sensitivity (Tomlinson *et al.*, 2002, Endocrinology 143: 1741-1747). In addition, these transgenic mice were reported not to become obese or diabetic on a high-fat diet (Tomlinson *et al.*, 2002, Endocrinology 143: 1741-1747). It has also been reported that FGF19 treatment prevented or reversed diabetes in mice made obese by genetic ablation of brown adipose tissue or the genetic absence of leptin (Fu *et al.*, 2004, Endocrinology 145: 2594-2603).

[0006] FGF21 acts through the interaction of FGFRs and beta klotho. FGFR1 is an abundant receptor in white adipose tissue and is most likely the main functional receptor for FGF21 in white adipose tissue. FGF21 expression is detected in the liver, thymus, adipose tissue, and islet beta-cells in the pancreas. It has been reported that the interaction of FGF21 with the beta klotho-FGFR complex stimulates glucose uptake, decreases glucagon secretion, improves insulin sensitivity and glucose clearance, promotes white adipose tissue in response to fasting, increases ketogenesis in liver in response to fasting, reduces plasma triglyceride levels, and increases energy expenditure (Iglesias *et al.*, 2012, European Journal of Endocrinology 167: 301-309).

[0007] Since FGF19 and FGF21 require both FGFRs and beta klotho for cell signaling, agents which mimic FGF19 and/or FGF21 may be desirable for their effects or glucose metabolism or lipid metabolism. However, it is not clear what features are required for an agent to confer FGF19-like or FGF21-like cell signaling activity.

SUMMARY

[0008] The present disclosure provides proteins that bind to beta klotho, including binding proteins such as antibodies that bind to beta klotho. Such binding proteins including antibodies, may bind to a beta klotho polypeptide, a beta klotho fragment and/or a beta klotho epitope. Such binding proteins, including antibodies, may be agonists (*e.g.*, induce FGF19-like or FGF21-like signaling of a FGF receptor or activate a beta klotho/FGF receptor complex).

[0009] The present disclosure also provides binding proteins, including antibodies or fragments thereof, that (i) bind to human beta klotho, (ii) induce FGF19-like signaling and/or FGF21-like signaling, and (iii) do not compete with FGF19 and/or FGF21 for the interaction with beta klotho. In one aspect, the present disclosure refers to an antibody or antigen-binding fragment thereof that binds to an epitope of human beta klotho and cynomolgus monkey beta klotho recognized by an antibody comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO:25 and a light chain variable region having the amino acid sequence of SEQ ID

NO:26 In another aspect, the present disclosure refers to an antibody or an antigen binding fragment thereof that binds to human beta klotho, wherein the antibody or the antigen-binding fragment thereof comprises: a heavy chain variable region (VH) comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:271, and a light chain variable region (VL) comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:276. In another aspect, the present disclosure refers to an antibody or an antigen binding fragment thereof that binds to human beta klotho, wherein the antibody or the antigen-binding fragment comprises a VH comprising the amino acid sequence of SEQ ID NO:271 and a VL comprising the amino acid sequence of SEQ ID NO:276. In yet another aspect, the present disclosure refers to an antibody that binds human beta klotho, wherein the antibody comprises a heavy chain comprising amino acids 23-472 of the amino acid sequence of SEQ ID NO:317 and a light chain comprising amino acids 23-240 of the amino acid sequence of SEQ ID NO:319. In another aspect, the present disclosure refers to an antibody or an antigen binding fragment thereof that binds to human beta klotho, wherein the antibody or antigen-binding fragment thereof comprises: (a) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:51, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:52; (b) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:77, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:78; (c) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:103, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:104; (d) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:129, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:130; (e) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:155, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:156; (f) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:181, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:182; (g) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:207, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:208; (h) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:233, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:234; or (i) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:259, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:260. In another aspect, the present disclosure refers to an isolated polynucleotide or polynucleotides encoding the antibody or the antigen-binding fragment thereof as disclosed herein. In yet another aspect, the present disclosure refers to an expression vector or vectors: (i) encoding the antibody an antigen-binding fragment thereof as disclosed herein, or (ii) comprising the polynucleotide or polynucleotides as disclosed herein. In another aspect, the present disclosure refers to an isolated cell producing the antibody or the antigen-binding fragment thereof as disclosed herein. In another aspect, the present disclosure refers to an isolated cell comprising the polynucleotide or polynucleotides or the expression vector or vectors

