

CLAIMS

1. An antibody or antigen-binding fragment thereof that binds human GDNF Family Receptor Alpha-like protein (GFRAL), which comprises:
 - (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO:46, a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:137, and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 225; and
 - (b) a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 301, a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 376, and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 426.
2. The antibody or antigen-binding fragment thereof of claim 1, wherein
 - (a) the heavy chain variable region is at least 90% identical to the amino acid sequence set forth in SEQ ID NO:3;
 - (b) the light chain variable region that is at least 90% identical to the amino acid sequence set forth in SEQ ID NO:4; or
 - (c) the heavy chain variable region is at least 90% identical to the amino acid sequence set forth in SEQ ID NO:3 and the light chain variable region is at least 90% identical to the amino acid sequence set forth in SEQ ID NO:4.
3. The antibody or antigen-binding fragment thereof of claim 1, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:3 and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:4.
4. The antibody or antigen-binding fragment thereof of claim 1, wherein
 - (a) the heavy chain variable region is at least 90% identical to the amino acid sequence set forth in SEQ ID NO:1982;
 - (b) the light chain variable region is at least 90% identical to the amino acid sequence set forth in SEQ ID NO:1997; or

- (c) the heavy chain variable region is at least 90% identical to the amino acid sequence set forth in SEQ ID NO:1982 and the light chain variable region is at least 90% identical to the amino acid sequence set forth in SEQ ID NO:1997.
- 5. The antibody or antigen-binding fragment thereof of claim 1, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:1982.
 - 6. The antibody or antigen-binding fragment thereof of claim 1, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:1997.
 - 7. The antibody or antigen-binding fragment thereof of claim 1, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:1982 and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:1997.
 - 8. An antibody or antigen-binding fragment thereof that binds human GFRAL, which comprises:
 - (a) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO:56, a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:147, and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO:233, and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 309, a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:382, and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO:432;
 - (b) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO:86, a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:177, and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO:261, and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO:337, a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:401, and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO:453;

- (c) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 91, a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:182, and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO:265, and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO:341, a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:385, and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO:456;
- (d) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 95, a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:187, and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO:269, and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO:345, a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:404, and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO:459;
- (e) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 124, a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:210, and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO:289, and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO:365, a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:418, and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO:474; or
- (f) a heavy chain variable region comprising a heavy chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a heavy chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:215, and a heavy chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO:293, and a light chain variable region comprising a light chain variable region CDR1 comprising the amino acid sequence set forth in SEQ ID NO:369, a light chain variable region CDR2 comprising the amino acid sequence set forth in SEQ ID NO:421,

and a light chain variable region CDR3 comprising the amino acid sequence set forth in SEQ ID NO:477.

9. The antibody or antigen-binding fragment thereof of any one of claims 1 to 8, which binds within domain 3 of human GFRAL.
10. The antibody or antigen-binding fragment thereof of any one of claims 1 to 8, which binds within amino acid residues 220-316 of SEQ ID NO:1797.
11. An antibody or antigen-binding fragment thereof of any one of claims 1 to 7, which-binds to one or more residues selected from the group consisting of: Met214, Pro216, Pro217, Gln290, Cys291, Thr292, Cys293, Arg294, Thr295, Ile296, Thr297, Gln298, Ser299, Glu301, Lys305, Gln308, His309, His312, and Ser315 of SEQ ID NO: 1797.
12. The antibody or antigen-binding fragment thereof of claim 11, which binds to at least Thr297, Gln298, and Ser299 of SEQ ID NO:1797.
13. The antibody or antigen-binding fragment thereof of any one of claims 1 to 12, which inhibits binding of GFRAL to RET.
14. The antibody or antigen-binding fragment thereof of any one of claims 1 to 13, which does not inhibit binding of GFRAL to GDF15.
15. The antibody or antigen-binding fragment thereof of any one of claims 1 or 4 to 8, which is a humanized antibody.
16. The antibody or antigen-binding fragment thereof of any one of claims 1 to 15, which is a chimeric antibody or a bispecific antibody.
17. The antibody or antigen-binding fragment thereof of any one of claims 1 to 16, which is a monoclonal antibody.
18. The antibody or antigen-binding fragment thereof of claim 17, which is an IgG1 antibody, an IgG2 antibody, or an IgG4 antibody.

19. The antibody or antigen-binding fragment thereof of claim 17, which is an IgG1 antibody.
20. The antibody or antigen-binding fragment thereof of claim 18 or claim 19, which comprises a kappa light chain.
21. The antibody or antigen-binding fragment thereof of any one of claims 1 to 17, wherein the antigen-binding fragment is an Fab, Fab', F(ab')₂, Fv, scFv, (scFv)₂, single chain antibody molecule, or dual variable region antibody.
22. The antibody or antigen-binding fragment thereof of any one of claims 1 to 21, which is conjugated or recombinantly fused to a diagnostic agent or a detectable agent.
23. An isolated polynucleotide encoding the antibody or antigen-binding fragment thereof of any one of claims 1 to 21.
24. A vector comprising the polynucleotide of claim 23.
25. A host cell comprising the polynucleotide of claim 23.
26. A host cell comprising the vector of claim 24.
27. A host cell that produces the antibody or antigen-binding fragment thereof of any one of claims 1 to 21.
28. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1 to 21 and a pharmaceutically acceptable carrier.
29. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 21 in the manufacture of a medicament for treating involuntary body weight loss in a human subject, wherein the human subject: (i) has cachexia, (ii) has cancer, (iii) is undergoing treatment for cancer, and/or (iv) has anorexia nervosa.

30. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 21 in the manufacture of a medicament for preventing involuntary body weight loss in a human subject, wherein the human subject: (i) has cachexia, (ii) has cancer, (iii) is undergoing treatment for cancer, and/or (iv) has anorexia nervosa.
31. Use of the antibody or antigen-binding fragment thereof of any one of claims 1 to 21 in the manufacture of a medicament for treating anorexia nervosa in a human subject.
32. The use of any one of claims 29 to 31, wherein the subject has an elevated level of GDF15.
33. The use of any one of claims 29 to 32, which comprises combination therapy with one or more additional therapeutic agents.