

We claim:

1. An isolated antibody or antigen-binding fragment thereof that binds specifically to tropomyosin receptor kinase B (TrkB), wherein the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 49, 59 and 68; and

three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 53, 63 and 72.

2. The isolated antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen-binding fragment thereof comprises the CDRs of a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 49/53, 59/63 and 68/72.

3. The isolated antibody or antigen-binding fragment thereof of any one of claims 1 and 2, comprising an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 49/53, 59/63 and 68/72.

4. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-3, comprising:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 50, 60 and 69;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 51, 61 and 70;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 52, 62 and 71;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 54, 64 and 73;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 55, 65 and 74; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 56, 66 and 75.

5. The isolated antibody or antigen-binding fragment of any one of claims 1-4, wherein the antibody or antigen-binding fragment thereof comprises a set of six CDRs (HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) selected from the group consisting of: (a) SEQ ID NOs: 4-6-8-12-14-16; (b) SEQ ID NOs: 20-22-24-28-30-32; (c) SEQ ID NOs: 36-38-40-44-46-48; (d) SEQ ID NOs: 50-51-52-54-55-56; (e) SEQ ID NOs: 60-61-62-64-65-66; and (f) SEQ ID NOs: 69-70-71-73-74-75.

6. The isolated antibody or antigen-binding fragment of any one of claims 1-5, wherein the antibody or antigen-binding fragment thereof binds human TrkB with a K_D of less than about 300nM as measured by surface plasmon resonance at 25°C or 37°C.

7. The isolated antibody or antigen-binding fragment of claim 6, wherein the antibody or antigen-binding fragment thereof binds human TrkB with a K_D selected from the group consisting of less than about 150 nM, less than about 50 pM, less than about 100 pM as measured by surface plasmon resonance at 25°C or 37°C.

8. The isolated antibody or antigen-binding fragment of any one of claims 1-5, wherein the antibody or antigen-binding fragment thereof binds human TrkB with a dissociative half life ($t_{1/2}$) selected from the group consisting of greater than about 10 minutes, greater than about 40 minutes, greater than about 120 minutes as measured by surface plasmon resonance at 25°C or 37°C.

9. The isolated antibody or antigen-binding fragment of any one of claims 1-5, wherein the antibody or antigen-binding fragment thereof activates human TrkB signaling in the absence of BDNF in cells engineered to express TrkB, with an EC_{50} of less than about 100 pM.

10. The isolated antibody or antigen-binding fragment of any one of claims 1-5, wherein the antibody or antigen-binding fragment thereof enhances activation of human TrkB signaling in the presence of BDNF in cells engineered to express TrkB, with an EC_{50} of less than about 100 pM.

11. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-5, which when injected into the hippocampus of humanized TrkB mice, demonstrates TrkB activation, as shown by an increase in TrkB phosphorylation.

12. The isolated antibody or antigen-binding fragment of any one of claims 1-5, wherein the antibody or antigen-binding fragment thereof demonstrates activation of the MAPK/ERK and PI3K/Akt signaling pathways, as demonstrated following incubation of primary mouse cortical neurons with an agonist anti-TrkB antibody.

13. The isolated antibody or antigen-binding fragment of any one of claims 1-12, wherein the antibody or antigen-binding fragment thereof enhances survival of retinal ganglion cells as shown in an optic nerve transection model in TrkB humanized rats.

14. The isolated antibody or antigen-binding fragment of any one of claims 1-12, wherein the antibody or antigen-binding fragment thereof promotes weight loss in humanized TrkB mice.

15. The isolated antibody or antigen-binding fragment of any one of claims 1-12, wherein the antibody or antigen-binding fragment thereof promotes a loss of fat mass in humanized TrkB mice.

16. The isolated antibody or antigen-binding fragment of any one of claims 1-12, wherein the antibody or antigen-binding fragment thereof promotes a decrease in food and water consumption in humanized TrkB mice.

17. The isolated antibody or antigen-binding fragment of any one of claims 1-12, wherein the antibody or antigen-binding fragment thereof promotes an increase in locomotor activity in humanized TrkB mice.

