ANTI-EPHRIN B2 ANTIBODIES AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63,570,724, filed March 27, 2024, which is hereby incorporated by reference in its entirety and for all purposes.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0002] The contents of the electronic sequence listing (062698-506001WO_Sequence_Listing_ST26.xml; Size: 102,400 bytes; and Date of Creation: March 25, 2025) are hereby incorporated by reference in their entirety.

BACKGROUND

[0003] Ephrin B2 is one of three transmembrane cell surface ligands for the erythropoietin-producing hepatoma (Eph) receptor subfamily of receptor tyrosine kinases (RTKs) and interacts with receptors including EphA5, EphB1-EphB4 and EphB6 (Coulthard et al. 2012; Eph Nomenclature Committee 1997). Receptor-ligand interaction leads to the formation of a heterotetramer, which promotes Eph/Eph interaction and the assembly of higher-order oligomers (Janes et al. 2011; Janes et al. 2012). Upon receptor oligomerization, bidirectional signaling can occur. In forward signaling, Eph receptors cross-phosphorylate tyrosine residues, inducing a conformational change in the receptor. The resulting change in conformation allows the binding of signaling molecules (e.g. Src homology domains 2 and 3, among others), which activate downstream signaling pathways (Vearing and Lackmann 2005 and Janes et al. 2012). In reverse signaling, Ephrins can signal into the cell via their cytoplasmic tail through phosphorylation by Src-family kinases as well as via protein interactions at the PDZ domain (Kullander and Klein, 2022). Eph/Ephrin signaling pathways stimulate cell proliferation, migration, recruitment of inflammatory cells and angiogenesis, processes that are critically involved in wound healing and fibrosis (Coulthard et al. 2012).

BRIEF SUMMARY

[0004] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:66, a CDR H2 as set forth in SEQ ID NO:67, and a CDR H3,

wherein said CDR H3 is a variant of SEQ ID NO:68; wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:69, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:70; and wherein the variant of SEQ ID NO:68 includes the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4, position 6, position 10, and position 11 relative to SEQ ID NO:68.

[0005] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:66, a CDR H2 as set forth in SEQ ID NO:67 and a CDR H3, wherein the CDR H3 is a variant of SEQ ID NO:68; wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:69, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:70; and wherein the variant of SEQ ID NO:68 includes the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4 and position 7 relative to SEQ ID NO:68.

[0006] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 set forth in SEQ ID NO:3; wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:5.

[0007] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:14, a CDR H2 as set forth in SEQ ID NO:15 and a CDR H3 set forth in SEQ ID NO:16; wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:17, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:18.

[0008] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:27, a CDR H2 as set forth in SEQ ID NO:28 and a CDR H3 set forth in SEQ ID NO:29; wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:30, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:31.

[0009] In another aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes a CDR H1 as set forth in SEQ ID NO:86, a CDR H2 as set forth in SEQ ID NO:87 and a CDR H3 set forth in SEQ ID NO:88; wherein the light chain variable domain includes a CDR L1 as set forth in SEQ ID NO:89, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:90.

[0010] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes SEQ ID NO:51; and wherein the light chain variable domain includes SEQ ID NO:52.

[0011] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes SEQ ID NO:64; and wherein the light chain variable domain includes SEQ ID NO:65.

[0012] In an aspect is provided an anti-Ephrin B2 antibody, wherein the anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 set forth in SEQ ID NO:3; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:5.

[0013] In an aspect is provided an anti-Ephrin B2 antibody, where the anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:14, a CDR H2 as set forth in SEQ ID NO:15 and a CDR H3 set forth in SEQ ID NO:16; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:17, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:18.

[0014] In an aspect is provided an anti-Ephrin B2 antibody, where the anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:27, a CDR H2 as set forth in SEQ ID NO:28 and a CDR H3 set forth in SEQ ID NO:29; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:30, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:31.

[0015] In an aspect is provided an anti-Ephrin B2 antibody, where the anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:86, a CDR H2 as set forth in SEQ ID NO:87 and a

CDR H3 set forth in SEQ ID NO:88; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:89, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:90.

[0016] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes CDR H1, CDR H2, and CDR H3, and the light chain variable domain includes CDR L1, CDR L2, and CDR L3, wherein the CDR H1 is SEQ ID NO:66, the CDR H2 is SEQ ID NO:67, the CDR H3 is a variant of SEQ ID NO:68, the CDR L1 is SEQ ID NO:69, the CDR L2 is LGS, and the CDR L3 is SEQ ID NO:70; and wherein the variant of SEQ ID NO:68 is the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4, position 6, position 10, and position 11 relative to SEQ ID NO:68.

[0017] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes CDR H1, CDR H2, and CDR H3, and the light chain variable domain includes CDR L1, CDR L2, and CDR L3, wherein the CDR H1 is SEQ ID NO:66, the CDR H2 is SEQ ID NO:67, the CDR H3 is a variant of SEQ ID NO:68, the CDR L1 is SEQ ID NO:69, the CDR L2 is LGS, and the CDR L3 is SEQ ID NO:70; and wherein the variant of SEQ ID NO:68 is the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4 and position 7 relative to SEQ ID NO:68.

[0018] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes CDR H1, CDR H2, and CDR H3, and the light chain variable domain includes CDR L1, CDR L2, and CDR L3, wherein the CDR H1 is SEQ ID NO:1, the CDR H2 is SEQ ID NO:2, the CDR H3 is SEQ ID NO:3, the CDR L1 is SEQ ID NO:4, the CDR L2 is LGS, and the CDR L3 is SEQ ID NO:5.

[0019] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes CDR H1, CDR H2, and CDR H3, and the light chain variable domain includes CDR L1, CDR L2, and CDR L3, wherein the CDR H1 is SEQ ID NO:14, the CDR H2 is SEQ ID NO:15 and the CDR H3 is SEQ ID NO:16, the CDR L1 is SEQ ID NO:17, the CDR L2 is LGS, and the CDR L3 is SEQ ID NO:18.

[0020] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes CDR H1, CDR H2, and CDR H3, and the light chain variable domain includes CDR L1, CDR L2, and CDR L3, wherein the CDR H1 is SEQ ID NO:27, the CDR H2 is SEQ ID NO:28 and the CDR H3 is SEQ ID NO:29, the CDR L1 is SEQ ID NO:30, the CDR L2 is LGS, and the CDR L3 is SEQ ID NO:31.

[0021] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes CDR H1, CDR H2, and CDR H3, and the light chain variable domain includes CDR L1, CDR L2, and CDR L3, wherein the CDR H1 is SEQ ID NO:86, the CDR H2 is SEQ ID NO:87 and the CDR H3 is SEQ ID NO:88, CDR L1 is SEQ ID NO:89, the CDR L2 is LGS, and the CDR L3 is SEQ ID NO:90.

[0022] In an aspect is provided an anti-Ephrin B2 antibody, wherein the anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes CDR H1, CDR H2, and CDR H3, and the light chain variable domain includes CDR L1, CDR L2, and CDR L3, wherein the CDR H1 is SEQ ID NO:1, the CDR H2 is SEQ ID NO:2, the CDR H3 is SEQ ID NO:3; the CDR L1 is SEQ ID NO:4, the CDR L2 is LGS, and the CDR L3 is SEQ ID NO:5.

