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SUMMARY

It has been found that anti-IGF-1R antibodies with abolished FcRn-binding can be used for the treatment of IGF-1R-related disorders in the eye (vascular eye diseases).

One aspect as reported herein is an anti-IGF-1R antibody that specifically binds to human IGF-1R and that has abolished FcRn binding, wherein the antibody comprises a first Fc-region polypeptide and a second Fc-region polypeptide, wherein the first and the second Fc-region polypeptide further comprise the mutations H310A, H433A and Y436A.

One aspect as reported herein is an anti-IGF-1R antibody as defined herein for use in inhibiting IGF-1R in the eye.

As reported herein is the use of an anti-IGF-1R antibody with abolished human neonatal Fc-receptor (FcRn) binding for inhibition of IGF-1R in the eye.

As reported herein is the use of an anti-IGF-1R antibody with abolished human neonatal Fc-receptor (FcRn) binding for the treatment of vascular eye diseases.

Patent Claims

1. An anti-IGF-1R antibody that specifically binds to human IGF-1R and that has abolished FcRn binding, wherein the antibody comprises a first Fc-region polypeptide and a second Fc-region polypeptide, wherein the first and the second Fc-region polypeptide further comprise the mutations H310A, H433A and Y436A.

2. The antibody according to claim 1, wherein the anti-IGF-1R antibody has

a) an antibody heavy chain comprising as HVRs the amino acid sequence of SEQ ID NO: 56 (HVR-H1), the amino acid sequence of SEQ ID NO: 57 (HVR-H2), and the amino acid sequence of SEQ ID NO: 58 (HVR-H3), and an antibody light chain comprising as HVRs the amino acid sequence of SEQ ID NO: 59 (HVR-L1), the amino acid sequence of SEQ ID NO: 60 (HVR-L2), and the amino acid sequence of SEQ ID NO: 61 (HVR-L3), or

b) an antibody heavy chain comprising as HVRs the amino acid sequence of SEQ ID NO: 64 (HVR-H1), the amino acid sequence of SEQ ID NO: 65 (HVR-H2), and the amino acid sequence of SEQ ID NO: 66 (HVR-H3), and an antibody light chain comprising as HVRs the amino acid sequence of SEQ ID NO: 67 (HVR-L1), the amino acid sequence of SEQ ID NO: 68 (HVR-L2), and the amino acid sequence of SEQ ID NO: 69 (HVR-L3), or

c) an antibody heavy chain comprising as HVRs the amino acid sequence of SEQ ID NO: 72 (HVR-H1), the amino acid sequence of SEQ ID NO: 73 (HVR-H2), and the amino acid sequence of SEQ ID NO: 74 (HVR-H3), and an antibody light chain comprising as HVRs the amino acid sequence of SEQ ID NO: 75 (HVR-L1), the amino acid sequence of SEQ ID NO: 76 (HVR-L2), and the amino acid sequence of SEQ ID NO: 77 (HVR-L3), or

d) an antibody heavy chain comprising as HVRs the amino acid sequence of SEQ ID NO: 80 (HVR-H1), the amino acid sequence of SEQ ID NO: 81 (HVR-H2), and the amino acid sequence of SEQ ID NO: 82 (HVR-H3), and an antibody light chain comprising as HVRs the amino acid sequence of SEQ ID NO: 83 (HVR-L1), the amino acid sequence of SEQ ID NO: 84 (HVR-L2), and the amino acid sequence of SEQ ID NO: 85 (HVR-L3), or

e) an antibody heavy chain comprising as HVRs the amino acid sequence of SEQ ID NO: 88 (HVR-H1), the amino acid sequence of SEQ ID NO: 89 (HVR-H2), and the amino acid sequence of SEQ ID NO: 90 (HVR-H3), and an antibody light chain comprising as HVRs the amino acid sequence of SEQ ID NO: 91 (HVR-L1), the amino acid sequence of SEQ ID NO: 92 (HVR-L2), and the amino acid sequence of SEQ ID NO: 93 (HVR-L3), or

f) an antibody heavy chain comprising as HVRs amino acid residues 31-35 (HVR-H1), amino acid residues 50-66 (HVR-H2) and amino acid residues 99-107 (HVR-H3) of SEQ ID NO: 02, and an antibody light chain comprising as HVRs amino acid residues 24-34 (HVR-L1), amino acid residues 50-56 (HVR-L2) and amino acid residues 89-98 (HVR-L3) of SEQ ID NO: 04, or

g) an antibody heavy chain comprising as HVRs amino acid residues 31-35 (HVR-H1), amino acid residues 50-66 (HVR-H2) and amino acid residues 99-107 (HVR-H3) of SEQ ID NO: 01 and an antibody light chain comprising as HVRs amino acid residues 24-34 (HVR-L1), amino acid residues 50-56 (HVR-L2) and amino acid residues 89-98 (HVR-L3) of SEQ ID NO: 03.

