

L48R, L48K, L50D, L50R, L50F, L50Y, L73R, L112E, L112D, L112F, L113D, L113R, L113F, L48H, L48Y, L50Q, L50W, L51Q, L70F, L72D, L72E, L72R, L72Y, L73N, L73Y, L75Q, L112H, L112Q, L112Y, L113S, L116H, L116Y, L51Y, L72F, L73Q, and L74H.

[0062]

In a further embodiment, the anti-hGDF15 antibody of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8 or an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 8 by having amino acid substitution selected from H49R, H49D, H48S, H71Y, H83R, and H120F, and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 9 by having amino acid substitution selected from L48K, L112D, L72F, and L74H.

[0063]

In the above embodiments, the amino acid substitution is indicated by an abbreviation representing heavy (H) or light (L) chain, the number representing its position, and an abbreviation representing the amino acid residue after substitution. For example, "H48R" means substitution to an arginine residue at position 48 of the heavy chain.

[0064]

In a further embodiment, the anti-hGDF15 antibody of the present disclosure comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9.

[0065]

In a further embodiment, the anti-hGDF15 antibody of the present disclosure comprises a heavy chain variable region comprising an amino acid

Claims

1. An anti-hGDF15 antibody, comprising
- 5 (i) a heavy chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID
NOS: 18, 38-44, and 149-150,
CDR2 comprising the amino acid sequence of SEQ ID NO: 19,
and
10 CDR3 comprising the amino acid sequence of SEQ ID NO: 20,
and
a light chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 21,
CDR2 comprising the amino acid sequence of SEQ ID NO: 22,
15 and
CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
- (ii) a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
CDR2 comprising an amino acid sequence selected from SEQ ID
20 NOS: 19, 45-48, 52-66, and 151-153, and
CDR3 comprising the amino acid sequence of SEQ ID NO: 20,
and
a light chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 21,
25 CDR2 comprising the amino acid sequence of SEQ ID NO: 22,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
- (iii) a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
30 CDR2 comprising the amino acid sequence of SEQ ID NO: 19,
and
CDR3 comprising an amino acid sequence selected from SEQ ID
NOS: 20, 49, 50 and 67-80, and

- a light chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 21,
CDR2 comprising the amino acid sequence of SEQ ID NO: 22,
and
5 CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
(iv) a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
CDR2 comprising the amino acid sequence of SEQ ID NO: 19,
and
10 CDR3 comprising the amino acid sequence of SEQ ID NO: 20;
and
a light chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID
NOS: 21, 81-89, 100-104, and 154,
15 CDR2 comprising the amino acid sequence of SEQ ID NO: 22,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
(v) a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
20 CDR2 comprising the amino acid sequence of SEQ ID NO: 19,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 20;
and
a light chain variable region that contains
25 CDR1 comprising the amino acid sequence of SEQ ID NO: 21,
CDR2 comprising an amino acid sequence selected from SEQ ID
NOS: 22, 90, 106-115, and 155-157, and
CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
or
30 (vi) a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
CDR2 comprising the amino acid sequence of SEQ ID NO: 19,
and

CDR3 comprising the amino acid sequence of SEQ ID NO: 20;
and

a light chain variable region that contains

CDR1 comprising the amino acid sequence of SEQ ID NO: 21,

5 CDR2 comprising the amino acid sequence of SEQ ID NO: 22,
and

CDR3 comprising an amino acid sequence selected from SEQ ID
NOS: 23, 91-99, and 118-132.