[0023] In an aspect is provided an anti-Ephrin B2 antibody, wherein the anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes CDR H1, CDR H2, and CDR H3, and the light chain variable domain includes CDR L1, CDR L2, and CDR L3, wherein the CDR H1 is SEQ ID NO:14, the CDR H2 is SEQ ID NO:15, the CDR H3 is SEQ ID NO:16, the CDR L1 is SEQ ID NO:17, the CDR L2 is LGS, and the CDR L3 is SEQ ID NO:18.

[0024] In an aspect is provided an anti-Ephrin B2 antibody, wherein the anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes CDR H1, CDR H2, and CDR H3, and the light chain variable domain includes CDR L1, CDR L2, and CDR L3, wherein the CDR H1 is SEQ ID NO:27, the CDR H2 is SEQ ID NO:28, the CDR H3 is SEQ ID NO:29, the CDR L1 is SEQ ID NO:30, the CDR L2 is LGS, and the CDR L3 is SEQ ID NO:31.

[0025] In an aspect is provided an anti-Ephrin B2 antibody, wherein the anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes CDR H1, CDR H2, and CDR H3, and the light chain variable domain includes CDR L1, CDR L2, and CDR L3, wherein the CDR H1 is SEQ ID NO:86, the CDR H2 is SEQ ID NO:87, the CDR H3 is SEQ ID NO:88, the CDR L1 is SEQ ID NO:89, the CDR L2 is LGS, and the CDR L3 is SEQ ID NO:90.

[0026] In another aspect is provided a method of treating fibrosis in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of an antibody provided herein including embodiments thereof.

[0027] In another aspect is provided a method of inhibiting migration of an Ephrin-B2 expressing cell, the method including contacting the cell with the anti-Ephrin B2 antibody provided herein including embodiments thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] **FIG.s 1A-1D.** B11 variant binding to human Ephrin B2. Biacore binding traces for B11-NTS (FIG. 1A), B11-DTS (FIG. 1B), and B11-QTS (FIG. 1C) and the measured K_Ds for the parental B11 (B11-NTS) and N-glycosylation removal variants (FIG. 1D) are shown.

[0029] **FIG. 2.** CDRs containing residue mutations, total library size and corresponding theoretical sequence diversity are shown for each maturation library derived from B11. The phage display libraries were generated for the B11 affinity maturation campaign.

[0030] **FIG.s 3A-3B**. B11 binding to full length vs truncated Ephrin B2 ECD. The unique B11 epitope is reflected by this Carterra SPR binding trace with the B11 scFv (FIG. 3A) and the representative anti-EphrinB2 scFv EB2-P01-A05 (FIG. 3B) binding to the recombinant EphrinB2 ECD deletion constructs 6His-HuEphrinB2-ECD-Del182-194-hIgG1-Fc and 6His-HuEphrinB2-ECD-Del197-218-hIgG1-Fc.

[0031] **FIG. 4A**. B11 variable heavy chain CDR3 mutations that increase binding affinity to full length EphrinB2 ECD, but not the residue 197-218 deletion construct. B11 affinity matured scFv clones derived from the single CDR mutation phage library are given. ELISA signals for parental B11 (WT) and each novel scFv for binding to either the recombinant full EphrinB2 ECD or the residue 197-218 deletion constructs are given with grey bars reflecting the magnitude of the signal

values. The heavy chain CDR3 residue mutations for each of the affinity matured clones are shown ("–" reflects residue conservation to parental B11). The critical mutation residue positions I96 and T99 according to Kabat numbering (e.g. I100 and T103 relative to the variable heavy chain domain of SEQ ID NO:51), are highlighted.

[0032] **FIG. 4B**. Key B11 HC CDR3 positions and residue substitutions that increase binding affinity to full length EphrinB2 ECD, but not the residue 197-218 deletion construct. The amino acid substitutions at heavy chain positions I96 and T99, according to Kabat numbering (e.g. I100 and T103 relative to the variable heavy chain domain of SEQ ID NO:51) observed for affinity matured clones that preserve the parental B11 epitope dependance on EphrinB2 ECD residues 197-218, are given.

[0033] **FIG. 5A**. B11 HC CDR3 mutations that increase binding affinity to both full length EphrinB2 ECD and the residue 197-218 deletion construct. B11 affinity matured scFv clones derived from the single CDR mutation phage library are given. ELISA signals for parental B11 (WT) and each novel scFv for binding to either the recombinant full EphrinB2 ECD or the residue 197-218 deletion constructs are given with grey bars reflecting the magnitude of the signal values. The heavy chain CDR3 residue mutations for each of the affinity matured clones are shown ("–" reflects residue conservation to parental B11). The critical mutation residues I96 and F100C in accordance with Kabat numbering are highlighted (e.g. I100 and F107 relative to the variable heavy chain domain of SEQ ID NO:51.

[0034] **FIG. 5B**. Key B11 HC CDR3 positions and residue substitutions that increase binding affinity to both full length EphrinB2 ECD and the residue 197-218 deletion construct. The amino acid substitutions at heavy chain Kabat positions I96, G98, G100B and F100C (e.g. I100, G102, G106, and F107 relative to the variable heavy chain domain of SEQ ID NO:51) observed for affinity matured clones that do not preserve the parental B11 epitope dependance on EphrinB2 ECD residues 197-218, are given.

[0035] **FIG. 6A.** ELISA binding of affinity matured B11 variants to 6HIS-huEphrinB2-Del182-194-huIgG1-Fc. IgG1 parental B11-QTS and affinity matured anti-EphrinB2 clones direct binding ELISA to recombinant EphrinB2 ECD construct 6HIS-huEphrinB2-Del182-194-huIgG1-Fc. EC50 values and relative change in EC50s compared with parental B11 are shown.

[0036] FIG. 6B. ELISA binding of affinity matured B11 variants to 6HIS-huEphrinB2-Del197-218-huIgG1-Fc. IgG1 parental B11-QTS and affinity matured anti-EphrinB2 clones direct binding ELISA to recombinant EphrinB2 ECD construct 6HIS-huEphrinB2-Del197-218-huIgG1-Fc. EC50 values are shown.

[0037] FIG.s 7A-7D. Octet binding of affinity matured B11 variants to Ephrin B2 ECD. Octet traces of parental B11 (FIG. 7A) and the affinity matured clones Ab11 (FIG. 7B), Ab51 (FIG. 7C), and Ab25 (FIG. 7D) to the recombinant human EphrinB2 ECD. K_D, K_{on}, and K_{dis} are given for each.

[0038] FIG. 8. FACS binding of affinity matured B11 variants to HEK293 cells overexpressing EphrinB2. Flow cytometry binding of the affinity matured B11 antibodies to HEK293 cells overexpressing human EphrinB2. Calculated EC50 values are given.