as disclosed herein. In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody or the antigen-binding fragment thereof as disclosed herein or the antibody as disclosed herein, and a pharmaceutically acceptable carrier. In another aspect, the present disclosure refers to a use of the antibody or the antigen-binding fragment thereof as disclosed herein or the antibody as disclosed herein in the manufacture of a medicament for treating Type 2 diabetes, gestational diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), obesity, dyslipidemia, Type 1 diabetes, cardiovascular disease, or metabolic syndrome in a subjectIn yet another aspect, the present disclosure refers to a method of making the antibody or antigen-binding fragment thereof as disclosed herein or the antibody as disclosed herein, comprising (a) culturing the cell as disclosed herein and (b) isolating the antibody or antigen-binding fragment thereof. In yet another aspect, the present disclosure refers to an antibody or the antigen-binding fragment thereof as disclosed herein or the antibody as disclosed herein for use in therapy.

[0010] In some examples, the anti-beta klotho antibodies are humanized antibodies that bind to a beta klotho polypeptide, a beta klotho fragment, or a beta klotho epitope. In certain examples, an anti-beta klotho antibody comprises a VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of a monoclonal antibody designated 5H23, 1C17, 1D19, 2L12, 3L3, 3N20, 4P5, 5C23, 5F7 or 1G19 as described herein, or a humanized variant thereof. In certain examples, an anti-beta klotho antibody can further comprise a VH FR1, VH FR2, VH FR3, VH FR4, VL FR1, VL FR2, VL FR3, and/or VL FR4 of a human immunoglobulin amino acid sequence or a variant thereof.

[0011] In some examples, a binding protein (*e.g.,* an anti-beta klotho antibody) comprises six CDRs or less than six CDRs. In some examples, a binding protein (*e.g.,* an anti-beta klotho antibody) comprises one, two, three, four, five, or six CDRs selected from VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3. In some examples, a binding protein (*e.g.,* an anti-beta klotho antibody) comprises one, two, three, four, five, or six CDRs selected from VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 of a monoclonal antibody designated as 5H23, 1C17, 1D19, 2L12, 3L3, 3N20, 4P5, 5C23, 5F7 or 1G19 as described herein, or a humanized variant thereof. In some examples, a binding protein (*e.g.,* an anti-beta klotho antibody) further comprises a scaffold region or frame work region, including a VH FR1, VH FR2, VH FR3, VH FR4, VL FR1, VL FR2, VL FR3, and/or VL FR4 of a human immunoglobulin amino acid sequence or a variant thereof.

[0046] An encoding nucleic acid sequence of cyno beta klotho is provided below:

