1, HCDR2, HCDR3, and the set of LCDR1, LCDR2, LCDR3 on a corresponding light chain comprise the amino acid sequences as shown in Table 9; or~~
- (ii) ~~the set of HCDR1, HCDR2, and HCDR3 comprise the amino acid sequences as~~

~~shown in Table 7, and the set of LCDR1, LCDR2, and LCDR3 on a corresponding light chain comprise the amino acid sequences as shown in Table 8.~~

2. The anti-TNFR2 antibody of claim 1, wherein the ~~antibody heavy chain~~ comprises a heavy chain variable region (VH) and ~~the light chain comprises~~ a light chain variable region (VL), ~~said VH comprising said HCDR1, HCDR2 and HCDR3 and said VL comprising said LCDR1, LCDR2 and LCDR3, wherein~~ said ~~heavy chain variable region~~VH and ~~light chain variable region~~VL ~~respectively~~ comprise the amino acid sequences selected from the group consisting of SEQ ID NOs:87-88, SEQ ID NOs:289-290, SEQ ID NOs:3-4, SEQ ID NOs:7-8, SEQ ID NOs:11-12, SEQ ID NOs:15-16, SEQ ID NOs:19-20, SEQ ID NOs:23-24, SEQ ID NOs:27-28, SEQ ID NOs:31-32, SEQ ID NOs:35-36, SEQ ID NOs:39-40, SEQ ID NOs:43-44, SEQ ID NOs:47-48, SEQ ID NOs:51-52, SEQ ID NOs:55-56, SEQ ID NOs:59-60, SEQ ID NOs:63-64, SEQ ID NOs:67-68, SEQ ID NOs:71-72, SEQ ID NOs:75-76, SEQ ID NOs:79-80, SEQ ID NOs:83-84, ~~SEQ ID NOs:87-88~~, SEQ ID NOs:91-92, SEQ ID NOs:95-96, SEQ ID NOs:99-100, SEQ ID NOs:103-104, SEQ ID NOs:107-108, SEQ ID NOs:111-112, SEQ ID NOs:115-116, SEQ ID NOs:119-120, SEQ ID NOs:123-124, SEQ ID NOs:127-128, SEQ ID NOs:131-132, SEQ ID NOs:135-136, SEQ ID NOs:139-140, SEQ ID NOs:143-144, SEQ ID NOs:147-148, SEQ ID NOs:151-152, SEQ ID NOs:157-158, SEQ ID NOs:163-164, SEQ ID NOs:169-170, SEQ ID NOs:175-176, SEQ ID NOs:181-182, SEQ ID NOs:193-194, SEQ ID NOs:199-200, SEQ ID NOs:205-206, SEQ ID NOs:211-212, SEQ ID NOs:217-218, SEQ ID NOs:223-224, SEQ ID NOs:229-230, SEQ ID NOs:233-234, SEQ ID NOs:237-238, SEQ ID NOs:241-242, SEQ ID NOs:245-246, SEQ ID NOs:249-250, SEQ ID NOs:253-254, ~~SEQ ID NOs:257-258~~, SEQ ID NOs:261-262, SEQ ID NOs:265-266, SEQ ID NOs:269-270, SEQ ID NOs:273-274, SEQ ID NOs:277-278, SEQ ID NOs:281-282, SEQ ID NOs:285-286, SEQ ID NOs:293-294, SEQ ID NOs:297-298, SEQ ID NOs:301-302, SEQ ID NOs:305-306, SEQ ID NOs:309-310, SEQ ID NOs:313-314, SEQ ID NOs:317-318, SEQ ID NOs:321-322, SEQ ID NOs:325-326, and SEQ ID NOs:329-330.

3. The anti-TNFR2 antibody of claim 1, wherein ~~the antibody comprises a heavy chain and a light chain~~, said heavy chain and ~~saida~~ light chain respectively comprise the amino acid sequences selected from the group consisting of SEQ ID NOs 432 and 260, SEQ ID NOs: 438 and 292, SEQ ID NOs: 291-292, SEQ ID NOs:235-236, SEQ ID NOs:239-240, SEQ