[0039] FIG.s 9A-9B. Anti-EphrinB2 antibodies reduce EphB4 phosphorylation in primary Human Umbilical Vein Endothelial Cells (HUVECs) stimulated with recombinant EphrinB2. Monoclonal antibodies Ab90, Ab18 and Ab25 suppress EphB4 phosphorylation in HUVECs (FIG. 9A); Ab25 has an IC50 of 1.2 nM (FIG. 9B).

[0040] FIG.s 10A-10D. Anti-EphrinB2 antibodies immunoprecipitate (IP) EphrinB2 from culture supernatants and normal human serum. Monoclonal antibodies Ab25, B11-QTS, Ab11, Ab51 and Ab18 immunoprecipiate EphrinB2 from the cell culture supernatant of CHO cells stably overexpressing EphrinB2. Higher-affinity anti-EphrinB2 antibodies Ab25 and Ab18 more efficiently IP EphrinB2 than the lower affinity antibodies B11-QTS and Ab11 (CHO-OE; FIG. 10A). Ab25 and Ab18 also IP EphrinB2 from supernatants of colon cancer cell line Colo205 (FIG. 10B), which secretes a lesser amount of EphrinB2 than CHO-OE cells (FIG. 10C). Additionally, Ab25 immunoprecipitates EphrinB2 from normal human serum (FIG. 10D).

[0041] FIG.s 11A-11B. Anti-EphrinB2 antibodies reduce primary Human Umbilical Vein Endothelial Cell (HUVEC) chemotaxis/motility. Monoclonal antibodies B11-QTS, Ab11, Ab51 and Ab25 reduced HUVEC chemotaxis/migration at 10 and 100 μg/mL (left and right bars, respectively, for each antibody shown) at 24 hrs (FIG. 11A) and 40 hrs (FIG. 11B). Treatment with a polyclonal anti-EphrinB2 antibody (R&D AF496; positive control) also reduces HUVEC migration while a non-specific IgG antibody (negative control) does not alter migration at either 10 or 100 μg/mL.

"Phase Area Bottom Normalized to Initial Top Value" metric was used for calculating chemotaxis. Significance is indicated relative to no antibody with 10% FBS ($p < 0.05$).

[0042] FIG.s 12A-12C. Monoclonal anti-EphrinB2 antibodies reduce primary Human Umbilical Vein Endothelial Cell (HUVEC) chemotaxis/motility (images). Treatment with a polyclonal anti-EphrinB2 antibody (R&D AF496) reduces HUVEC chemotaxis/migration at 10 and 100 μg/mL (positive control, right panel), while a non-specific IgG antibody treatment does not significantly alter chemotaxis even at 100 μg/mL (negative control, left panel). Images from 2, 24 and 36 hrs following cell seeding are shown (FIG. 12A). Monoclonal anti-EphrinB2 antibody B11-QTS (left) and Ab11 (right) inhibit HUVEC migration at 10 and 100 μg/mL relative to no antibody (FIG. 12B). Monoclonal anti-EphrinB2 antibody Ab51 (left) and Ab25 (right) inhibit HUVEC migration at 10 and 100 μg/mL relative to no antibody (FIG. 12C). All contain 10% FBS in lower chamber of transwell. Lighter color cells have migrated to lower chamber of transwell.

[0043] FIG.s 13A-13D. Monoclonal anti-EphrinB2 antibodies reduce primary Human Umbilical Vein Endothelial Cell (HUVEC) chemotaxis/motility. Timecourse of HUVEC cell chemotaxis/migration under multiple conditions (10%, 2% or no FBS). B11-QTS (FIG. 13A), Ab11 (FIG. 13B), Ab51 (FIG. 13C) and Ab25 (FIG. 13D) reduce HUVEC cell migration at 10 and 100 μg/mL under all conditions evaluated. Comparable inhibition is observed with a polyclonal anti-EphrinB2 antibody (R&D AF496) at 100 μg/mL and 10% FBS, while non-specific IgG antibody does not inhibit chemotaxis/cell migration under the same conditions.

[0044] FIG.s 14A-14B. In vivo efficacy studies using anti-Ephrin B2 antibodies in the bleomycin lung injury and fibrosis model. Data illustrating that anti-Ephrin B2 suppresses lung fibrosis as measured by a decrease in hydroxyproline, an indication that collagen content in fibrotic tissue has decreased (FIG. 14A). Data expressed as Mean +/- SEM; *$p<0.05$ One-Way ANOVA with Dunnett's multiple comparison vs +PBS. Results show that anti-Ephrin B2 decreases hydroxyproline ranging from 55% to 87% compared to the vehicle control (FIG. 14B).

[0045] FIG.s 15A-15B. In vivo efficacy studies using anti-Ephrin B2 antibodies in the bleomycin lung injury and fibrosis model illustrates that antibodies suppress inflammation. (FIG. 15A) Data illustrating that anti-EphrinB2 reduces systemic inflammation in bleo-induced lung fibrosis model as shown by a decrease in plasma pro-inflammatory cytokines. (FIG. 15B) Data illustrating that anti-

Ephrin B2 attenuates lung inflammation as shown by a decrease in Bronchoalveolar lavage fluid (BALF) pro-inflammatory cytokines. Data expressed as Mean +/- SEM; *p<0.05 One-Way ANOVA with Dunnett's multiple comparison vs vehicle group (+PBS).

[0046] FIG.s 16A-16C. In vivo efficacy studies using anti-Ephrin B2 antibodies in the scleroderma skin fibrosis model illustrate that Ab25 attenuated bleomycin (Bleo)-induced skin fibrosis. (FIG. 16A) Anti-EphrinB2 antibodies decrease hydroxyproline production in the bleomycin skin fibrosis model compared to the vehicle control. (FIG. 16B) In Bleo skin fibrosis mouse model administration of Ab25 reduced dermal thickness compared to vehicle-treated control (PBS). (FIG. 16C) Representative skin images of Masson Trichrome (MT)-stained histological sections acquired at 100X magnification. Dermis (D); Epidermis (E); skeletal muscle (*); deep subcuticular tissue (SC); Black line indicates the thickness of the dermis in the vehicle control group for comparison. The image shows that bleo increased dermal thickness compared to control and treatment with anti-Ephrin B2 antibody was able to reduce this.

[0047] FIG.s 17A-17D. Shows ephrinB2-EphB receptor competition ELISA. Data show AB25 blocks ephrinB2-EphB2 (FIG. 17A), ephrinB2-EphB3 (FIG. 17B), and EFNB2-EphB4 (FIG. 17AC) interaction. IC50 values are shown in FIG. 17D.

[0048] FIG.s 18A-18D. BLI sensograms of B11-affinity matured AB25 binding to human (hu) (FIG. 18A), cynomolgus (cyno) (FIG. 18B), mouse (mu) (FIG. 18C) and rat (FIG. 18D) EphrinB2 proteins.

[0049] FIG. 19. BLI Kinetic values of B11 affinity-matured variant AB25 binding to human, cyno, mouse and rat EphrinB2-ECD proteins.

[0050] FIG. 20. Cross Species Kinetics SPR K_{on} verses K_{off}.

[0051] FIG.s 21A-21D. SPR Traces for AB25 Binding to human (FIG. 21A), cynomolgus (FIG. 21B), mouse (FIG. 21C), and rat (FIG. 21D) Ephrin B2.