atgaagcctggatgtgccgccggaagccccggcaacgagtggatcttcttcagcaccgacga
gatcaccatccggtacagaaacaccatgagcaacggcggcctgcagcggagcgtgatcctgt
ctgctctgaccctgctgagagccgtgaccggcttcagcggagatggcagagccgtgtggtcc
aagaaccccaacttcacccccgtgaacgagagccagctgttcctgtacgataccttccccaa
gaacttcttctggggcgtgggcacaggcgccctgcaggtggaaggatcctggaagaaggacg
gcaagggccccagcatctgggaccactttgtgcacacccacctgaagaacgtgtccagcacc
aacggcagcagcgacagctacatctttctggaaaaggacctgagcgccctggacttcatcgg
cgtgtccttctaccagttcagcatcagctggcccagactgttccccgacggcatcgtgacag
tggccaatgccaagggcctgcagtactacaacaccctgctggacagcctggtgctgcggaac
atcgagcccatcgtgaccctgtaccactgggacctgccactggctctgcaggagaaatacgg
cggctggaagaacgacaccatcatcgacatcttcaacgactacgccacctactgcttccaga
ccttcggcgacagagtgaagtactggatcacaatccacaacccctacctggtggcctggcac
ggctatggcaccggaatgcatgcccctggcgagaagggaaatctggccgccgtgtacaccgt
gggccacaacctgatcaaggcccacagcaaagtgtggcacaactacaatacccacttccggc
cccaccagaagggctggctgtctatcacactgggcagccactggatcgagcctaaccgcagc
gagaacaccatggacatcctgaagtgccagcagagcatggtgtccgtgctgggatggttcgc
caaccccattcacggcgacggcgattaccccgagggcatgaagaagaagctgctgagcatcc
tgcccctgttcagcgaggccgagaagaacgaagtgcggggcaccgccgatttcttcgccttt
agcttcggccccaacaacttcaagcccctgaataccatggccaagatgggccagaatgtgtc
cctgaacctgagagaggccctgaactggatcaagctggagtacaacaacccccggatcctga
tcgccgagaacggctggttcaccgacagccacgtgaaaaccgaggacaccaccgccatctat
atgatgaagaacttcctgagccaggtgctgcaggctatccggctggatgagatccgggtgtt
cggctacaccgcctggtcactgctggacggcttcgaatggcaggacgcctacaccatcagac
ggggcctgttctacgtggacttcaacagcaagcagaaagagcggaagcccaagagcagcgcc
cactactacaagcagatcatcagagagaatggcttcagcctgaaagaggccacccccgacgt
gcagggccagttcccttgtgatttctcttggggcgtgaccgagagcgtgctgaagcctgaaa
gcgtggccagcagcccccagttcagcgacccttacctgtacgtgtggaacgccaccggcaac
cggctgctgcatagagtggaaggcgtgcggctgaaaaccagacccgcccagtgcaccgactt
cgtgaacatcaagaaacagctggaaatgctggcccggatgaaagtgacccactacagattcg
ccctggactgggccagcgtgctgcctaccggaaatctgagcgccgtgaacagacaggccctg
cggtactacagatgcgtggtgtccgagggcctgaagctgggcatcagcgccatggtcaccct
gtactaccctacccacgcccacctgggactgcctgaacctctgctgcatgctggcggctggc
tgaaccctagcaccgtggaagcctttcaggcctacgccgggctgtgcttccaggaactgggc

VEDLDRVLTVTSTDEYLDLSAPFEQYSPGGQDTPSSSSSGDDSVFAHDLLPPAPPSSGGSRT
(SEQ ID NO:313)

[0087] Binding proteins, such as anti-beta klotho antibodies, as described herein bind to beta klotho alone or in complex with an FGF receptor, such as FGFR4. An encoding nuclic acid sequence of human FGFR4 is provided below:

