HUMANIZED MONOCLONAL ANTIBODIES THAT TARGET VE-PTP (HPTP-β)

CROSS REFERENCE

[0001] This application claims the benefit of United States Provisional Application No. 62/364,381, filed July 20, 2016, and United States Provisional Application No. 62/377,072, filed August 19, 2016, each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Monoclonal antibodies generated from non-human organisms can elicit an immune response when administered to humans. Segments of these non-human monoclonal antibodies can be replaced with humanized sequences through a humanization process to reduce the likelihood of drug immunogenicity while preserving target specificity.

INCORPORATION BY REFERENCE

[0003] Each patent, publication, and non-patent literature cited in the application is hereby incorporated by reference in its entirety as if each was incorporated by reference individually.

SUMMARY OF THE INVENTION

[0003a] In one aspect, the present disclosure relates to an antibody comprising:

a) a heavy chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 30, wherein the heavy chain comprises:

i) a sequence that is at least 90% identical to SEQ ID NO: 54; a sequence that is SEQ ID NO: 55; and a sequence that is SEQ ID NO: 56;

ii) a sequence that is SEQ ID NO: 54; a sequence that is at least 94% identical to SEQ ID NO: 55; and a sequence that is SEQ ID NO: 56; or

iii) a sequence that is SEQ ID NO: 54; a sequence that is SEQ ID NO: 55; and a sequence that is at least 92% identical to SEQ ID NO: 56; and

b) a light chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 34, wherein the light chain comprises:

i) a sequence that is at least 90% identical to SEQ ID NO: 57; a sequence that is SEQ ID NO: 58; and a sequence that is SEQ ID NO: 59;

ii) a sequence that is SEQ ID NO: 57; a sequence that is at least 85% identical to SEQ ID NO: 58; and a sequence that is SEQ ID NO: 59; or

iii) a sequence that is SEQ ID NO: 57; a sequence that is SEQ ID NO: 58; and a sequence that is at least 88% identical to SEQ ID NO: 59,

wherein the antibody binds human protein tyrosine phosphatase-beta (HPTP-β).

[0003b] In another aspect, the present disclosure relates to an antibody as disclosed herein for use as a medicament.

[0003c] In another aspect, the present disclosure relates to a use of a therapeutically-effective amount of an antibody, the antibody comprising:

a) a heavy chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 30, wherein the heavy chain comprises:

i) a sequence that is at least 90% identical to SEQ ID NO: 54; a sequence that is SEQ ID NO: 55; and a sequence that is SEQ ID NO: 56;

ii) a sequence that is SEQ ID NO: 54; a sequence that is at least 94% identical to SEQ ID NO: 55; and a sequence that is SEQ ID NO: 56; or

iii) sequence that is SEQ ID NO: 54; a sequence that is SEQ ID NO: 55; and a sequence that is at least 92% identical to SEQ ID NO: 56; and

b) a light chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 34, wherein the light chain comprises:

i) a sequence that is at least 90% identical to SEQ ID NO: 57: a sequence that is SEQ ID NO: 58; and a sequence that is SEQ ID NO: 59;

ii) a sequence that is SEQ ID NO: 57; a sequence that is at least 85% identical to SEQ ID NO: 58; and a sequence that is SEQ ID NO: 59; or

iii) a sequence that is SEQ ID NO: 57; a sequence that is SEQ ID NO: 58; and a sequence that is at least 88% identical to SEQ ID NO: 59;

wherein the antibody binds HPTP-β in the manufacture of a medicament for treating an ocular condition in a subject in need thereof, and wherein the medicament is to be administered to the subject.

[0004] In some examples, the disclosure provides a compound comprising a sequence that is at least 80% identical to SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, or SEQ ID NO: 12.

[0005] In some examples, the disclosure provides a compound comprising a sequence that is at least 80% identical to SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, or SEQ ID NO: 23.

[0006] In some examples, the disclosure provides a compound comprising: a) a heavy chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 30; and b) a light chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 34.