[0052] FIG. 22. Amino acid residues involved in anti-Ephrin B2 antibody AB25 and EphrinB2 interactions. Numbering of VH and VL residues are relative to SEQ ID NO:12 and 13, respectively. Numbering of human Ephrin B2 protein is relative to SEQ ID NO:79.

[0053] **FIG. 23.** Shows HCDR1 hydrophobic residues Tyr^{H32} and Tyr^{H33} interacting with hu ephrinB2. Tyr^{H32} forms H-bond with Glu94. Tyr^{H33} forms two contacts, a H-bond with Gly123 and a π-H bond with Leu 121.

[0054] **FIG. 24.** Shows HCDR2 amino residues involved in complex formation with G-H loop of hu ephrinB2.Asn^{H52}, Ser^{H55} and Asn^{H57} form H-bonds with Glu125. Leu121 forms H-bonds with Trp^{H50} and Thr^{H58}. Asn^{H57} forms additional H-bond with Ser118.

[0055] **FIG. 25.** LCDR1 residues that complex with the E-F loop of human ephrinB2. Ser^{L32} forms H-bond with K109 in human ephrinB2. Asn^{L33} and Gly^{L34} form H-bonds with Asn100. Asn^{L33} forms additional H bond with Leu98 of human ephrinB2.

[0056] **FIG. 26.** HCDR3 residue interacting with E-F loop of hu ephrinB2. The high affinity mutation Lys^{H102} forms salt bridge with negatively charged Glu94 while Arg^{H106} forms a H-bond with Asn95 in human ephrinB2.

[0057] **FIG. 27.** LCDR3 residues Leu^{L97} and Ser^{L99} forming H-bonds with Trp122 in G-H loop of human ephrinB2.

[0058] **FIG. 28.** Shows sequence alignment for human, cynomolgus, mouse and rat EFNB2-ECD. The AB25 binding sites (indicated by boxes) in EFNB2 are conserved across species. From top to bottom, the sequences shown are the consensus (SEQ ID NO:100), cynomolgus (SEQ ID NO:101), human (SEQ ID NO:102), mouse (SEQ ID NO:103) and rat (SEQ ID NO:104) sequences.

DETAILED DESCRIPTION

[0059] While various embodiments and aspects of the present invention are shown and described herein, it will be obvious to those skilled in the art that such embodiments and aspects are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention.

[0060] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, without limitation, patents, patent applications, articles, books,

manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

[0061] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0062] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art. See, e.g., Singleton et al., DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY 2nd ed., J. Wiley & Sons (New York, NY 1994); Sambrook et al., MOLECULAR CLONING, A LABORATORY MANUAL, Cold Springs Harbor Press (Cold Springs Harbor, NY 1989), which is incorporated herein in its entirety and for all purposes. Any methods, devices and materials similar or equivalent to those described herein can be used in the practice of this invention. The following definitions are provided to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure.

[0063] As used herein, the term "about" means a range of values including the specified value, which a person of ordinary skill in the art would consider reasonably similar to the specified value. In embodiments, the term "about" means within a standard deviation using measurements generally acceptable in the art. In embodiments, about means a range extending to +/- 10% of the specified value. In embodiments, about means the specified value.

[0064] As used herein, the terms "includes" or “including” are used to indicate that the list of elements or steps that follow is not exhaustive. This means that additional elements or steps may be present in the invention, even if they are not explicitly mentioned. The terms "includes" or “including” are synonymous with "comprising" and are considered open-ended, allowing for the inclusion of other unrecited elements or steps.

[0065] As used herein, the terms “consists” or "consisting of" are used as closed-ended terms that exclude any element, step, or ingredient not specifically mentioned after the term. Use of the terms “consists” or "consisting of" means that the recited feature is limited to only those components and does not allow for the inclusion of any additional elements.

[0066] "Nucleic acid" refers to nucleotides (e.g., deoxyribonucleotides or ribonucleotides) and polymers thereof in either single-, double- or multiple-stranded form, or complements thereof; or nucleosides (e.g., deoxyribonucleosides or ribonucleosides). In embodiments, "nucleic acid" does not include nucleosides. The terms "polynucleotide," "oligonucleotide," "oligo" or the like refer, in the usual and customary sense, to a linear sequence of nucleotides. The term "nucleoside" refers, in the usual and customary sense, to a glycosylamine including a nucleobase and a five-carbon sugar (ribose or deoxyribose). Non limiting examples, of nucleosides include, cytidine, uridine, adenosine, guanosine, thymidine and inosine. The term "nucleotide" refers, in the usual and customary sense, to a single unit of a polynucleotide, i.e., a monomer. Nucleotides can be ribonucleotides, deoxyribonucleotides, or modified versions thereof. Examples of polynucleotides contemplated herein include single and double stranded DNA, single and double stranded RNA, and hybrid molecules having mixtures of single and double stranded DNA and RNA. Examples of nucleic acid, e.g. polynucleotides contemplated herein include any types of RNA, e.g. mRNA, siRNA, miRNA, and guide RNA and any types of DNA, genomic DNA, plasmid DNA, and minicircle DNA, and any fragments thereof. The term "duplex" in the context of polynucleotides refers, in the usual and customary sense, to double strandedness. Nucleic acids can be linear or branched. For example, nucleic acids can be a linear chain of nucleotides or the nucleic acids can be branched, e.g., such that the nucleic acids comprise one or more arms or branches of nucleotides. Optionally, the branched nucleic acids are repetitively branched to form higher ordered structures such as dendrimers and the like.

[0067] Nucleic acids, including e.g., nucleic acids with a phosphothioate backbone, can include one or more reactive moieties. As used herein, the term reactive moiety includes any group capable of reacting with another molecule, e.g., a nucleic acid or polypeptide through covalent, non-covalent or other interactions. By way of example, the nucleic acid can include an amino acid reactive moiety that reacts with an amio acid on a protein or polypeptide through a covalent, non-covalent or other interaction.

[0068] The terms also encompass nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation,

phosphodiester derivatives including, e.g., phosphoramidate, phosphorodiamidate, phosphorothioate (also known as phosphothioate having double bonded sulfur replacing oxygen in the phosphate), phosphorodithioate, phosphonocarboxylic acids, phosphonocarboxylates, phosphonoacetic acid, phosphonoformic acid, methyl phosphonate, boron phosphonate, or O-methylphosphoroamidite linkages (see Eckstein, OLIGONUCLEOTIDES AND ANALOGUES: A PRACTICAL APPROACH, Oxford University Press, which is incorporated herein in its entirety and for all purposes) as well as modifications to the nucleotide bases such as in 5-methyl cytidine or pseudouridine.; and peptide nucleic acid backbones and linkages. Other analog nucleic acids include those with positive backbones; non-ionic backbones, modified sugars, and non-ribose backbones (e.g. phosphorodiamidate morpholino oligos or locked nucleic acids (LNA) as known in the art), including those described in U.S. Patent Nos. 5,235,033 and 5,034,506, and Chapters 6 and 7, ASC Symposium Series 580, CARBOHYDRATE MODIFICATIONS IN ANTISENSE RESEARCH, Sanghui & Cook, eds, which are incorporated herein in their entirety and for all purposes. Nucleic acids containing one or more carbocyclic sugars are also included within one definition of nucleic acids. Modifications of the ribose-phosphate backbone may be done for a variety of reasons, e.g., to increase the stability and half-life of such molecules in physiological environments or as probes on a biochip. Mixtures of naturally occurring nucleic acids and analogs can be made; alternatively, mixtures of different nucleic acid analogs, and mixtures of naturally occurring nucleic acids and analogs may be made. In embodiments, the internucleotide linkages in DNA are phosphodiester, phosphodiester derivatives, or a combination of both.

