

[0010] In an example, an anti-TrkB antibody of the present disclosure is more potent in inducing activation of TrkB downstream signaling pathways than the natural TrkB ligand, BDNF. In a further example, an anti-TrkB antibody of the present disclosure regulates gene expression through TrkB-mediated signaling pathways in a comparable pattern to that of BDNF.

[0011] In an example, an anti-TrkB antibody of the present disclosure binds a novel epitope in the extracellular domain of human TrkB. In a further example, an anti-TrkB antibody of the present disclosure does not cross-react with TrkB from other species, in particular does not cross-react with rodent TrkB.

[0012] In one example, an anti-TrkB antibody of the present disclosure can be formulated to high concentrations for intravitreal injections into the eye.

[0013] In a further example, an anti-TrkB antibody of the present disclosure has a low immunogenicity risk as measured by the method described in example 5.

[0014] In another example, the CDR sequences of an anti-TrkB antibody of the present disclosure have low sequence liabilities as determined by the method described in example 4.

[0015] In yet another example, an anti-TrkB antibody of the present disclosure does not reduce BDNF induced ERK phosphorylation.

[0016] In a further example, an anti-TrkB antibody of the present disclosure is specific for TrkB phosphorylation and/or activation and does not unspecifically phosphorylate/activate TrkA or TrkC. In another example, an anti-TrkB antibody does not bind unspecifically to human VEGF.

[0017] Further aspects and examples encompass polynucleotide(s) molecule(s) encoding antibodies of the present disclosure, expression vectors and viral vectors as well as host cells comprising such polynucleotide(s) molecule(s), and methods of making antibodies of the present disclosure. The present disclosure further provides therapeutic uses for the antibodies of the present disclosure, in particular for retinal/eye diseases.

a light chain comprising the amino acid sequence of SEQ ID NO: 45 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 46 or 47.

[0021] In a particular preferred example the anti-TrkB antibody is a humanized anti-TrkB antibody.

[0022] In another aspect, the present disclosure provides an anti-TrkB antibody or an antigen-binding fragment thereof for use in medicine.

[0023] In one example, the present disclosure provides an anti-TrkB antibody or an antigen-binding fragment thereof for use in the treatment of retinal or eye diseases.

[0024] In one example, the present disclosure provides an anti-TrkB antibody or an antigen-binding fragment thereof for use in the treatment of neural/neuronal eye or retinal diseases. In another aspect, the present disclosure provides use of the antibody or the antigen-binding fragment as described herein in the manufacture of a medicament for the treatment of neural/neuronal eye or retinal diseases.

[0025] In one example, the present disclosure provides an anti-TrkB antibody or an antigen-binding fragment thereof for use in the treatment of geographic atrophy. In another aspect, the present disclosure provides use of the antibody or the antigen-binding fragment as described herein in the manufacture of a medicament for the treatment of geographic atrophy.

[0026] In one example, the present disclosure provides an anti-TrkB antibody or an antigen-binding fragment thereof for use in the treatment of age-related macular degeneration or diabetic retinopathy.

[0026a] In another aspect, the present disclosure provides use of the antibody or the antigen-binding fragment as described herein in the manufacture of a medicament for the treatment of age-related macular degeneration, diabetic retinopathy, diabetic macular edema, retinitis pigmentosa, inherited retinal dystrophy, inherited

macular dystrophy, myopic degeneration, retinal vein occlusions, retinal artery occlusions, endophthalmitis, uveitis, cystoid macular edema, choroidal neovascular membrane secondary to any retinal diseases, optic neuropathies, glaucoma, retinal detachment, toxic retinopathy, radiation retinopathy, and traumatic retinopathy, prodromal and mild-to-moderate alzheimer's diseases, delaying disease progression of patients with Alzheimer's disease, Huntington's disease, Parkinson's disease, major depressive disorder, schizophrenia, cognitive impairment associated with schizophrenia, prevention of first-episode psychosis in individuals with attenuated psychosis syndrome, prevention of relapse in patients with schizophrenia, treatment-resistant depression, hyperphagia, obesity or metabolic syndrome.

