Claims

1. An isolated monoclonal antibody or immunologically active fragment thereof that binds to CD47, wherein the antibody or fragment thereof has a reduced FcγR binding affinity as compared to a wildtype IgG1, wherein the antibody or fragment thereof does not cause a significant level of red blood cell depletion, platelet depletion, or both after administration.

2. The antibody or fragment of claim 1, wherein the antibody or fragment thereof binds to a discontinuous epitope on CD47, and wherein the discontinuous epitope comprises amino acids residues Y37, K39, K41, K43, G44, R45, D46, D51, H90, N93, E97, T99, E104, or E106 of CD47 when numbered in accordance with SEQ ID NO: 147.

3. The antibody or fragment of claim 2, wherein the discontinuous epitope comprises the KGRD (SEQ ID NO: 56) loop (residues 43-46) when numbered in accordance with SEQ ID NO: 147.

4. The antibody or fragment of claim 2 or claim 3, wherein the discontinuous epitope comprises amino acid residues Y37, T102 and E104 of CD47 when numbered in accordance with SEQ ID NO: 147.

5. The antibody or fragment of any one of claims 1-4, wherein the antibody is an IgG isotype selected from the group consisting of IgG1 isotype, IgG2 isotype, IgG3 isotype, and IgG4 isotype.

6. The antibody or fragment of claim 5, wherein the IgG isotype is a human IgG isotype.

7. The antibody or fragment of claim 6, wherein the antibody comprises a modified amino acid at position 297.

8. The antibody or fragment of claim 7, wherein the antibody comprises a N297A mutation.

9. The antibody or fragment of any one of claims 5-8, wherein the antibody is a human IgG1 isotype.

10. The antibody or fragment of claim 9, wherein the antibody comprises a modified amino acid at position 234 and/or 235.

11. The antibody or fragment of claim 10, wherein the antibody comprises L235E, L235A, and/or L234A.

12. The antibody or fragment of any one of claims 5-8, wherein the antibody is a human IgG2 isotype.

13. The antibody or fragment of any one of claims 5-8, wherein the antibody is a human IgG3 isotype.

14. The antibody or fragment of claim 13, wherein the antibody comprises a modified amino acid at position 435.

15. The antibody or fragment of claim 14, wherein the antibody comprises a R435H mutation.

16. The antibody or fragment of any one of claims 5-8, wherein the antibody is a human IgG4 isotype.

17. The antibody or fragment of claim 16, wherein the antibody has a modified amino acid at position 228.

18. The antibody or fragment of claim 17, wherein the antibody comprises a S228P mutation (IgG4P).

19. The antibody or fragment of any one of claims 16-18, wherein the antibody has a modified amino acid at position 235.

20. The antibody or fragment of claim 19, wherein the antibody comprises a L235E mutation.

21. The antibody or fragment of claim 20, wherein the antibody comprises a S228P and a L235E mutation (IgG4PE).

22. The antibody or fragment of any one of claims 1-21, wherein the antibody or fragment does not cause a significant level of agglutination of red blood cells.

23. The antibody or fragment of any one of claims 1-22, wherein the antibody or fragment prevents CD47 from interacting with signal-regulatory-protein α (SIRPα).

24. The antibody or fragment of any one of claims 1-23, wherein the antibody or fragment promotes macrophage-mediated phagocytosis of a CD47-expressing cell.

25. The antibody or fragment of any one of claims 1-24, wherein the antibody or fragment is chimeric or humanized.

26. The antibody or fragment of any one of claims 1-25, wherein the CD47 is human CD47.

27. The antibody or fragment of any one of claims 2-26, wherein the discontinuous epitope comprises Y37, K39, K41, K43, G44, R45, D46, D51, H90, N93, E97, T99, T102, E104, and E106 of CD47 when numbered in accordance with SEQ ID NO: 147.

28. The antibody or fragment of any one of claims 1-27, wherein the antibody or fragment binds to CD47 in a head to side orientation, wherein a VH chain of the antibody or fragment is positioned near the membrane of a CD47 expressing cell, and wherein a VL chain of the antibody or fragment occludes a SIRPα binding site on CD47.

29. The antibody or fragment of any one of claims 1-27, wherein the antibody or fragment binds to CD47 in a head to side orientation, wherein a VL chain of the antibody or fragment is positioned near the membrane of a CD47 expressing cell, and wherein a VH chain of the antibody or fragment occludes a SIRPα binding site on CD47.

30. The antibody or fragment of any one of claims 1-29, wherein the antibody or fragment is a full-length antibody.

31. A pharmaceutical composition comprising the antibody or fragment of any one of claims 1-30 and a carrier.

32. Use of the antibody or fragment of any one of claims 1-30, or the pharmaceutical composition of claim 31, in the manufacture of a medicament for the treatment of cancer in a subject.

33. The use of claim 32, wherein the subject is a human.

34. The use of claim 32 or claim 33, wherein the treatment further comprises the administration of chemotherapy.

35. The use of any one of claim 32-34, wherein the antibody or fragment is to be administered to the subject at a dose of at least 10 mg/kg.

36. The use of any one of claims 32-35, wherein the antibody or fragment is to be administered to the subject at a dose of at least 30 mg/kg.

37. The antibody or fragment of any one of claims 1-30, or the pharmaceutical composition of claim 31, for use in therapy.