[0069] Nucleic acids can include nonspecific sequences. As used herein, the term "nonspecific sequence" refers to a nucleic acid sequence that contains a series of residues that are not designed to be complementary to or are only partially complementary to any other nucleic acid sequence. By way of example, a nonspecific nucleic acid sequence is a sequence of nucleic acid residues that does not function as an inhibitory nucleic acid when contacted with a cell or organism.

[0070] A polynucleotide is typically composed of a specific sequence of four nucleotide bases: adenine (A); cytosine (C); guanine (G); and thymine (T) (uracil (U) for thymine (T) when the polynucleotide is RNA). Thus, the term “polynucleotide sequence” is the alphabetical representation of a polynucleotide molecule; alternatively, the term may be applied to the polynucleotide molecule itself. This alphabetical representation can be input into databases in a

computer having a central processing unit and used for bioinformatics applications such as functional genomics and homology searching. Polynucleotides may optionally include one or more non-standard nucleotide(s), nucleotide analog(s) and/or modified nucleotides.

[0071] The term "complement," as used herein, refers to a nucleotide (e.g., RNA or DNA) or a sequence of nucleotides capable of base pairing with a complementary nucleotide or sequence of nucleotides. As described herein and commonly known in the art the complementary (matching) nucleotide of adenosine is thymidine and the complementary (matching) nucleotide of guanosine is cytosine. Thus, a complement may include a sequence of nucleotides that base pair with corresponding complementary nucleotides of a second nucleic acid sequence. The nucleotides of a complement may partially or completely match the nucleotides of the second nucleic acid sequence. Where the nucleotides of the complement completely match each nucleotide of the second nucleic acid sequence, the complement forms base pairs with each nucleotide of the second nucleic acid sequence. Where the nucleotides of the complement partially match the nucleotides of the second nucleic acid sequence only some of the nucleotides of the complement form base pairs with nucleotides of the second nucleic acid sequence. Examples of complementary sequences include coding and a non-coding sequences, wherein the non-coding sequence contains complementary nucleotides to the coding sequence and thus forms the complement of the coding sequence. A further example of complementary sequences are sense and antisense sequences, wherein the sense sequence contains complementary nucleotides to the antisense sequence and thus forms the complement of the antisense sequence.

[0072] As described herein the complementarity of sequences may be partial, in which only some of the nucleic acids match according to base pairing, or complete, where all the nucleic acids match according to base pairing. Thus, two sequences that are complementary to each other, may have a specified percentage of nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region).

[0073] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*, hydroxyproline, γ-carboxyglutamate, and O-

phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, *i.e.*, an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid. The terms "non-naturally occurring amino acid" and "unnatural amino acid" refer to amino acid analogs, synthetic amino acids, and amino acid mimetics which are not found in nature.

[0074] Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0075] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may In embodiments be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymers. A "fusion protein" refers to a chimeric protein encoding two or more separate protein sequences that are recombinantly expressed as a single moiety.

[0076] An amino acid or nucleotide base "position" is denoted by a number that sequentially identifies each amino acid (or nucleotide base) in the reference sequence based on its position relative to the N-terminus (or 5'-end). Due to deletions, insertions, truncations, fusions, and the like that must be taken into account when determining an optimal alignment, in general the amino acid residue number in a test sequence determined by simply counting from the N-terminus will not necessarily be the same as the number of its corresponding position in the reference sequence. For example, in a case where a variant has a deletion relative to an aligned reference sequence, there will be no amino acid in the variant that corresponds to a position in the reference sequence at the site of deletion. Where there is an insertion in an aligned reference sequence, that insertion will not

correspond to a numbered amino acid position in the reference sequence. In the case of truncations or fusions there can be stretches of amino acids in either the reference or aligned sequence that do not correspond to any amino acid in the corresponding sequence.

[0077] The terms "numbered with reference to" or "corresponding to," when used in the context of the numbering of a given amino acid or polynucleotide sequence, refers to the numbering of the residues of a specified reference sequence when the given amino acid or polynucleotide sequence is compared to the reference sequence. An amino acid residue in a protein "corresponds" to a given residue when it occupies the same essential structural position within the protein as the given residue. One skilled in the art will immediately recognize the identity and location of residues corresponding to a specific position in a protein (*e.g.,* Ephrin B2) in other proteins with different numbering systems. For example, by performing a simple sequence alignment with a protein (*e.g.,* Ephrin B2) the identity and location of residues corresponding to specific positions of the protein are identified in other protein sequences aligning to the protein. For example, a selected residue in a selected protein corresponds to glutamic acid at position 138 when the selected residue occupies the same essential spatial or other structural relationship as a glutamic acid at position 138. In some embodiments, where a selected protein is aligned for maximum homology with a protein, the position in the aligned selected protein aligning with glutamic acid 138 is the to correspond to glutamic acid 138. Instead of a primary sequence alignment, a three dimensional structural alignment can also be used, *e.g.,* where the structure of the selected protein is aligned for maximum correspondence with the glutamic acid at position 138, and the overall structures compared. In this case, an amino acid that occupies the same essential position as glutamic acid 138 in the structural model is the to correspond to the glutamic acid 138 residue.

[0078] "Conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, "conservatively modified variants" refers to those nucleic acids that encode identical or essentially identical amino acid sequences. Because of the degeneracy of the genetic code, a number of nucleic acid sequences will encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations.

Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence.

[0079] As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the disclosure.

[0080] The following eight groups each contain amino acids that are conservative substitutions for one another:

1) Alanine (A), Glycine (G);

2) Aspartic acid (D), Glutamic acid (E);

3) Asparagine (N), Glutamine (Q);

4) Arginine (R), Lysine (K);

5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V);

6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W);

7) Serine (S), Threonine (T); and

8) Cysteine (C), Methionine (M)

(*see, e.g.*, Creighton, *Proteins* (1984)).

[0081] In embodiments, amino acid sequence variants (e.g., antibody variants of the anti-Ephrin B2 antibodies and antigen-binding fragments thereof including one or more amino acid residue alterations) of the antibodies provided herein are contemplated. For example, it may be desirable to

improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, for example, antigen binding.

[0082] In embodiments, antibody variants having one or more amino acid substitutions are provided. Sites of interest for substitutional mutagenesis include the CDRs and FRs. Such variants may be "conservatively modified variants" wherein the substitution comprises exchanging one or more amino acids with another from the same group as set out above. Such variants may be "non-conservatively modified variants" wherein the substitution comprises exchanging one or more amino acids with another from a different group as set out above.

