

What is claimed:

1. An isolated antibody or antigen-binding fragment thereof that binds human leptin receptor (LEPR) and activates LEPR signaling, which competes for binding to LEPR with a reference antibody or antigen-binding fragment thereof that comprises:
 - (i) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO:2; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (ii) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO:18; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (iii) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 26; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (iv) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 34; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (v) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 42; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (vi) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 50; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (vii) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 58; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region

that comprises the amino acid sequence set forth in SEQ ID NO: 10;

(viii) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 66; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;

(ix) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 74; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;

(x) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 82; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90;

(xi) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 98; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90; and/or

(xii) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 106; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90.

2. An isolated antibody or antigen-binding fragment thereof that binds to the same epitope of leptin receptor (LEPR) as a reference antibody or antigen-binding fragment thereof that comprises:

- (i) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO:2; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
- (ii) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain

that comprises the amino acid sequence set forth in SEQ ID NO: 10;

(x) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 82; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90;

(xi) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 98; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90; and/or

(xii) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 106; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90;

and activates LEPR signaling.

3. The isolated antibody or antigen-binding fragment thereof of claim 1 or 2, wherein the reference antibody or antigen-binding fragment comprises:

a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 26; and

a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10.

4. An isolated antibody or antigen-binding fragment thereof that binds human leptin receptor (LEPR), wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain variable region comprising the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:18, SEQ ID NO: 26, SEQ ID NO: 34, SEQ ID NO: 42, SEQ ID NO: 50, SEQ ID NO: 58, SEQ ID NO: 66, SEQ ID NO: 74, SEQ ID NO: 82, SEQ ID NO: 98 or SEQ ID NO: 106; and

(b) a light chain variable region comprising the LCDR1, LCDR2 and LCDR3 of a light chain

variable region comprising the amino acid sequence of SEQ ID NO:10 or SEQ ID NO: 90.

5. The antibody or antigen-binding fragment thereof of claim 4 comprising:

(i) a heavy chain variable region that comprises an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO:6, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO:8; and a light chain variable region comprising a LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence set forth in SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:16;

(ii) a heavy chain variable region that comprises an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 20, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO:22, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO:24; and a light chain variable region comprising a LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence set forth in SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:16;

(iii) a heavy chain variable region that comprises an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 28, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO:30, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO:32; and a light chain variable region comprising a LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence set forth in SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:16;

(iv) a heavy chain variable region that comprises an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 36, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO:38, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO:40; and a light chain variable region comprising a LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence set forth in SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:16;

(v) a heavy chain variable region that comprises an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 44, an HCDR2 comprising the amino acid sequence set forth in

SEQ ID NO:46, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO:48; and a light chain variable region comprising a LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence set forth in SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:16;

(vi) a heavy chain variable region that comprises an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 52, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO:54, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO:56; and a light chain variable region comprising a LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence set forth in SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:16;

(vii) a heavy chain variable region that comprises an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 60, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO:62, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO:64; and a light chain variable region comprising a LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence set forth in SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:16;

(viii) a heavy chain variable region that comprises an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 68, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO:70, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO:72; and a light chain variable region comprising a LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence set forth in SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:16;

(ix) a heavy chain variable region that comprises an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 76, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO:78, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO:80; and a light chain variable region comprising a LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence set forth in SEQ ID NO:14, and an LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:16;

(x) a heavy chain variable region that comprises an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 84, an HCDR2 comprising the amino acid sequence set forth in

SEQ ID NO:86, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO:88; and a light chain variable region comprising a LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 92, an LCDR2 comprising the amino acid sequence set forth in SEQ ID NO:94, and an LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:96;

(xi) a heavy chain variable region that comprises an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 100, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO:102, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO:104; and a light chain variable region comprising a LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 92, an LCDR2 comprising the amino acid sequence set forth in SEQ ID NO:94, and an LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:96; and/or

(xii) a heavy chain variable region that comprises an HCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 108, an HCDR2 comprising the amino acid sequence set forth in SEQ ID NO:110, and an HCDR3 comprising the amino acid sequence set forth in SEQ ID NO:112; and a light chain variable region comprising a LCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 92, an LCDR2 comprising the amino acid sequence set forth in SEQ ID NO:94, and an LCDR3 comprising the amino acid sequence set forth in SEQ ID NO:96.

6. The isolated antibody or antigen-binding fragment thereof of claim 4, comprising:

(i) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO:2; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;

(ii) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO:18; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;

(iii) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 26; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;

chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90; and/or

(xii) a heavy chain variable region that comprises the HCDR1, HCDR2 and HCDR3 of a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 106; and a light chain variable region that comprises the LCDR1, LCDR2 and LCDR3 of a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90.