atgcggctgctgctggccctgttgggggtcctgctgagtgtgcctgggcctccagtcttgtc
cctggaggcctctgaggaagtggagcttgagccctgcctggctcccagcctggagcagcaag
agcaggagctgacagtagcccttgggcagcctgtgcgtctgtgctgtgggcgggctgagcgt
ggtggccactggtacaaggagggcagtcgcctggcacctgctggccgtgtacggggctggag
gggccgcctagagattgccagcttcctacctgaggatgctggccgctacctctgcctggcac
gaggctccatgatcgtcctgcagaatctcaccttgattacaggtgactccttgacctccagc
aacgatgatgaggaccccaagtcccatagggacccctcgaataggcacagttacccccagca
agcaccctactggacacacccccagcgcatggagaagaaactgcatgcagtacctgcgggga
acaccgtcaagttccgctgtccagctgcaggcaaccccacgcccaccatccgctggcttaag
gatggacaggcctttcatggggagaaccgcattggaggcattcggctgcgccatcagcactg
gagtctcgtgatggagagcgtggtgccctcggaccgcggcacatacacctgcctggtagaga
acgctgtgggcagcatccgctataactacctgctagatgtgctggagcggtccccgcaccgg
cccatcctgcaggccgggctcccggccaacaccacagccgtggtgggcagcgacgtggagct
gctgtgcaaggtgtacagcgatgcccagccccacatccagtggctgaagcacatcgtcatca
acggcagcagcttcggagccgacggtttcccctatgtgcaagtcctaaagactgcagacatc
aatagctcagaggtggaggtcctgtacctgcggaacgtgtcagccgaggacgcaggcgagta
cacctgcctcgcaggcaattccatcggcctctcctaccagtctgcctggctcacggtgctgc
cagaggaggaccccacatggaccgcagcagcgcccgaggccaggtatacggacatcatcctg
tacgcgtcgggctccctggccttggctgtgctcctgctgctggccgggctgtatcgagggca
ggcgctccacggccggcacccccgcccgcccgccactgtgcagaagctctcccgcttccctc
tggcccgacagttctccctggagtcaggctcttccggcaagtcaagctcatccctggtacga
ggcgtgcgtctctcctccagcggccccgccttgctcgccggcctcgtgagtctagatctacc
tctcgacccactatgggagttcccccgggacaggctggtgcttgggaagcccctaggcgagg
gctgctttggccaggtagtacgtgcagaggcctttggcatggaccctgcccggcctgaccaa
gccagcactgtggccgtcaagatgctcaaagacaacgcctctgacaaggacctggccgacct
ggtctcggagatggaggtgatgaagctgatcggccgacacaagaacatcatcaacctgcttg
gtgtctgcacccaggaagggcccctgtacgtgatcgtggagtgcgccgccaagggaaacctg
cgggagttcctgcgggcccggcgccccccaggccccgacctcagccccgacggtcctcggag

WHAT IS CLAIMED:

1. An antibody or antigen-binding fragment thereof that binds to an epitope of human beta klotho and cynomolgus monkey beta klotho recognized by an antibody comprising a heavy chain variable region having the amino acid sequence of SEQ ID NO:25 and a light chain variable region having the amino acid sequence of SEQ ID NO:26.

2. The antibody or the antigen-binding fragment thereof of claim 1, wherein the antibody or the antigen-binding fragment thereof binds to an epitope comprising:

(i) at least one of amino acid residues 657, 701 and/or 703 of the human beta klotho;

(ii) at least two of amino acid residues 657, 701 and/or 703 of the human beta klotho; or

(iii) amino acid residues 657, 701 and 703 of the human beta klotho.

3. The antibody or the antigen-binding fragment thereof of claims 1 or 2, wherein the antibody or the antigen-binding fragment thereof induces FGF19-like signaling and/or FGF21-like signaling in a cell that expresses human beta klotho and an FGF receptor.

4. An antibody or an antigen-binding fragment thereof that binds to human beta klotho, wherein the antibody or the antigen-binding fragment thereof comprises: a heavy chain variable region (VH) comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:271, and a light chain variable region (VL) comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:276.

5. The antibody or the antigen-binding fragment thereof of claim 4, wherein:

(a) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:12, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:2, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:3, the VL CDR1 comprises the

amino acid sequence of SEQ ID NO:4, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:5, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:6;

(b) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:7, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:8, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:9; the VL CDR1 comprises the amino acid sequence of SEQ ID NO:10, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:11, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:6;

(c) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:1, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:2, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:3; the VL CDR1 comprises the amino acid sequence of SEQ ID NO:4, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:5, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:6;

(d) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:13, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:14, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:15; the VL CDR1 comprises the amino acid sequence of SEQ ID NO:16, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:11, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:17;

(e) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:18, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:19, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:20; the VL CDR1 comprises the amino acid sequence of SEQ ID NO:21, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:22, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:23; or

(f) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:1, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:24, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:3; the VL CDR1 comprises the amino acid sequence of SEQ ID NO:4, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:5, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:6.

6. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the VH has at least 80% sequence identity to SEQ ID NO:25.

7. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the VL has at least 80% sequence identity to SEQ ID NO:26.

8. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:25 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:26.

9. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the VH comprises the amino acid sequence of SEQ ID NO:25.

10. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the VL comprises the amino acid sequence of SEQ ID NO:26.

11. The antibody or the antigen-binding fragment thereof of claim 4, wherein the VH comprises the amino acid sequence of SEQ ID NO:25 and the VL comprises the amino acid sequence of SEQ ID NO:26.

12. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:271 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:276.

13. The antibody or the antigen-binding fragment thereof of claim 4, 5 or 12, wherein the VH comprises the amino acid sequence of SEQ ID NO:271.

14. The antibody or the antigen-binding fragment thereof of claim 4,5 or 12, wherein the VL comprises the amino acid sequence of SEQ ID NO:276.

15. An antibody or an antigen-binding fragment thereof that binds to human beta klotho, wherein the antibody or the antigen-binding fragment comprises

a VH comprising the amino acid sequence of SEQ ID NO:271 and a VL comprising the amino acid sequence of SEQ ID NO:276.

16. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the antibody comprises a heavy chain comprising amino acids 23-472 of the amino acid sequence of SEQ ID NO:317.

17. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the antibody comprises a light chain comprising amino acids 23-240 of the amino acid sequence of SEQ ID NO:319.

18. The antibody or the antigen-binding fragment thereof of claim 4 or 5, wherein the antibody comprises (i) a heavy chain that is 90% identical to amino acids 23-472 of the amino acid sequence of SEQ ID NO:317, and (ii) a light chain that is 90% identical to amino acids 23-240 of the amino acid sequence of SEQ ID NO:319.

19. An antibody that binds human beta klotho, wherein the antibody comprises a heavy chain comprising amino acids 23-472 of the amino acid sequence of SEQ ID NO:317 and a light chain comprising amino acids 23-240 of the amino acid sequence of SEQ ID NO:319.

20. An antibody or an antigen-binding fragment thereof that binds to human beta klotho, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:51, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:52;

(b) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:77, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:78;

(c) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:103, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:104;

(d) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:129, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:130;

(e) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:155, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:156;

(f) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:181, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:182;

(g) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:207, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:208;

(h) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:233, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:234; or

(i) a VH comprising a VH CDR1, a VH CDR2, and a VH CDR3 from the amino acid sequence of SEQ ID NO:259, and a VL comprising a VL CDR1, a VL CDR2, and a VL CDR3 from the amino acid sequence of SEQ ID NO:260.

21. The antibody or an antigen-binding fragment thereof of claim 20, wherein:

(a) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:27, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:28, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:29, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:30, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:31, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:32;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:33, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:34, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:35, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:36, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:37, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:32;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:38, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:28, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:29, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:30, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:31, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:32;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:39, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:40, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:41, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:42, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:37, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:43;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:44, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:45, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:46, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:47, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:48, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:49; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:27, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:50, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:29, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:30, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:31, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:32;

(b) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:53, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:54, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:55, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:56, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:57, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:58;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:59, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:60, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:61, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:62, the VL CDR2

comprises the amino acid sequence of SEQ ID NO:63, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:58;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:64, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:54, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:55, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:56, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:57, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:58;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:65, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:66, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:67, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:68, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:63, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:69;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:70, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:71, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:72, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:73, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:74, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:75; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:53, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:76, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:55, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:56, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:57, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:58;

(c) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:79, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:80, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:81, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:82, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:83, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:84;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:85, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:86,

the VH CDR3 comprises the amino acid sequence of SEQ ID NO:87, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:88, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:89, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:84;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:90, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:80, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:81, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:82, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:83, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:84;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:91, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:92, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:93, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:94, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:89, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:95;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:96, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:97, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:98, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:99, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:100, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:101; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:79, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:102, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:81, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:82, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:83 and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:84;

(d) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:105, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:106, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:107, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:108, the VL CDR2 comprises the amino acid sequence of SEQ ID