[0083] Furthermore, in embodiments, any native residue in the polypeptide may also be substituted with alanine, as has been previously described for alanine scanning mutagenesis (MacLennan et al. (1998) Acta Physiol Sc and Suppl 643: 55-67; Sasaki et al. (1998) Adv Biophys 35: 1-24). Amino acid substitutions to the antibodies of the invention may be made by known methods for example by PCR mutagenesis (U.S. Pat. No. 4,683,195). Amino acid substitutions may be introduced into an antibody of interest and the products screened for a desired activity, for example, retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

[0084] In embodiments, an antibody provided herein is altered to increase or decrease the extent to which the antibody is glycosylated. Addition or deletion of glycosylation sites to an antibody may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

[0085] In embodiments, wherein the antibody includes an Fc region, the carbohydrate attached thereto may be altered. In embodiments, native antibodies produced by mammalian cells include a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. See, e.g., Wright et al., TIBTECH 15:26-32 (1997). The oligosaccharide may include various carbohydrates, e.g., mannose, N-acetyl glucosamine (GlcNAc),

galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure. In embodiments, modifications of the oligosaccharide in an antibody of the invention may be made in order to create antibody variants with improved properties.

[0086] In embodiments, antibody variants are provided having a carbohydrate structure that lacks fucose attached (directly or indirectly) to an Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. The amount of fucose is determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 (e.g. complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (Eu numbering of Fc region residues); however, Asn297 may also be located about ±3 amino acids upstream or downstream of position 297, i.e., between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have improved ADCC function. See, for example, US Patent Publication Nos. US 2003/0157108; US 2004/0093621. Examples of publications related to "defucosylated" or "fucose-deficient" antibody variants include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; WO2002/031140; Okazaki et al., J. Mol. Biol. 336:1239-1249 (2004); Yamane-Ohnuki et al., Biotech. Bioeng. 87: 614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka et al., Arch. Biochem. Biophys. 249:533-545 (1986); US Pat Appl No US 2003/0157108 A1, Presta, L; and WO 2004/056312 A1, Adams et al., especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, FUT8, knockout CHO cells (see, e.g., Yamane-Ohnuki et al., Biotech. Bioeng. 87: 614 (2004); Kanda et al., Biotechnol. Bioeng., 94(4):680-688 (2006); and WO2003/085107).

[0087] In embodiments, antibody variants are further provided with bisected oligosaccharides, e.g., in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, e.g., in WO 2003/011878; U.S. Pat. No.

6,602,684; and US 2005/0123546 (Umana et al.). In embodiments, antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody variants may have improved CDC function. Such antibody variants are described, for example, in WO 1997/30087; WO 1998/58964; and WO 1999/22764 (Raju, S.).

[0088] In embodiments, one or more amino acid modifications may be introduced into the Fc region of an antibody provided herein, thereby generating an Fc region variant. The Fc region variant may comprise a human Fc region sequence (e.g., a human IgG1, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid residue alteration (e.g., a substitution) at one or more amino acid positions.

[0089] In embodiments, the invention contemplates an antibody variant that possesses some but not all effector functions, which make it a desirable candidate for applications in which the half-life of the antibody in vivo is important yet effector functions (such as complement and ADCC) are unnecessary or deleterious. In vitro and/or in vivo cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express Fc(RIII only, whereas monocytes express Fc(RI, Fc(RII and Fc(RIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, Annu. Rev. Immunol. 9:457-492 (1991).

[0090] Non-limiting examples of in vitro assays to assess ADCC activity of a molecule of interest are described in U.S. Pat. No. 5,500,362 (see, e.g. Hellstrom et al., Proc. Nat'l Acad. Sci. USA 83:7059-7063 (1986) and Hellstrom, I et al., Proc. Nat'l Acad. Sci. USA 82:1499-1502 (1985); U.S. Pat. No. 5,821,337; and Bruggemann et al., J. Exp. Med. 166:1351-1361 (1987)). Alternatively, non-radioactive assays methods may be employed (see, for example, ACTI™ non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, CA; and CYTOTOX 96® non-radioactive cytotoxicity assay (Promega, Madison, WI). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed in vivo, for example, in a animal model such as that disclosed in Clynes et al., Proc. Nat'l Acad. Sci. USA 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is

unable to bind C1q and hence lacks CDC activity. See, for example, C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (see, e.g., Gazzano-Santoro et al., J. Immunol. Methods 202:163 (1996); Cragg et al., Blood 101:1045-1052 (2003); and Cragg et al., Blood 103:2738-2743 (2004)). FcRn binding and in vivo clearance/half life determinations can also be performed using methods known in the art (see, e.g., Petkova et al., Int'l. Immunol. 18(12):1759-1769 (2006)).

[0091] In embodiments, antibodies with reduced effector function include those with substitution of one or more of Fc region residues 238, 265, 269, 270, 297, 327 and 329 (U.S. Pat. No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (U.S. Pat. No. 7,332,581).

[0092] Antibody variants with improved or diminished binding to FcRs are described. (See, e.g., U.S. Pat. No. 6,737,056; WO 2004/056312, and Shields et al., J. Biol. Chem. 9(2): 6591-6604 (2001)).

[0093] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (*see, e.g.*, NCBI web site http://www.ncbi.nlm.nih.gov/BLAST/ or the like). Such sequences are then said to be "substantially identical." This definition also refers to, or may be applied to, the compliment of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 25 amino acids or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

[0094] "Percentage of sequence identity" is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide or polypeptide

sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

[0095] A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of, e.g., a full length sequence or from 20 to 600, about 50 to about 200, or about 100 to about 150 amino acids or nucleotides in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith and Waterman (1970) *Adv. Appl. Math.* 2:482c, which is incorporated herein in its entirety and for all purposes, by the homology alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, which is incorporated herein in its entirety and for all purposes, by the search for similarity method of Pearson and Lipman (1988) *Proc. Nat'l. Acad. Sci. USA* 85:2444, which is incorporated herein in its entirety and for all purposes, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (*see, e.g.,* Ausubel *et al.*, *Current Protocols in Molecular Biology* (1995 supplement)), which is incorporated herein in its entirety and for all purposes.