10 2. The antibody of claim 1, wherein the antibody
comprises

a heavy chain variable region that contains

CDR1 comprising the amino acid sequence of SEQ ID
NO: 18,

15 CDR2 comprising the amino acid sequence of SEQ ID
NO: 19, and

CDR3 comprising the amino acid sequence of SEQ ID
NO: 20, and

a light chain variable region that contains

20 CDR1 comprising the amino acid sequence of SEQ ID
NO: 21,

CDR2 comprising the amino acid sequence of SEQ ID
NO: 22, and

25 CDR3 comprising the amino acid sequence of SEQ ID
NO: 23.

3. An anti-hGDF15 antibody, comprising

(1) a heavy chain variable region that contains

CDR1 comprising an amino acid sequence selected from SEQ ID
30 NOS: 38 and 39,

CDR2 comprising the amino acid sequence of SEQ ID NO: 19,
and

- CDR3 comprising the amino acid sequence of SEQ ID NO: 20;
and
a light chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID
5 NO: 85,
CDR2 comprising the amino acid sequence of SEQ ID NO: 22,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
(2) a heavy chain variable region that contains
10 CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
CDR2 comprising an amino acid sequence selected from SEQ ID
NOS: 52 and 66, and
CDR3 comprising the amino acid sequence of SEQ ID NO: 20;
and
15 a light chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID
NO: 85,
CDR2 comprising the amino acid sequence of SEQ ID NO: 22,
and
20 CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
(3) a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
CDR2 comprising an amino acid sequence selected from SEQ ID
NO: 19, and
25 CDR3 comprising the amino acid sequence of SEQ ID NO: 77;
and
a light chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID
NO: 85,
30 CDR2 comprising the amino acid sequence of SEQ ID NO: 22,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
(4) a heavy chain variable region that contains

- CDR1 comprising an amino acid sequence selected from SEQ ID NOS: 38 and 39,
CDR2 comprising the amino acid sequence of SEQ ID NO: 19,
and
5 CDR3 comprising the amino acid sequence of SEQ ID NO: 20;
and
a light chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID NO: 21,
10 CDR2 comprising the amino acid sequence of SEQ ID NO: 22,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 95;
(5) a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
15 CDR2 comprising an amino acid sequence selected from SEQ ID NOS: 52 and 66, and
CDR3 comprising the amino acid sequence of SEQ ID NO: 20;
and
a light chain variable region that contains
20 CDR1 comprising an amino acid sequence selected from SEQ ID NO: 21,
CDR2 comprising the amino acid sequence of SEQ ID NO: 22,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 95;
25 (6) a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
CDR2 comprising an amino acid sequence selected from SEQ ID NO: 19, and
CDR3 comprising the amino acid sequence of SEQ ID NO: 77;
30 and
a light chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID NO: 21,

CDR2 comprising the amino acid sequence of SEQ ID NO: 22,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 95;
(7) a heavy chain variable region that contains

5 CDR1 comprising an amino acid sequence selected from SEQ ID
NOS: 38 and 39,
CDR2 comprising the amino acid sequence of SEQ ID NO: 19,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 20;
10 and
a light chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID
NO: 21,
CDR2 comprising the amino acid sequence of SEQ ID NO: 155
15 and
CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
(8) a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
CDR2 comprising an amino acid sequence selected from SEQ ID
20 NOS: 52, 66, and 152, and
CDR3 comprising the amino acid sequence of SEQ ID NO: 20;
and
a light chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID
25 NO: 21,
CDR2 comprising the amino acid sequence of SEQ ID NO: 155,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
(9) a heavy chain variable region that contains
30 CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
CDR2 comprising an amino acid sequence selected from SEQ ID
NO: 19, and

CDR3 comprising the amino acid sequence of SEQ ID NO: 77;
and
a light chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID
5 NO: 21,
CDR2 comprising the amino acid sequence of SEQ ID NO: 155,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
(10) a heavy chain variable region that contains
10 CDR1 comprising an amino acid sequence selected from SEQ ID
NOS: 38 and 39,
CDR2 comprising the amino acid sequence of SEQ ID NO: 19,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 20;
15 and
a light chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID
NO: 21,
CDR2 comprising the amino acid sequence of SEQ ID NO: 157
20 and
CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
(11) a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
CDR2 comprising an amino acid sequence selected from SEQ ID
25 NOS: 52, 66 and 152, and
CDR3 comprising the amino acid sequence of SEQ ID NO: 20;
and
a light chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID
30 NO: 21,
CDR2 comprising the amino acid sequence of SEQ ID NO: 157,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 23;