NO:109, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:110;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:111, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:112, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:113, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:114, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:115, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:110;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:116, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:106, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:107, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:108, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:109, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:110;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:117, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:118, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:119, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:120, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:115, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:121;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:122, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:123, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:124, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:125, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:126, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:127; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:105, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:128, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:107, the VL CDR1 comprises the amino acid sequence of SEQ ID

NO:108, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:109, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:110;

(e) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:131, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:132, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:133, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:134, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:135, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:136;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:137, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:138, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:139, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:140, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:141, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:136;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:142, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:132, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:133, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:134, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:135, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:136;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:143, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:144, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:145, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:146, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:141, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:147;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:148, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:149, the VH CDR3 comprises the amino acid sequence of SEQ ID

NO:150, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:151, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:152, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:153; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:131, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:154, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:133, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:134, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:135, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:136;

(f) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:157, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:158, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:159, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:160, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:161, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:162;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:163, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:164, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:165, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:166, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:167, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:162;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:168, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:158, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:159, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:160, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:161, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:162;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:169, the VH CDR2 comprises the amino acid sequence of SEQ ID

NO:170, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:171, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:172, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:167, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:173;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:174, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:175, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:176, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:177, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:178, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:179; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:157, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:180, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:159, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:160, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:161, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:162;

(g) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:183, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:184, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:185, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:186, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:187, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:188;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:189, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:190, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:191, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:192, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:193, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:188;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:194, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:184, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:185, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:186, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:187, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:188;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:195, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:196, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:197, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:198, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:193, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:199;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:200, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:201, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:202, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:203, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:204, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:205; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:183, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:206, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:185, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:186, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:187, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:188;

(h) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:209, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:210, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:211, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:212, the VL CDR2 comprises the amino acid sequence of SEQ ID

NO:213, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:214;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:215, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:216, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:217, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:218, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:219, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:214;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:220, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:210, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:211, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:212, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:213, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:214;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:221, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:222, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:223, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:224, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:219, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:225;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:226, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:227, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:228, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:229, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:230, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:231; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:209, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:232, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:211, the VL CDR1 comprises the amino acid sequence of SEQ ID

NO:212, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:213, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:214; or

(i) (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:235, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:236, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:237, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:238, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:239, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:240;

(ii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:241, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:242, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:243, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:244, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:245, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:240;

(iii) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:246, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:236, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:237, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:238, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:239, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:240;

(iv) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:247, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:248, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:249, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:250, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:245, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:251;

(v) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:252, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:253, the VH CDR3 comprises the amino acid sequence of SEQ ID

NO:254, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:255, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:256, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:257; or

(vi) the VH CDR1 comprises the amino acid sequence of SEQ ID NO:235, the VH CDR2 comprises the amino acid sequence of SEQ ID NO:258, the VH CDR3 comprises the amino acid sequence of SEQ ID NO:237, the VL CDR1 comprises the amino acid sequence of SEQ ID NO:238, the VL CDR2 comprises the amino acid sequence of SEQ ID NO:239, and the VL CDR3 comprises the amino acid sequence of SEQ ID NO:240.

22. The antibody or the antigen-binding fragment thereof of claim 20 or 21, wherein:

(a) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:51 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:52;

(b) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:77 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:78;

(c) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:103 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:104;

(d) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:129 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:130;

(e) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:155 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:156;

(f) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:181 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:182;

(g) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:207 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:208;

(h) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:233 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:234; or

(i) the VH has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:259 and the VL has at least 80% sequence identity to the amino acid sequence of SEQ ID NO:260.