[0096] An example of an algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.* (1977) *Nuc. Acids Res.* 25:3389-3402, and Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410, respectively, which are incorporated herein in their entirety and for all purposes. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either

match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a word length (W) of 11, an expectation (E) or 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a word length of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (*see* Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915, which is incorporated herein in its entirety and for all purposes) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

[0097] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (*see, e.g.*, Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5787, which is incorporated herein in its entirety and for all purposes). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

[0098] An indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where

the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

[0099] Antibodies are large, complex molecules (molecular weight of ~150,000 or about 1320 amino acids) with intricate internal structure. A natural antibody molecule contains two identical pairs of polypeptide chains, each pair having one light chain and one heavy chain. Each light chain and heavy chain in turn consists of two regions: a variable ("V") region, involved in binding the target antigen, and a constant ("C") region that interacts with other components of the immune system. The light and heavy chain variable regions (also referred to herein as light chain variable (VL) domain and heavy chain variable (VH) domain, respectively) come together in 3-dimensional space to form a variable region that binds the antigen (for example, a receptor on the surface of a cell). Within each light or heavy chain variable region, there are three short segments (averaging 10 amino acids in length) called the complementarity determining regions ("CDRs"). The six CDRs in an antibody variable domain (three from the light chain and three from the heavy chain) fold up together in 3-dimensional space to form the actual antibody binding site which docks onto the target antigen. The part of a variable region not contained in the CDRs is called the framework ("FR"), which forms the environment for the CDRs. The position and length of the CDRs can be defined in accordance with the Kabat numbering system; Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)., or the IMGT numbering system; Lefranc, M.P. et al. Nucl. Acids Res. 27:209-212 (1999), Ruiz, M. e al. Nucl. Acids Res. 28:219-221 (2000). In embodiments, the CDRs of the antibodies provided herein including embodiments thereof may be the amino acid sequences as defined by Kabat numbering or IMGT numbering as set forth in Table 1.

[0100] An "antibody fragment" as provided herein refers to a polypeptide capable of binding to an antigen and including one or more structural domains (e.g., light chain variable domain, heavy chain variable domain) of an antibody. Non-limiting examples of antibody fragment include single-domain antibodies or nanobodies, monospecific Fab_2, bispecific Fab_2, trispecific Fab_3, monovalent IgGs, scFv, bispecific antibodies, bispecific diabodies, trispecific triabodies, scFv-Fc, minibodies,

IgNAR, V-NAR, hcIgG, VhH, or peptibodies. A "peptibody" as provided herein refers to a peptide moiety attached (through a covalent or non-covalent linker) to the Fc domain of an antibody. Further non-limiting examples of antibody fragmentknown in the art include antibodies produced by cartilaginous fish or camelids. A general description of antibodies from camelids and the variable regions thereof and methods for their production, isolation, and use may be found in references WO97/49805 and WO 97/49805 which are incorporated by reference herein in their entirety and for all purposes. Likewise, antibodies from cartilaginous fish and the variable regions thereof and methods for their production, isolation, and use may be found in WO2005/118629, which is incorporated by reference herein in its entirety and for all purposes.

[0101] The terms "CDR L1", "CDR L2" and "CDR L3" as provided herein refer to the complementarity determining regions (CDR) 1, 2, and 3 of the variable light (L) chain of an antibody. In embodiments, the variable light chain provided herein includes in N-terminal to C-terminal direction a CDR L1, a CDR L2 and a CDR L3. Likewise, the terms "CDR H1", "CDR H2" and "CDR H3" as provided herein refer to the complementarity determining regions (CDR) 1, 2, and 3 of the variable heavy (H) chain of an antibody. In embodiments, the variable heavy chain provided herein includes in N-terminal to C-terminal direction a CDR H1, a CDR H2 and a CDR H3.

[0102] The terms "FR L1", "FR L2", "FR L3" and "FR L4" as provided herein are used according to their common meaning in the art and refer to the framework regions (FR) 1, 2, 3 and 4 of the variable light (L) chain of an antibody. In embodiments, the variable light chain provided herein includes in N-terminal to C-terminal direction a FR L1, a FR L2, a FR L3 and a FR L4. Likewise, the terms "FR H1", "FR H2", "FR H3" and "FR H4" as provided herein are used according to their common meaning in the art and refer to the framework regions (FR) 1, 2, 3 and 4 of the variable heavy (H) chain of an antibody. In embodiments, the variable heavy chain provided herein includes in N-terminal to C-terminal direction a FR H1, a FR H2, a FR H3 and a FR H4.

[0103] An exemplary immunoglobulin (antibody) structural unit comprises a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kD) and one "heavy" chain (about 50-70 kD). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (VL), variable light chain (VL) domain or light chain

variable region and variable heavy chain (VH), variable heavy chain (VH) domain or heavy chain variable region refer to these light and heavy chain regions, respectively. The terms variable light chain (VL), variable light chain (VL) domain and light chain variable region as referred to herein may be used interchangeably. The terms variable heavy chain (VH), variable heavy chain (VH) domain and heavy chain variable region as referred to herein may be used interchangeably. The Fc (i.e. fragment crystallizable region) is the "base" or "tail" of an immunoglobulin and is typically composed of two heavy chains that contribute two or three constant domains depending on the class of the antibody. By binding to specific proteins, the Fc region ensures that each antibody generates an appropriate immune response for a given antigen. The Fc region also binds to various cell receptors, such as Fc receptors, and other immune molecules, such as complement proteins.

[0104] The term “antibody” is used according to its commonly known meaning in the art. Antibodies exist, e.g., as intact immunoglobulins or as a number of well-characterized fragments produced by digestion with various peptidases. Thus, for example, pepsin digests an antibody below the disulfide linkages in the hinge region to produce $F(ab)'_2$, a dimer of Fab which itself is a light chain joined to V_H-C_{H1} by a disulfide bond. The $F(ab)'_2$ may be reduced under mild conditions to break the disulfide linkage in the hinge region, thereby converting the $F(ab)'_2$ dimer into an Fab' monomer. The Fab' monomer is essentially Fab with part of the hinge region (see Fundamental Immunology (Paul ed., 3d ed. 1993), which is incorporated herein in its entirety and for all purposes. While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill will appreciate that such fragments may be synthesized *de novo* either chemically or by using recombinant DNA methodology. Thus, the term antibody, as used herein, also includes antibody fragments either produced by the modification of whole antibodies, or those synthesized de novo using recombinant DNA methodologies (e.g., single chain Fv) or those identified using phage display libraries (see, e.g., McCafferty *et al.*, *Nature* 348:552-554 (1990), which is incorporated herein in its entirety and for all purposes). The term “antibody” as referred to herein further includes antibody fragment such as single domain antibodies. Thus, in embodiments an antibody includes a single monomeric variable antibody domain. Thus, in embodiments, the antibody, includes a variable light chain (VL) domain or a variable heavy chain (VH) domain. In embodiments, the antibody is a variable light chain (VL) domain or a variable heavy chain (VH) domain.

[0105] For preparation of monoclonal or polyclonal antibodies, any technique known in the art can be used (*see, e.g.*, Kohler & Milstein, *Nature* 256:495-497 (1975); Kozbor *et al.*, *Immunology Today* 4:72 (1983); Cole *et al.*, pp. 77-96 in *Monoclonal Antibodies and Cancer Therapy* (1985), which are incorporated herein in their entirety and for all purposes). "Monoclonal" antibodies (mAb) refer to antibodies derived from a single clone. Techniques for the production of single chain antibodies (U.S. Pat. No. 4,946,778, which is incorporated herein in its entirety and for all purposes) can be adapted to produce antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms such as other mammals, may be used to express humanized antibodies. Alternatively, phage display technology can be used to identify antibodies and heteromeric Fab fragments that specifically bind to selected antigens (*see, e.g.*, McCafferty *et al.*, *Nature* 348:552-554 (1990); Marks *et al.*, *Biotechnology* 10:779-783 (1992), which is incorporated herein in its entirety and for all purposes).