[0026b] In another aspect, the present disclosure provides use of the antibody or the antigen-binding fragment as described herein in the manufacture of a medicament for the treatment of hearing loss, cis plating induced hearing loss or noise and age-related hearing loss.

[0027] In another aspect, the present disclosure provides a pharmaceutical composition comprising an anti-TrkB antibody or an antigen-binding fragment thereof and a pharmaceutically acceptable carrier.

[0028] In one example, the present disclosure provides an anti-TrkB antibody or an antigen-binding fragment thereof or a pharmaceutical composition comprising the anti-TrkB antibody or an antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment thereof is administered by a parenteral route, intravenous route, intravitreal route or subcutaneous route of administration.

[0029] In another aspect, the present disclosure provides an isolated polynucleotide or polynucleotides comprising a sequence encoding a light chain or light

chain variable region of an antibody or antigen-binding fragment thereof and a heavy chain or heavy chain variable region of an antibody or antigen-binding fragment thereof.

[0030] In another aspect, the present disclosure provides an expression vector comprising an isolated polynucleotide or polynucleotides encoding a light chain or light chain variable region of an antibody or antigen-binding fragment thereof and a heavy chain or heavy chain variable region of an antibody or antigen-binding fragment thereof.

[0031] In another aspect, the present disclosure provides a viral vector comprising an isolated polynucleotide or polynucleotides encoding a light chain or light chain variable region of an antibody or antigen-binding fragment thereof and a heavy chain or heavy chain variable region of an antibody or antigen-binding fragment thereof.

[0032] In another aspect, the present disclosure provides a host cell comprising an expression vector or an isolated polynucleotide or polynucleotides encoding a light chain or light chain variable region of an antibody or antigen-binding fragment thereof and a heavy chain or heavy chain variable region of an antibody or antigen-binding fragment thereof.

[0033] In another aspect, the present disclosure provides a method for producing an anti-TrkB antibody or an antigen-binding fragment thereof comprising:

obtaining a host cell comprising an expression vector or an isolated polynucleotide or polynucleotides encoding a light chain or light chain variable region of an antibody or antigen-binding fragment thereof and a heavy chain or heavy chain variable region of an antibody or antigen-binding fragment thereof; and cultivating the host cell.

[0034] In one example, the method for producing an anti-TrkB antibody or antigen-binding fragment thereof further comprises recovering and purifying the anti-TrkB antibody or antigen-binding fragment thereof.

[0035] The present disclosure provides an anti-TrkB antibody or antigen-binding fragment thereof that binds to at least one amino acid

CLAIMS

1. An anti-TrkB antibody or an antigen-binding fragment thereof comprising:
 - a. a light chain variable region comprising a light chain complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO: 48; a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 49; and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 50 (L-CDR3); and
 - b. a heavy chain variable region comprising a heavy chain complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO: 51; a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 52; and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 53, or
 - c. a heavy chain variable region comprising a heavy chain complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO: 55; a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 56; and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 57, or
 - d. a heavy chain variable region comprising a heavy chain complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO: 58; a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 59; and a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 60.
2. The anti-TrkB antibody or the antigen-binding fragment thereof according to claim 1, wherein the antibody or the antigen-binding fragment thereof comprises:
 - a. a variable light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 2 and a variable heavy chain

comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence SEQ ID NO: 12,

- b. a variable light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 3 and a variable heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence SEQ ID NO: 13,
- c. a variable light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 4 and a variable heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence SEQ ID NO: 14,
- d. a variable light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 5 and a variable heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence SEQ ID NO: 15,
- e. a variable light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 6 and a variable heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence SEQ ID NO: 16,