7. The isolated antibody or antigen-binding fragment thereof of claim 5 or 6 comprising:
- (i) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO:2; and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (ii) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO:18; and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (iii) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 26; and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (iv) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 34; and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (v) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 42; and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (vi) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 50; and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (vii) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 58; and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;
 - (viii) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO:

66; and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;

(ix) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 74; and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 10;

(x) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 82; and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90;

(xi) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 98; and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90; and/or

(xii) a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 106; and a light chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 90.

8. The isolated antibody or antigen-binding fragment thereof of claim 7 which is a full antibody comprising two heavy chains and two light chains inter-connected by disulfide bonds wherein:

the heavy chains comprise heavy chain variable regions that comprise the amino acid sequence set forth in SEQ ID NO: 26; and

the light chains comprise light chain variable regions that comprise the amino acid sequence set forth in SEQ ID NO: 10.

9. The antibody of claim 8 wherein the heavy chains comprise an IgG4 heavy chain constant region.

10. The antibody of claim 8 which is bispecific.

11. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1 to 10, and a pharmaceutically acceptable carrier or diluent.

12. Use of the pharmaceutical composition of claim 11 and a pharmaceutically acceptable carrier or diluent thereof in the manufacture of a medicament for treating leptin deficiency or leptin resistance in a subject in need thereof.

13. Use of the pharmaceutical composition of claim 11 and a pharmaceutically acceptable carrier or diluent thereof in the manufacture of a medicament for treating lipodystrophy, obesity, metabolic syndrome, diet-induced food craving, functional hypothalamic amenorrhea, type 1 diabetes, type 2 diabetes, insulin resistance, severe insulin resistance due to mutation in insulin receptor, Alzheimer's disease, leptin deficiency, leptin resistance, Leprechaunism/Donohue syndrome, ~~and~~ or Rabson-Mendenhall syndrome in a subject in need thereof.

14. Use of the pharmaceutical composition of claim 11 and a pharmaceutically acceptable carrier or diluent thereof in the manufacture of a medicament for treating congenital generalized lipodystrophy, acquired generalized lipodystrophy, familial partial lipodystrophy, acquired partial lipodystrophy, centrifugal abdominal lipodystrophy, lipoatrophia annularis, localized lipodystrophy, ~~and~~ or HIV-associated lipodystrophy, in a subject in need thereof.

15. Use of the pharmaceutical composition of claim 11 and a pharmaceutically acceptable carrier or diluent thereof in the manufacture of a medicament for restoring leptin signaling in a subject having a signaling-defective or signaling-impaired LEPR mutation.

16. The use of claim 15, wherein the signaling-defective or signaling-impaired LEPR mutation is LEPR-A409E or LEPR-P316T.

17. The use of claim 15 or 16, wherein the subject suffers from early-onset obesity.

18. The use according to any one of claims 12 through 17, wherein the medicament further comprising a second therapeutic agent to the subject, wherein the second therapeutic agent is selected from the group consisting of a recombinant human leptin, a PCSK9 inhibitor, a

statin, ezetimibe, insulin, an insulin variant, an insulin secretagogue, metformin, a sulfonylurea, a sodium glucose cotransporter 2 (SGLT2) Inhibitor, a GLP-1 agonist/analogue, a glucagon (GCG) inhibitor, a glucagon receptor (GCGR) inhibitor, an angiopoietin-like protein (ANGPTL) inhibitor, Phentermine, Orlistat, Topiramate, Bupropion, Topiramate/Phentermine, Bupropion/Naltrexone, Bupropion/Zonisamide, Pramlintide/Metrelepin, Lorcaserin, Cetilistat, Tesofensine, and Velneperit.

19. A pen delivery device comprising the pharmaceutical composition of claim 11.

20. An autoinjector comprising the pharmaceutical composition of claim 11.

21. A nucleic acid encoding a heavy chain variable region that comprises the amino acid sequence set forth in SEQ ID NO: 26; and/or a light chain variable regions that comprises the amino acid sequence set forth in SEQ ID NO: 10.

22. A vector comprising the nucleic acid of claim 21.

23. A host cell comprising the nucleic acid of claim 21.

24. A method for making an antibody or antigen-binding fragment comprising culturing a host cell comprising the nucleic acid of claim 21 under conditions permitting production of the antibody or fragment, and recovering the antibody or fragment so produced.