

Claims

1. An isolated antibody or antigen-binding fragment thereof that binds human cannabinoid type 1 receptor (CB1) (e.g. SEQ ID NO:1), comprising six complementarity determining

regions (CDRs): CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3, wherein
CDR-H1 has an amino acid sequence S-Y-T-F-T-R-Y-W (SEQ ID NO: 116);
CDR-H2 has an amino acid sequence I-D-P-Y-D-S-E-T (SEQ ID NO: 117);
CDR-H3 has an amino acid sequence A-R-S-Q-P-R-Y-Y-A-M-D-Y (SEQ ID NO:
118);

CDR-L1 has an amino acid sequence Q-E-I-S-G-F (SEQ ID NO: 122);
CDR-L2 has an amino acid sequence: A-A-S (SEQ ID NO: 123); and
CDR-L3 has an amino acid sequence: L-Q-Y-S-S-Y-P-Y-T (SEQ ID NO: 124); or

CDR-H1 has an amino acid sequence G-Y-E-F-S-Y-Y-W (SEQ ID NO: 308);
CDR-H2 has an amino acid sequence I-Y-P-G-D-G-D-T (SEQ ID NO: 309);
CDR-H3 has an amino acid sequence A-R-G-R-E-A-A-W-F-A-Y (SEQ ID NO: 310);
CDR-L1 has an amino acid sequence Q-S-V-S-S-F-R-Y-S-Y (SEQ ID NO: 314);
CDR-L2 has an amino acid sequence Y-A-S (SEQ ID NO: 315); and
CDR-L3 has an amino acid sequence Q-H-S-W-E-I-P-F-T (SEQ ID NO: 316).

2. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises the (HCDR set/LCDR set) pair selected from the group consisting of SEQ ID NOs: (116, 117, 118/ 122, 123, 124); (128, 129, 130/ 134, 135, 136); (140, 141, 142/ 146, 147, 148); (152, 153, 154/ 158, 159, 160); (164, 165, 166/ 170, 171, 172); (188, 189, 190/ 194, 195, 196); (200, 201, 202/ 206, 207, 208); (212, 213, 214/ 218, 219, 220); (224, 225, 226/ 230, 231, 232); (236, 237, 238/ 242, 243, 244); (248, 249, 250/ 254, 255, 256); (260, 261, 262/ 266, 267, 268); (272, 273, 274/ 278, 279, 280); (284, 285, 286/ 290, 291, 292); (296, 297, 298/ 302, 303, 304); (308, 309, 310/ 314, 315, 316); and (320, 321, 322/ 326, 327, 328).

3. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises the HC/LC pair selected from the group consisting of SEQ ID NOs: 113/119, 125/131, 137/143, 149/155, 161/167, 185/191, 197/203, 209/215, 221/227, 233/239, 245/251, 257/263, 269/275, 281/287, 293/299, 305/311,

and 317/323.

4. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises the heavy and light chain CDRs of a variable heavy (VH)/variable light (VL) pair selected from the group consisting of SEQ ID NOs: 114/120, 126/132, 138/144, 150/156, 162/168, 186/192, 198/204, 210/216, 222/228, 234/240, 246/252, 258/264, 270/276, 282/288, 294/300, 306/312, and 318/324.
5. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the fragment comprises a Fab fragment, a Fab' fragment, a F(ab)₂ fragment or a scFv fragment.
6. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-5, wherein the antibody or antigen-binding fragment thereof comprises a human Fc region selected from the group consisting of an IgG1, IgG2, IgG3, IgG4, IgA, IgD, IgE, and IgM Fc.
7. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-5, wherein the antibody or antigen-binding fragment thereof comprises a modified human Fc region.
8. The isolated antibody or antigen-binding fragment thereof of claim 7, wherein the modified human Fc region comprises a mutation selected from the group consisting of L234A/L235A, S228P, A330S, P331S, E233P/L234V/L235A, A327G/A330S/P331S, L234F/L235E/P331S, and N297Q.
9. A multispecific binding protein comprising an antigen-binding fragment of any one of claims 1-8.
10. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-8, wherein the antibody or antigen-binding fragment thereof is a humanized antibody.
11. An isolated nucleic acid molecule encoding an antibody or antigen-binding fragment thereof of any one of claims 1-8 and 10 or the multispecific binding protein of claim 9.

12. An expression vector comprising the nucleic acid molecule of claim 11.

13. An isolated host cell comprising the expression vector of claim 12.

5 14. A pharmaceutical composition comprising an isolated antibody or antigen-binding fragment thereof of any one of claims 1-8 and 10 or the multispecific binding protein of claim 9 and at least one pharmaceutically acceptable excipient.

10 15. Use of the isolated antibody or antigen-binding fragment thereof of any one of claims 1-8 and 10 or the multispecific binding protein of claim 9 in the preparation of a pharmaceutical composition for treating a disease or disorder selected from the group consisting of obesity, syndromic obesities including Prader-Willi syndrome (PWS), Alström syndrome, Bardet-Biedel syndrome (BBS), Albright Hereditary Osteodystrophy (AHO), and SIM1 deletion syndrome; diabetes and related complications; dyslipidemia; liver diseases such as, for
15 example, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease, and primary biliary cirrhosis; fibrosis, for example, kidney fibrosis; chronic kidney disease; diabetic neuropathy, focal segmental glomerulosclerosis, renal disease; metabolic diseases, osteoporosis, atherosclerosis, inflammatory disease, cardiovascular disease, cancer, pain, systemic sclerosis, multiple sclerosis spasticity, glaucoma, and nicotine addiction.

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16. An antibody conjugate comprising the isolated antibody or antigen-binding fragment thereof of any one of claims 1-8 and 10 or the multispecific binding protein of claim 9, wherein the antibody or antigen-binding fragment thereof is conjugated to an agent selected from the group consisting of a therapeutic agent, a cytotoxic agent, an immunoadhesion
25 molecule, and an imaging agent.