- f. a variable light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 7 and a variable heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence SEQ ID NO: 17,
 - g. a variable light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 8 and a variable heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence SEQ ID NO: 18,
 - h. a variable light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 9 and a variable heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence SEQ ID NO: 19, or
 - i. a variable light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 10 and a variable heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence SEQ ID NO: 20.
3. The anti-TrkB antibody according to claim 1, wherein the antibody comprises:
- a. a light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 21 and and a heavy chain comprising an

amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 22 or 23,

- b. a light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 24 and and a heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 25 or 26,
- c. a light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 27 and and a heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 28 or 29,
- d. a light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 30 and and a heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 31 or 32,
- e. a light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 33 and and a heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 34 or 35,

- f. a light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 36 and and a heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 37 or 38,
 - g. a light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 39 and and a heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 40 or 41,
 - h. a light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 42 and and a heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 43 or 44,
 - i. a light chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 45 and and a heavy chain comprising an amino acid sequence at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% identical to the amino acid sequence of SEQ ID NO: 46 or 47.
4. The anti-TrkB antibody or the antigen-binding fragment thereof according to claim 1, wherein the antibody or the antigen-binding fragment thereof comprises:
- a. a variable light chain and a variable heavy chain comprising the amino acid sequences of SEQ ID NO: 2 and SEQ ID NO: 12, respectively,

- b. a variable light chain and a variable heavy chain comprising the amino acid sequences of SEQ ID NO: 3 and SEQ ID NO: 13, respectively,
 - c. a variable light chain and a variable heavy chain comprising the amino acid sequences of SEQ ID NO: 4 and SEQ ID NO: 14, respectively,
 - d. a variable light chain and a variable heavy chain comprising the amino acid sequences of SEQ ID NO: 5 and SEQ ID NO: 15, respectively,
 - e. a variable light chain and a variable heavy chain comprising the amino acid sequences of SEQ ID NO: 6 and SEQ ID NO: 16, respectively,
 - f. a variable light chain and a variable heavy chain comprising the amino acid sequences of SEQ ID NO: 7 and SEQ ID NO: 17, respectively,
 - g. a variable light chain and a variable heavy chain comprising the amino acid sequences of SEQ ID NO: 8 and SEQ ID NO: 18, respectively,
 - h. a variable light chain and a variable heavy chain comprising the amino acid sequences of SEQ ID NO: 9 and SEQ ID NO: 19, respectively, or
 - i. a variable light chain and a variable heavy chain comprising the amino acid sequences of SEQ ID NO: 10 and SEQ ID NO: 20, respectively.
5. The anti-TrkB antibody according to claim 1, wherein the antibody comprises:
- a. a light chain comprising the amino acid sequence of SEQ ID NO: 21 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 22 or 23,
 - b. a light chain comprising the amino acid sequence of SEQ ID NO: 24 and a heavy chain comprising the amino acid sequence of SEQ ID NO: 25 or 26,

- c. a light chain comprising the amino acid sequence of SEQ ID NO: 27 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 28
or 29,
 - d. a light chain comprising the amino acid sequence of SEQ ID NO: 30 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 31
or 32,
 - e. a light chain comprising the amino acid sequence of SEQ ID NO: 33 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 34
or 35,
 - f. a light chain comprising the amino acid sequence of SEQ ID NO: 36 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 37
or 38,
 - g. a light chain comprising the amino acid sequence of SEQ ID NO: 39 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 40
or 41,
 - h. a light chain comprising the amino acid sequence of SEQ ID NO: 42 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 43
or 44, or
 - i. a light chain comprising the amino acid sequence of SEQ ID NO: 45 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 46
or 47, respectively.
6. The anti-TrkB antibody according to claim 1, wherein the antibody comprises:
- a light chain comprising the amino acid sequence of SEQ ID NO: 21 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 22
or 23.

7. The anti-TrkB antibody according to claim 1, wherein the antibody comprises:

a light chain comprising the amino acid sequence of SEQ ID NO: 24 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 25
or 26.

8. The anti-TrkB antibody according to claim 1, wherein the antibody comprises:

a light chain comprising the amino acid sequence of SEQ ID NO: 27 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 28
or 29.