23. The antibody or the antigen-binding fragment thereof of claim 20 or 21, wherein:

(a) the VH comprises the amino acid sequence of SEQ ID NO:51 and the VL comprises the amino acid sequence of SEQ ID NO:52;

(b) the VH comprises the amino acid sequence of SEQ ID NO:77 and the VL comprises the amino acid sequence of SEQ ID NO:78;

(c) the VH comprises the amino acid sequence of SEQ ID NO:103 and the VL comprises the amino acid sequence of SEQ ID NO:104;

(d) the VH comprises the amino acid sequence of SEQ ID NO:129 and the VL comprises the amino acid sequence of SEQ ID NO:130;

(e) the VH comprises the amino acid sequence of SEQ ID NO:155 and the VL comprises the amino acid sequence of SEQ ID NO:156;

(f) the VH comprises the amino acid sequence of SEQ ID NO:181 and the VL comprises the amino acid sequence of SEQ ID NO:182;

(g) the VH comprises the amino acid sequence of SEQ ID NO:207 and the VL comprises the amino acid sequence of SEQ ID NO:208;

(h) the VH comprises the amino acid sequence of SEQ ID NO:233 and the VL comprises the amino acid sequence of SEQ ID NO:234; or

(i) the VH comprises the amino acid sequence of SEQ ID NO:259 and the VL comprises the amino acid sequence of SEQ ID NO:260.

24. The antibody or the antigen-binding fragment of claims 1-8, 12-18, and 20-22, which is a humanized antibody.

25. The antibody or the antigen-binding fragment of any one of claims 1-18 and 20-24, which is a chimeric antibody.

26. The antibody or the antigen-binding fragment thereof of any one of claims 1-15 and 20-23, wherein the antigen-binding fragment is an Fab, Fab', F(ab')2, Fv, scFv, (scFv)2, single chain antibody molecule, or dual variable region antibody, or wherein the antibody is a bispecific antibody.

27. An isolated polynucleotide or polynucleotides encoding the antibody or the antigen-binding fragment thereof of any one of claims 1-18 and 20-26 or the antibody of claim 19.

28. An expression vector or vectors: (i) encoding the antibody an antigen-binding fragment thereof of any of claims 1-18 and 20-26 or the antibody of claim 19, or (ii) comprising the polynucleotide or polynucleotides of claim 27.

29. An isolated cell producing the antibody or the antigen-binding fragment thereof of any one of claims 1-18 and 20-26 or the antibody of claim 19.

30. An isolated cell comprising the polynucleotide or polynucleotides of claim 27 or the expression vector or vectors of claim 28.

31. A pharmaceutical composition comprising the antibody or the antigen-binding fragment thereof of any one of claims 1-18 and 20-26 or the antibody of claim 19, and a pharmaceutically acceptable carrier.

32. Use of the antibody or the antigen-binding fragment thereof of any one of claims 1-18 and 20-26 or the antibody of claim 19 in the manufacture of a medicament for treating Type 2 diabetes, gestational diabetes, insulin resistance, hyperinsulinemia, glucose intolerance, nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), obesity, dyslipidemia, Type 1 diabetes, cardiovascular disease, or metabolic syndrome in a subject.

33. The use of claim 32, wherein the antibody or the antigen-binding fragment is to be used in combination with one or more additional therapeutic agents.

34. The use of claim 33, wherein the one or more additional therapeutic agents is selected from the group consisting of biguanides, sulphonylureas, thiazolidinediones, GLP-1 analogues, PPAR gamma agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, bromocriptine, bile acid sequestrants, insulin, alpha glucosidase inhibitors, metformin, SGLT-2 inhibitors, appetite suppression agents, and weight loss drugs.

35. The use of any one of claims 32-34, wherein the subject is human.

36. A method of making the antibody or antigen-binding fragment thereof of any one of claims 1 to 18 and 20-26 or the antibody of claim 19, comprising (a) culturing the cell of claim 29 or 30 and (b) isolating the antibody or antigen-binding fragment thereof.

37. The method of claim 36, further comprising formulating the antibody or antigen-binding fragment thereof as a sterile pharmaceutical composition.

38. An antibody or the antigen-binding fragment thereof of any one of claims 1-18 and 20-26 or the antibody of claim 19 for use in therapy.

BINDING PROTEINS AND METHODS OF USE THEREOF

ABSTRACT

The present disclosure provides binding proteins, such as antibodies, that bind beta klotho, including human beta klotho, and methods of their use.

Figure 1A and 1B