[0004] Agonistic anti-TrkB antibodies have been described in the US20100196390 and US20100150914 as well as their proposed use in the treatment of e.g. Charcot-Marie-Tooth disease or diabetes.

[0005] However, there remains a significant need for new potent agonistic anti-TrkB antibodies that can be used to activate the TrkB pathway and thereby allow their use in therapeutic interventions of e.g. neurodegenerative and psychiatric disorders.

SUMMARY

[0006] The present disclosure provides monoclonal antibodies that specifically bind to human TrkB. The antibodies of the present disclosure have agonistic activity and induce TrkB phosphorylation and/or activation. The antibodies of the present disclosure are useful, for example for the treatment of eye or retinal diseases such as, geographic atrophy secondary to age-related macular degeneration, diabetic retinopathy, glaucoma, and/or diabetic macular edema.

[0007] The present disclosure provides an anti-TrkB antibody, in particular a humanized anti-TrkB antibody, having one or more of the properties described herein below.

[0008] In an example, an anti-TrkB antibody of the present disclosure binds with high affinity to human TrkB. In an example, an anti-TrkB antibody of the present disclosure binds to human TrkB at a K_D < 10 nM. In another example, an anti-TrkB antibody of the present disclosure binds to human TrkB at a K_D < 5 nM.

[0009] In an example, an anti-TrkB antibody of the present disclosure activates TrkB with high potency. In an example, an anti-TrkB antibody of the present disclosure activates human TrkB with an EC_{50} < 100 pM. In a further example, an anti-TrkB antibody of the present disclosure activates human TrkB with an EC_{50} < 50 pm.

[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 aspect, 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.

[0018] In one aspect, the present disclosure provides an anti-TrkB antibody or an antigen-binding fragment thereof comprising:

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 48 (L-CDR1); the amino acid sequence of SEQ ID NO: 49 (L-CDR2); and the amino acid sequence of SEQ ID NO: 50 (L-CDR3); and

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 51 (H-CDR1); the amino acid sequence of SEQ ID NO: 52 (H-CDR2); and the amino acid sequence of SEQ ID NO: 53 (H-CDR3), or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 55 (H-CDR1); the amino acid sequence of SEQ ID NO: 56 (H-CDR2); and the amino acid sequence of SEQ ID NO: 57 (H-CDR3), or

a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 58 (H-CDR1); the amino acid sequence of SEQ ID NO: 59 (H-CDR2); and the amino acid sequence of SEQ ID NO: 60 (H-CDR3).

[0019] In one example, the present disclosure provides an anti-TrkB antibody or an antigen-binding fragment thereof comprising:

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,

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,

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,

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,

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,

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,

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,

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

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.

[0020] In one example, the present disclosure provides an anti-TrkB antibody or an antigen-binding fragment thereof comprising:

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,

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,

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,

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,

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,

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,

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,

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

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.

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

[0022] In one 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.

[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.

[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.

[0027] In one 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 one 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 one 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 one 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 one 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 one 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] In one aspect, the present disclosure provides an anti-TrkB antibody or antigen-binding fragment thereof that binds to at least one amino acid

residue within amino acid regions 92-112, 130-143 and/or 205-219 of the extracellular domain of human TrkB with the SEQ ID NO: 54.

[0036] In one example, the present in disclosure vention provides an anti-TrkB antibody or antigen-binding fragment thereof that binds to at least one amino acid residue within amino acid regions 92-112 and 130-143; or 92-112 and 205-219; or 130-143 and 205-219; or 92-112 and 130-143 and 205-219 of the extracellular domain of human TrkB with the SEQ ID NO: 54.

[0037] In one example, the present disclosure provides an anti-TrkB antibody or antigen-binding fragment thereof that binds to at least one amino acid residue within any of the aforementioned combinations and further also to at least one amino acid residue within amino acid regions 313-330 and/or 348-367 of the extracellular domain of human TrkB with the SEQ ID NO: 54.

[0038] In one example, the present disclosure provides an anti-TrkB antibody or antigen-binding fragment thereof that binds to at least one amino acid residue within amino acid regions 92-112, 130-143, 205-219, 313-330 and 348-367 of the extracellular domain of human TrkB with the SEQ ID NO: 54.

[0038a] In one aspect, the present disclosure provides an anti-TrkB antibody that competes for binding to TrkB with any one of the following antibodies:

a. an antibody having 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,

b. an antibody having 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,

c. an antibody having 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. an antibody having 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. an antibody having 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. an antibody having 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. an antibody having 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. an antibody having 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. an antibody having 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] **FIGURE 1:** Epitope mapping of BDNF, 277-antibody, C2 or C20 antibodies to the extracellular domain of human TrkB.

[0040] **FIGURE 2:** qPCR expression data (y-axis) for regulated genes (x-axis) with regard to synaptic plasticity in SH-SY5Y cells after treatment with BDNF, control IgG1 (anti-2,4,6-trinitrophenyl, anti-TNP) or D003 antibody.

[0041] **FIGURE 3:** Plot of the concentration of 277-antibody in ocular compartments as indicated and plasma after ivt injection of 1 mg of 277-antibody into rabbit eyes as a function of time.

[0042] **FIGURE 4:** Calculated ocular PK of IgG1 antibodies. Y-axis shows the vitreal concentration and x-axis the days post ivt application. The time post