9. The anti-TrkB antibody according to claim 1, wherein the antibody comprises:

a light chain comprising the amino acid sequence of SEQ ID NO: 30 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 31
or 32.

10. The anti-TrkB antibody according to claim 1, wherein the antibody comprises:

a light chain comprising the amino acid sequence of SEQ ID NO: 33 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 34
or 35.

11. The anti-TrkB antibody according to claim 1, wherein the antibody comprises:

a light chain comprising the amino acid sequence of SEQ ID NO: 36 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 37
or 38.

12. The anti-TrkB antibody according to claim 1, wherein the antibody comprises:

a light chain comprising the amino acid sequence of SEQ ID NO: 39 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 40
or 41.

13. The anti-TrkB antibody according to claim 1, wherein the antibody comprises:

a light chain comprising the amino acid sequence of SEQ ID NO: 42 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 43
or 44.

14. The anti-TrkB antibody according to claim 1, wherein the antibody comprises:

a light chain comprising the amino acid sequence of SEQ ID NO: 45 and
and a heavy chain comprising the amino acid sequence of SEQ ID NO: 46
or 47.

15. An antibody or an antigen-binding fragment according to any of claims 1 to 14 for use in medicine.

16. Use of the antibody or the antigen-binding fragment according to any of claims 1 to 14 in the manufacture of a medicament for the treatment of neural/neuronal eye or retinal diseases.

17. Use of the antibody or the antigen-binding fragment according to any of claims 1 to 14 in the manufacture of a medicament for the treatment of geographic atrophy.

18. Use of the antibody or the antigen-binding fragment according to any of claims 1 to 14 in the manufacture of a medicament for the treatment of age-related macular degeneration, diabetic retinopathy, diabetic macular edema, retinitis

pigmentosa, inherited retinal dystrophy, inherited macular dystrophy, myopic degeneration, retinal vein occlusions, retinal artery occlusions, endophthalmitis, uveitis, cystoid macular edema, choroidal neovascular membrane secondary to any retinal diseases, optic neuropathies, glaucoma, retinal detachment, toxic retinopathy, radiation retinopathy, and traumatic retinopathy, prodromal and mild-to-moderate alzheimer's diseases, delaying disease progression of patients with Alzheimer's disease, Huntington's disease, Parkinson's disease, major depressive disorder, schizophrenia, cognitive impairment associated with schizophrenia, prevention of first-episode psychosis in individuals with attenuated psychosis syndrome, prevention of relapse in patients with schizophrenia, treatment-resistant depression, hyperphagia, obesity or metabolic syndrome.

19. Use of the antibody or the antigen-binding fragment according to any of claims 1 to 14 in the manufacture of a medicament for the treatment of hearing loss, cis plating induced hearing loss or noise and age-related hearing loss.

20. A pharmaceutical composition comprising an antibody or an antigen-binding fragment according to any of claims 1 to 14 and a pharmaceutically acceptable carrier.

21. The antibody or the antigen-binding fragment thereof according to any of claims 1 to 14 or the pharmaceutical composition according to claim 20, wherein said antibody or antigen-binding fragment thereof is to be administered by a parenteral route, intravenous route, intravitreal route or subcutaneous route of administration.

22. An isolated polynucleotide or polynucleotides comprising a sequence encoding a light chain or light chain variable region of an antibody or antigen-binding fragment thereof and a heavy chain or heavy chain variable region of an antibody or antigen-binding fragment thereof according to any of claims 1 to 14.

23. An expression vector comprising the isolated polynucleotide or polynucleotides of claim 22.

24. A viral vector comprising the isolated polynucleotide or polynucleotides of claim 22.

25. A host cell comprising an isolated polynucleotide or polynucleotides according to claim 22 or an expression vector according to claim 23.

26. A method for producing an anti-TrkB antibody or antigen-binding fragment thereof comprising:

- a. obtaining a host cell according to claim 25; and
- b. cultivating the host cell.

27. The method according to claim 26, further comprising recovering and purifying the antibody or antigen-binding fragment thereof.