3. The antibody according to claim 1 or 2, wherein the anti-IGF-1R antibody comprises

a) a heavy chain variable domain VH of SEQ ID NO: 62 and a light chain variable domain VL of SEQ ID NO: 63, or

b) a heavy chain variable domain VH of SEQ ID NO: 70 and a light chain variable domain VL of SEQ ID NO: 71, or

c) a heavy chain variable domain VH of SEQ ID NO: 78 and a light chain variable domain VL of SEQ ID NO: 79, or

d) a heavy chain variable domain VH of SEQ ID NO: 86 and a light chain variable domain VL of SEQ ID NO: 87, or

e) a heavy chain variable domain VH of SEQ ID NO: 94 and a light chain variable domain VL of SEQ ID NO: 95, or

f) a heavy chain variable domain VH of SEQ ID NO: 05 and a light chain variable domain VL of SEQ ID NO: 07, or

g) a heavy chain variable domain VH of SEQ ID NO: 06 and a light chain variable domain of SEQ ID NO: 08.

4. The antibody according to any one of claims 1 to 3, wherein

i) the first Fc-region polypeptide is selected from the group comprising human IgG1 Fc-region polypeptide, human IgG2 Fc-region polypeptide, human IgG3 Fc-region polypeptide, human IgG4 Fc-region polypeptide, human IgG1 Fc-region polypeptide with the mutations L234A, L235A, human IgG1 Fc-region polypeptide with the mutations Y349C, T366S, L368A, Y407V, human IgG1 Fc-region polypeptide with the mutations L234A, L235A, Y349C, T366S, L368A, Y407V, human IgG1 Fc-region polypeptide with the mutations P329G, human IgG1 Fc-region polypeptide with the mutations L234A, L235A, P329G, human IgG1 Fc-region polypeptide with the mutations P329G, Y349C, T366S, L368A, Y407V, human IgG1 Fc-region polypeptide with the mutations L234A, L235A, P329G, Y349C, T366S, L368A, Y407V, human IgG4 Fc-region polypeptide with the mutations S228P, L235E, human IgG4 Fc-region polypeptide with the mutations S228P, L235E, P329G, human IgG4 Fc-region polypeptide with the mutations Y349C, T366S, L368A, Y407V, human IgG4 Fc-region polypeptide with the mutations S228P, L235E, Y349C, T366S, L368A, Y407V, human IgG4 Fc-region polypeptide with the mutations P329G, human IgG4 Fc-region polypeptide with the mutations P329G,

Y349C, T366S, L368A, Y407V, and human IgG4 Fc-region polypeptide with the mutations S228P, L235E, P329G, Y349C, T366S, L368A, Y407V, and

ii) the second Fc-region polypeptide is selected from the group comprising human IgG1 Fc-region polypeptide, human IgG2 Fc-region polypeptide, human IgG3 Fc-region polypeptide, human IgG4 Fc-region polypeptide, human IgG1 Fc-region polypeptide with the mutations L234A, L235A, human IgG1 Fc-region polypeptide with the mutations S354C, T366W, human IgG1 Fc-region polypeptide with the mutations L234A, L235A, S354C, T366W, human IgG1 Fc-region polypeptide with the mutations P329G, human IgG1 Fc-region polypeptide with the mutations L234A, L235A, P329G, human IgG1 Fc-region polypeptide with the mutations P329G, S354C, T366W, human IgG1 Fc-region polypeptide with the mutations L234A, L235A, P329G, S354C, T366W, human IgG4 Fc-region polypeptide with the mutations S228P, L235E, human IgG4 Fc-region polypeptide with the mutations S228P, L235E, P329G, human IgG4 Fc-region polypeptide with the mutations S354C, T366W, human IgG4 Fc-region polypeptide with the mutations S228P, L235E, S354C, T366W, human IgG4 Fc-region polypeptide with the mutations P329G, human IgG4 Fc-region polypeptide with the mutations P329G, S354C, T366W, and human IgG4 Fc-region polypeptide with the mutations S228P, L235E, P329G, S354C, T366W.