18. The isolated antibody or antigen-binding fragment thereof of any one of claims 1-12, wherein the antibody or antigen-binding fragment thereof exhibits one or more properties selected from the group consisting of:

- (a) is an agonist antibody;
- (b) binds human TrkB with a K_D of less than about 200nM as measured by surface plasmon resonance at 25°C or at 37°C;
- (c) binds human TrkB with a dissociative half life ($t_{1/2}$) of greater than about 10 minutes as measured by surface plasmon resonance at 25°C or at 37°C;
- (d) activates human TrkB signaling in the absence of brain derived neurotrophic factor (BDNF) in cells engineered to express human TrkB with an EC_{50} of less than about 100 pM;
- (e) enhances TrkB phosphorylation when injected into the hippocampus of mice homozygous for human TrkB receptor ($TrkB^{hu/hu}$);
- (f) promotes weight loss when injected into mice homozygous for human TrkB receptor ($TrkB^{hu/hu}$);
- (g) increases retinal ganglion cell (RGC) survival as assessed in an optic nerve transection model in humanized TrkB rats;
- (h) activates the MAPK/ERK and PI3K/Akt signaling pathways;
- (i) enhances/increases the survival of neuronal cells *in vitro*; and
- (j) blocks the binding of TrkB to BDNF and/or NT-4 with an IC_{50} of less than 5nM.

19. A pharmaceutical composition comprising the antibody or antigen-binding fragment of any one of claims 1-12, and a pharmaceutically acceptable carrier or diluent.

20. An isolated nucleic acid molecule comprising a polynucleotide sequence that encodes an anti-TrkB antibody or fragment thereof according to any one of claims 1 – 12.

21. A vector comprising the polynucleotide sequence of claim 20.

22. A cell expressing the vector of claim 21.

23. A use of a composition for enhancing a biological activity mediated by TrkB, the use comprising:

contacting TrkB with a biologically effective amount of an agonist anti-TrkB antibody of any one of claims 1-12, or contacting TrkB with a pharmaceutical composition containing a biologically effective amount of an agonist anti-TrkB antibody of any one of claims 1-5.

24. The use of claim 23, wherein the biological activity is neuronal protection or neuronal survival and neuronal protection or neuronal survival is enhanced upon contact of TrkB with an agonist anti-TrkB antibody.

25. The use of claim 23, wherein contacting TrkB with an agonist anti-TrkB antibody results in neuroprotection and survival of retinal ganglion cells (RGCs).

26. A use of a composition for treating or preventing a disease or disorder associated with TrkB activity or expression, or for ameliorating at least one symptom associated with the disease or disorder associated with TrkB activity or expression, the use comprising administering a therapeutically effective amount of an agonist anti-TrkB antibody of any one of claims 1-12, or administering a pharmaceutical composition containing a therapeutically effective amount of an agonist anti-TrkB antibody of any one of claims 1-12 to a subject in need of such treatment.

27. The use of claim 26, wherein the disease or disorder is a disease or disorder of the eye selected from the group consisting of glaucoma, diabetic retinopathy, age-related macular degeneration, ischemic optic neuropathy, optic neuritis, retinal ischemia, photoreceptor degeneration, retinitis pigmentosa and retinal artery or vein occlusions.

28. The use of claim 27, wherein the disease or disorder is glaucoma.

29. A use of a composition for achieving a reduction of body weight in a subject, the use comprising administering a TrkB agonist, wherein the TrkB agonist is an antibody or antigen-binding fragment thereof specific for TrkB according to any one of claims 1-5, or a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof, to the subject.

30. A use of a composition for achieving a reduction of fat mass in a subject, the use comprising administering a TrkB agonist, wherein the TrkB agonist is an antibody or antigen-binding fragment thereof specific for TrkB according to any one of claims 1-5, or a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof, to the subject.

31. A use of a composition for promoting neuronal survival in a subject, the method comprising administering a therapeutically effective amount of a TrkB agonist, wherein the TrkB agonist is an antibody or antigen-binding fragment thereof specific for TrkB according to any one of claims 1-5, or a pharmaceutical composition comprising a therapeutically effective amount of the antibody or antigen-binding fragment thereof, to the subject.

32. The use of any one of claims 23-31, wherein contacting TrkB is carried out by injecting a patient with an injectable formulation comprising an antibody or antigen-binding fragment thereof as claimed in any one of claims 1-12.