[0007] In some examples, the discloosure provides a compound comprising: a) a heavy chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 29; and b) a light chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 35.

[0008] In some examples, the disclosure provides a compound comprising: a) a heavy chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 30; and b) a

CLAIMS

WHAT IS CLAIMED IS:

1. An antibody comprising:

a) a heavy chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 30, wherein the heavy chain comprises:

i) a sequence that is at least 90% identical to SEQ ID NO: 54; a sequence that is SEQ ID NO: 55; and a sequence that is SEQ ID NO: 56;

ii) a sequence that is SEQ ID NO: 54; a sequence that is at least 94% identical to SEQ ID NO: 55; and a sequence that is SEQ ID NO: 56; or

iii) a sequence that is SEQ ID NO: 54; a sequence that is SEQ ID NO: 55; and a sequence that is at least 92% identical to SEQ ID NO: 56; and

b) a light chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 34, wherein the light chain comprises:

i) a sequence that is at least 90% identical to SEQ ID NO: 57; a sequence that is SEQ ID NO: 58; and a sequence that is SEQ ID NO: 59;

ii) a sequence that is SEQ ID NO: 57; a sequence that is at least 85% identical to SEQ ID NO: 58; and a sequence that is SEQ ID NO: 59; or

iii) a sequence that is SEQ ID NO: 57; a sequence that is SEQ ID NO: 58; and a sequence that is at least 88% identical to SEQ ID NO: 59,

wherein the antibody binds human protein tyrosine phosphatase-beta (HPTP-β).

2. The antibody of claim 1, wherein the heavy chain is at least 85% identical to SEQ ID NO: 30; and the light chain is at least 85% identical to SEQ ID NO: 34.

3. The antibody of claim 1, wherein the heavy chain is at least 90% identical to SEQ ID NO: 30; and the light chain is at least 90% identical to SEQ ID NO: 34.

4. The antibody of claim 1, wherein the heavy chain is at least 95% identical to SEQ ID NO: 30; and the light chain is at least 95% identical to SEQ ID NO: 34.

5. The antibody of claim 1, wherein the heavy chain is SEQ ID NO: 30 and the light chain is SEQ ID NO: 34.

6. The antibody of claim 1, wherein the antibody inhibits a tyrosine phosphatase.

7. The antibody of claim 1, wherein the antibody inhibits HPTP-β.

8. The antibody of claim 1, wherein the antibody further inhibits vascular endothelial protein tyrosine phosphatase (VE-PTP).

9. The antibody of claim 1, wherein the antibody activates tyrosine kinase with immunoglobulin and epidermal growth factor homology domains 2 (Tie2).

10. The antibody of claim 1, wherein the antibody activates Akt.

11. The antibody of claim 1, wherein the antibody binds an extracellular domain of HPTP-β.

12. The antibody of claim 1, wherein the antibody binds a first FN3 repeat of an extracellular domain of HPTP-β.

13. The antibody of claim 12, wherein a binding affinity (K_D) of the antibody to the extracellular domain of HPTP-β is about 70 pM to about 70 nM.

14. The antibody of claim 1, wherein:

a) a heavy chain that comprises a sequence that is SEQ ID NO: 54; a sequence that is SEQ ID NO: 55; and a sequence that is SEQ ID NO: 56; and

b) a light chain comprises a sequence that is SEQ ID NO: 57; a sequence that is SEQ ID NO: 58; and a sequence that is SEQ ID NO: 59.