5. The antibody according to any one of claims 1 to 4, wherein

i) the first Fc-region polypeptide has an amino acid sequence selected from the group comprising SEQ ID NO: 14, 15, 16, 17, 18, 19, 21, 23, 24, 25, 27, 29, 30, 32, 34, 35, 36, and 38, and

ii) the second Fc-region polypeptide has an amino acid sequence selected from the group comprising SEQ ID NO: 14, 15, 16, 17, 18, 20, 22, 23, 24, 26, 28, 29, 30, 31, 33, 35, 37, and 39.

6. The antibody according to any one of claims 1 to 4, wherein

i) the Fc-region polypeptide is a human IgG1 Fc-region polypeptide and the second Fc-region polypeptide is a human IgG1 Fc-region polypeptide, or

ii) the first Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A and the second Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, or

iii) the first Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, P329G and the second Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, P329G, or

iv) the first Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, S354C, T366W and the second Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, Y349C, T366S, L368A, Y407V, or

v) the first Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, P329G, S354C, T366W and the second Fc-region polypeptide is a human IgG1 Fc-region polypeptide with the mutations L234A, L235A, P329G, Y349C, T366S, L368A, Y407V, or

vi) the first Fc-region polypeptide is a human IgG4 Fc-region polypeptide and the second Fc-region polypeptide is a human IgG4 Fc-region polypeptide, or

vii) the first Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E and the second Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, or

viii) the first Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, P329G and the second Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, P329G, or

ix) the first Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, S354C, T366W and the second Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, Y349C, T366S, L368A, Y407V, or

x) the first Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, P329G, S354C, T366W and the second Fc-region polypeptide is a human IgG4 Fc-region polypeptide with the mutations S228P, L235E, P329G, Y349C, T366S, L368A, Y407V.

7. The antibody according to any one of claims 1 to 6, wherein

i) the first Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 14 and the second Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 14, or

ii) the first Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 18 and the second Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 18, or

iii) the first Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 24 and the second Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 24, or

iv) the first Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 22 and the second Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 21, or

v) the first Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 28 and the second Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 27, or

vi) the first Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 17 and the second Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 17, or

vii) the first Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 29 and the second Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 29, or

viii) the first Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 30 and the second Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 30, or

ix) the first Fc-region polypeptide is has the amino acid sequence of SEQ ID NO: 33 and the second Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 34, or

x) the first Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 39 and the second Fc-region polypeptide has the amino acid sequence of SEQ ID NO: 38.

8. An anti-IGF-1R antibody according to any one of claims 1 to 7 for use in inhibiting IGF-1R in the eye.

9. An anti-IGF-1R antibody according to any one of claims 1 to 7 for intravitreal application.

10. An anti-IGF-1R antibody according to any one of claims 1 to 7 for the treatment of vascular eye diseases.

11. A pharmaceutical formulation comprising an anti-IGF-1R antibody according to any one of claims 1 to 7 and optionally a pharmaceutically acceptable carrier.

12. An anti-IGF-1R antibody according to any one of claims 1 to 7 for use as a medicament.

13. An anti-IGF-1R antibody according to any one of claims 1 to 7 for use in treating vascular eye diseases.

14. An anti-IGF-1R antibody according to any one of claims 1 to 7 for use in a method of treatment.

15. An anti-IGF-1R antibody according to any one of claims 1 to 7 for use in a method of treating an individual having a vascular eye disease comprising

administering to the individual an effective amount of the anti-IGF-1R antibody according to any one of claims 1 to 7.

16. The antibody according to claim 15, wherein the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent.

17. An anti-IGF-1R antibody according to any one of claims 1 to 7 for use in a method of inhibiting angiogenesis in an individual comprising administering to the individual an effective of the anti-IGF-1R antibody according to any one of claims 1 to 7 to inhibit IGF-1R signaling.

18. Use of an anti-IGF-1R antibody according to any one of claims 1 to 7 in the manufacture of a medicament.

19. The use according to claim 18, wherein the medicament is for treatment of a vascular eye disease.

20. The use according to any one of claims 18 to 19, wherein the medicament is for use in a method of treating a vascular eye disease comprising administering to an individual having a vascular eye disease an effective amount of the medicament.

21. The use according to claim 20, wherein the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent.

22. The use according to any one of claims 18 to 21, wherein the medicament is for inhibiting angiogenesis.

23. The use according to any one of claims 18 to 22, wherein the medicament is for use in a method of inhibiting angiogenesis in an individual comprising administering to the individual an amount of the medicament effective to inhibit IGF-1R mediated signaling.

24. A pharmaceutical formulations comprising an anti-IGF-1R antibody according to any one of claims 1 to 7.