- (12) a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
CDR2 comprising an amino acid sequence selected from SEQ ID
NO: 19, and
5 CDR3 comprising the amino acid sequence of SEQ ID NO: 77;
and
a light chain variable region that contains
CDR1 comprising an amino acid sequence selected from SEQ ID
NO: 21,
10 CDR2 comprising the amino acid sequence of SEQ ID NO: 157,
and
CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
4. An anti-hGDF15 antibody, comprising
15 a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID
NO: 137,
CDR2 comprising the amino acid sequence of SEQ ID
NO: 138, and
20 CDR3 comprising the amino acid sequence of SEQ ID
NO: 139, and
a light chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID
NO: 140,
25 CDR2 comprising the amino acid sequence of SEQ ID
NO: 141, and
CDR3 comprising the amino acid sequence of SEQ ID
NO: 142.
- 30 5. An anti-hGDF15 antibody, comprising
a heavy chain variable region that contains
CDR1 comprising the amino acid sequence of SEQ ID
NO: 143,

CDR2 comprising the amino acid sequence of SEQ ID NO: 144, and

CDR3 comprising the amino acid sequence of SEQ ID NO: 145, and

5 a light chain variable region that contains

CDR1 comprising the amino acid sequence of SEQ ID NO: 146,

CDR2 comprising the amino acid sequence of SEQ ID NO: 147, and

10 CDR3 comprising the amino acid sequence of SEQ ID NO: 148.

6. The antibody of any one of claims 1-3, wherein the antibody comprises

15 a heavy chain variable region that contains

FR1 comprising the amino acid sequence of SEQ ID NO: 37, or FR1 comprising the amino acid sequence of SEQ ID NO: 51; or a light chain variable region that contains

FR2 comprising the amino acid sequence of SEQ ID NO: 105,

20 FR3 comprising the amino acid sequence of SEQ ID NO: 116, or

FR3 comprising the amino acid sequence of SEQ ID NO: 117.

7. The antibody of any one of claims 1 to 3 and 6, 25 wherein the antibody comprises

a heavy chain variable region comprising an amino acid sequence having 90% or more sequence identity to the amino acid sequence of SEQ ID NO: 8, or the amino acid sequence of SEQ ID NO: 8 or an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 8 by having amino acid modification of 1 to 20 amino acid residues; and

30

a light chain variable region comprising an amino acid sequence having 90% or more sequence identity to the amino

acid sequence of SEQ ID NO: 9, or the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 9 by having amino acid modification of 1 to 20 amino acid residues.

5

8. The antibody of claim 7, wherein the antibody comprises

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8 or an amino acid sequence that
10 differs from the amino acid sequence of SEQ ID NO: 8 by having amino acid substitution selected from 48R and 48S, and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence that
15 differs from the amino acid sequence of SEQ ID NO: 9 by having amino acid substitution selected from 69Y, 87K, and 87N.

9. The antibody of claim 7 or 8, wherein the
20 antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 8 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 9.

25 10. A polynucleotide encoding the antibody of any one of claims 1 to 9.

11. An expression vector comprising the polynucleotide of claim 10.

30

12. A transformed cell comprising the polynucleotide of claim 10.

13. A pharmaceutical composition comprising the antibody of any one of claims 1 to 9.

14. The antibody of any one of claims 1 to 9, for use
5 in therapy.

15. The antibody of any one of claims 1 to 9, for use in treating a disease or symptom associated with GDF15, wherein the disease or symptom associated with GDF15 is
10 cancer or cachexia.

16. The antibody for use of claim 15, wherein the disease or symptom associated with GDF15 is cancer.

15 17. The antibody for use of claim 15, wherein the disease or symptom associated with GDF15 is cachexia.

18. The antibody for use of claim 17, wherein the cachexia is cancer cachexia.
20

19. Use of the antibody of any one of claims 1 to 9 in the manufacture of a medicament for treating a disease or symptom associated with GDF15, wherein the disease or symptom associated with GDF15 is cancer or cachexia.
25

20. The use of claim 19, wherein the disease or symptom associated with GDF15 is cancer.

21. The use of claim 19, wherein the disease or
30 symptom associated with GDF15 is cachexia.

22. The use of claim 21, wherein the cachexia is cancer cachexia.