15. The antibody of claim 1 for use as a medicament.

16. Use of a therapeutically-effective amount of an antibody, the antibody comprising:

a) a heavy chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 30, wherein the heavy chain comprises:

i) a sequence that is at least 90% identical to SEQ ID NO: 54; a sequence that is SEQ ID NO: 55; and a sequence that is SEQ ID NO: 56;

ii) a sequence that is SEQ ID NO: 54; a sequence that is at least 94% identical to SEQ ID NO: 55; and a sequence that is SEQ ID NO: 56; or

iii) sequence that is SEQ ID NO: 54; a sequence that is SEQ ID NO: 55; and a sequence that is at least 92% identical to SEQ ID NO: 56; and

b) a light chain that comprises a sequence that is at least 80% identical to SEQ ID NO: 34, wherein the light chain comprises:

i) a sequence that is at least 90% identical to SEQ ID NO: 57: a sequence that is SEQ ID NO: 58; and a sequence that is SEQ ID NO: 59;

ii) a sequence that is SEQ ID NO: 57; a sequence that is at least 85% identical to SEQ ID NO: 58; and a sequence that is SEQ ID NO: 59; or

iii) a sequence that is SEQ ID NO: 57; a sequence that is SEQ ID NO: 58; and a sequence that is at least 88% identical to SEQ ID NO: 59;

wherein the antibody binds HPTP-β in the manufacture of a medicament for treating an ocular condition in a subject in need thereof, and wherein the medicament is to be administered to the subject.

17. The use of claim 16, wherein the condition is diabetic retinopathy.

18. The use of claim 16, wherein the condition is neovascularization.

19. The use of claim 16, wherein the condition is vascular leak.

20. The use of claim 16, wherein the condition is increased intraocular pressure.

21. The use of claim 16, wherein the condition is ocular edema.

22. The use of claim 16, wherein the condition is diabetic macular edema.

23. The use of claim 16, wherein the condition is ocular hypertension.

24. The use of claim 16, wherein the condition is ocular inflammation.

25. The use of claim 16, wherein the administration is to an eye of the subject.

26. The use of claim 16, wherein the administration is intravitreal.

27. The use of claim 16, wherein the administration is subcutaneous.

28. The use of claim 16, wherein the administration is topical.

29. The use of claim 16, wherein the subject is a human.

30. The use of claim 16, wherein the therapeutically-effective amount of the antibody is from about 0.25 mg to about 200 mg.

31. The use of claim 16, wherein the therapeutically-effective amount of the antibody is from about 1 mg/kg to about 10 mg/kg.

32. The use of claim 16, wherein the therapeutically effective amount of the antibody is from about 1 mg to about 50 mg.

33. The use of claim 16, wherein the therapeutically-effective amount of the antibody is from about 50 mg to about 200 mg.

34. The use of claim 16, wherein the heavy chain is at least 85% identical to SEQ ID NO: 30; and the light chain is at least 85% identical to SEQ ID NO: 34.

35. The use of claim 16, wherein the heavy chain is at least 90% identical to SEQ ID NO: 30; and the light chain so is at least 90% identical to SEQ ID NO: 34.

36. The use of claim 16, wherein the heavy chain is at least 95% identical to SEQ ID NO: 30; and the light chain is at least 95% identical to SEQ ID NO: 34.

37. The use of claim 16, wherein the heavy chain is SEQ ID NO: 30 and the light chain is SEQ ID NO: 34.

38. The use of claim 16, wherein the antibody inhibits a tyrosine phosphatase in the subject.

39. The use of claim 16, wherein the antibody inhibits HPTP-β in the subject.

40. The use of claim 16, wherein the antibody inhibits VE-PTP in the subject.

41. The use of claim 16, wherein the antibody activates Tie2 in the subject.

42. The use of claim 16, wherein the antibody activates Akt in the subject.

43. The use of claim 16, wherein the antibody binds an extracellular domain of HPTP-β in the subject.

44. The use of claim 16, wherein the antibody binds a first FN3 repeat of an extracellular domain of HPTP-β in the subject.

45. The use of claim 44, wherein a binding affinity (K_D) of the antibody to the extracellular domain of HPTP-β is about 70 pM to about 70 nM.

46. The use of claim 16, wherein:

a) the heavy chain comprises a sequence that is SEQ ID NO: 54; a sequence that is SEQ ID NO: 55; and a sequence that is SEQ ID NO: 56; and

b) the light chain comprises a sequence that is SEQ ID NO: 57; a sequence that is SEQ ID NO: 58; and a sequence that is SEQ ID NO: 59.