ID NOs:243-244, SEQ ID NOs:247-248, SEQ ID NOs:251-252, SEQ ID NOs:255-256, SEQ ID NOs:259-260, SEQ ID NOs:263-264, SEQ ID NOs:267-268, SEQ ID NOs:271-272, SEQ ID NOs:275-276, SEQ ID NOs:279-280, SEQ ID NOs:283-284, SEQ ID NOs:287-288, SEQ ID NOs:295-296, SEQ ID NOs:299-300, SEQ ID NOs:303-304, SEQ ID NOs:307-308, SEQ ID NOs:311-312, SEQ ID NOs:315-316, SEQ ID NOs:319-320, SEQ ID NOs:323-324, SEQ ID NOs:327-328, SEQ ID NOs:331-332, ~~SEQ ID NOs 432 and 260~~, SEQ ID NOs: 433 and 304, SEQ ID NOs: 434 and 308, SEQ ID NOs: 434 and 308, SEQ ID NOs: 435 and 236, SEQ ID NOs: 436 and 244, SEQ ID NOs: 437 and 284, and SEQ ID NOs: 439 and 296.

4. The anti-TNFR2 antibody of any of claims 1, 2, or 3, wherein the antibody is an IgG, a Fv, a scFv, a Fab, a F(ab')₂, a minibody, a diabody, a triabody, ~~a nanobody~~, a bispecific antibody, ~~or a single domain antibody~~.

5. The anti-TNFR2 antibody of claim 4, wherein said IgG is IgG1, IgG2, IgG3, or IgG4.

6. The anti-TNFR2 antibody of claim 1, wherein the antibody agonizes TNFR2.

7. The anti-TNFR2 antibody of claim 6, wherein the antibody agonizes TNFR2 in an Fc independent manner.

8. The anti-TNFR2 antibody of claim 1, wherein the antibody has an EC₅₀ binding measurement of about 0.05-100 nM.

9. The anti-TNFR2 antibody of claim 1, wherein the antibody has an EC₅₀ functional agonism measurement of about 0.05-100 nM.

10. The anti-TNFR2 antibody of claim 1, wherein the antibody activates signaling through TNFR2 at a level of at least 80% as compared to signaling activated by TNF.

11. The anti-TNFR2 antibody of claim 1, wherein the antibody activates signaling through TNFR2 at a level of at least 95% as compared to signaling activated by TNF.

12. A composition comprising the anti-TNFR2 antibody of any one of claims 1-3 and a pharmaceutically acceptable carrier.

13. An isolated polynucleotide sequence encoding the anti-TNFR2 antibody of any one of claims 1-3.

14. A vector comprising the polynucleotide sequence of claim 13.

15. A host cell comprising the vector of claim 14.

16. Use of a composition comprising the anti-TNFR2 antibody of any one of claims 1-8 in the manufacture of a medicament for ~~A method of~~ modulating activities or functions of regulatory T cells in a subject, ~~comprising the step of administering to the subject a composition comprising an effective amount of the anti-TNFR2 antibody of any one of claims 1-3.~~

17. The ~~method-use~~ of claim 16, wherein the regulatory T cells are CD4⁺CD25⁺Foxp3⁺.

18. The ~~method-use~~ of claim 16, wherein the ~~method-use~~ stimulates proliferation of the regulatory T cells.

19. The ~~method-use~~ of claim 16, wherein the ~~method-use~~ activates said regulatory T cells.

20. The ~~method-use~~ of claim 16, wherein the ~~method-use~~ modulates immune responses mediated by said regulatory T cells.

21. Use of a composition comprising the anti-TNFR2 antibody of any one of claims 1-8 in the manufacture of a medicament for ~~A method of~~ modulating activities or functions of myeloid-derived suppressor cells (MDSCs) in a subject, ~~comprising the step of administering to the subject a composition comprising an effective amount of the anti-TNFR2 antibody of claim 1-3.~~

22. The ~~method-use~~ of claim 21, wherein the ~~method-use~~ stimulates proliferation of the

MDSCs.

23. The ~~method~~use of claim 21, wherein the ~~method~~use activates said MDSCs.

5 24. Use of a composition comprising the anti-TNFR2 antibody of any one of claims 1-8 in the manufacture of a medicament for ~~A method of~~ treating a disease in a subject, ~~comprising the step of administering to the subject a composition comprising an effective amount of the anti-TNFR2 antibody of any of claims 1-3.~~

10 25. The ~~method~~use of claim 24, wherein the disease is a cancer, an autoimmune disease, GvHD, a viral infection, or a bacterial infection.