[0106] An antibody may be or include a single-chain antibody. A single-chain antibody may be or include a single-chain variable fragment (scFv). A scFv typically a fusion protein of the variable regions of the heavy (VH) and light chains (VL) of immunoglobulins, connected with a short linker peptide of 10 to about 25 amino acids. The linker may usually be rich in glycine for flexibility, as well as serine or threonine for solubility. The linker can either connect the N-terminus of the VH with the C-terminus of the VL, or vice versa.

[0107] In embodiments, the antibody fragment is a Fab' fragment. Fab' fragments differ from Fab fragments by the presence of additional residues including one or more cysteines from the antibody hinge region at the C-terminus of the CH1 domain. $F(ab')_2$ antibody fragments are pairs of Fab' fragments linked by cysteine residues in the hinge region. Other chemical couplings of antibody fragments are also known.

[0108] In embodiments, the antibody fragment is Fv fragment. A "Fv" fragment contains a complete antigen-recognition and binding site consisting of a dimer of one heavy and one light chain variable domain in tight, non-covalent association. In this configuration, the three CDRs of each variable domain interact to define an antigen-biding site on the surface of the VH-VL dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody.

[0109] In embodiments, the antibody fragment may also form a tandem Fd segment, which comprise a pair of tandem Fd segments (VH-CH1-VH-CH1) to form a pair of antigen binding

regions. These "linear antibodies" can be bispecific or monospecific as described in, for example, Zapata et al. 1995, Protein Eng. 8(10):1057-1062.

[0110] The epitope of a mAb is the region of its antigen to which the mAb binds. Two antibodies bind to the same or overlapping epitope if each competitively inhibits (blocks) binding of the other to the antigen. That is, a 1x, 5x, 10x, 20x or 100x excess of one antibody inhibits binding of the other by at least 30% but preferably 50%, 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans *et al.*, Cancer Res. 50:1495, 1990, which is incorporated herein in its entirety and for all purposes). Alternatively, two antibodies have the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

[0111] For preparation of suitable antibodies of the invention and for use according to the invention, e.g., recombinant, monoclonal, or polyclonal antibodies, many techniques known in the art can be used (see, e.g., Kohler & Milstein, Nature 256:495-497 (1975); Kozbor et al., Immunology Today 4: 72 (1983); Cole et al., pp. 77-96 in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc. (1985); Coligan, Current Protocols in Immunology (1991); Harlow & Lane, Antibodies, A Laboratory Manual (1988); and Goding, Monoclonal Antibodies: Principles and Practice (2d ed. 1986), which are incorporated herein in their entirety and for all purposes). The genes encoding the heavy and light chains of an antibody of interest can be cloned from a cell, e.g., the genes encoding a monoclonal antibody can be cloned from a hybridoma and used to produce a recombinant monoclonal antibody. Gene libraries encoding heavy and light chains of monoclonal antibodies can also be made from hybridoma or plasma cells. Random combinations of the heavy and light chain gene products generate a large pool of antibodies with different antigenic specificity (see, e.g., Kuby, Immunology (3rd ed. 1997), which is incorporated herein in its entirety and for all purposes). Techniques for the production of single chain antibodies or recombinant antibodies (U.S. Patent 4,946,778, U.S. Patent No. 4,816,567, which are incorporated herein in their entirety and for all purposes) can be adapted to produce antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms such as other mammals, may be used to express humanized or human antibodies (see, e.g., U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, Marks et al., Bio/Technology 10:779-783 (1992); Lonberg et al., Nature

368:856-859 (1994); Morrison, Nature 368:812-13 (1994); Fishwild et al., Nature Biotechnology 14:845-51 (1996); Neuberger, Nature Biotechnology 14:826 (1996); and Lonberg & Huszar, Intern. Rev. Immunol. 13:65-93 (1995), which are incorporated herein in their entirety and for all purposes). Alternatively, phage display technology can be used to identify antibodies and heteromeric Fab fragments that specifically bind to selected antigens (see, e.g., McCafferty et al., Nature 348:552-554 (1990); Marks et al., Biotechnology 10:779-783 (1992), which are incorporated herein in their entirety and for all purposes). Antibodies can also be made bispecific, i.e., able to recognize two different antigens (see, e.g., WO 93/08829, Traunecker et al., EMBO J. 10:3655-3659 (1991); and Suresh et al., Methods in Enzymology 121:210 (1986), which are incorporated herein in their entirety and for all purposes). Antibodies can also be heteroconjugates, e.g., two covalently joined antibodies, or immunotoxins (see, e.g., U.S. Patent No. 4,676,980 , WO 91/00360; WO 92/200373; and EP 03089, which are incorporated herein in their entirety and for all purposes).

[0112] Methods for humanizing or primatizing non-human antibodies are well known in the art (e.g., U.S. Patent Nos. 4,816,567; 5,530,101; 5,859,205; 5,585,089; 5,693,761; 5,693,762; 5,777,085; 6,180,370; 6,210,671; and 6,329,511; WO 87/02671; EP Patent Application 0173494; Jones et al. (1986) Nature 321:522; and Verhoyen et al. (1988) Science 239:1534, which are incorporated herein in their entirety and for all purposes). Humanized antibodies are further described in, e.g., Winter and Milstein (1991) Nature 349:293, which is incorporated herein in its entirety and for all purposes. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as import residues, which are typically taken from an import variable domain. Humanization can be essentially performed following the method of Winter and co-workers (see, e.g., Morrison et al., PNAS USA, 81:6851-6855 (1984), Jones et al., Nature 321:522-525 (1986); Riechmann et al., Nature 332:323-327 (1988); Morrison and Oi, Adv. Immunol., 44:65-92 (1988), Verhoeyen et al., Science 239:1534-1536 (1988) and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992), Padlan, Molec. Immun., 28:489-498 (1991); Padlan, Molec. Immun., 31(3):169-217 (1994), which are incorporated herein in their entirety and for all purposes), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such humanized antibodies are chimeric antibodies (U.S. Patent No. 4,816,567, which is incorporated herein in its entirety and for all purposes), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice,

humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies. For example, polynucleotides comprising a first sequence coding for humanized immunoglobulin framework regions and a second sequence set coding for the desired immunoglobulin complementarity determining regions can be produced synthetically or by combining appropriate cDNA and genomic DNA segments. Human constant region DNA sequences can be isolated in accordance with well known procedures from a variety of human cells.

[0113] A "chimeric antibody" is an antibody molecule in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen binding site (variable region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc.; or (b) the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region having a different or altered antigen specificity. The preferred antibodies of, and for use according to the invention include humanized and/or chimeric monoclonal antibodies.

[0114] The phrase "specifically (or selectively) binds" to an antibody or "specifically (or selectively) immunoreactive with", when referring to a protein or peptide, refers to a binding reaction that is determinative of the presence of the protein, often in a heterogeneous population of proteins and other biologics. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein at least two times the background and more typically more than 10 to 100 times background. Specific binding to an antibody under such conditions requires an antibody that is selected for its specificity for a particular protein. For example, polyclonal antibodies can be selected to obtain only a subset of antibodies that are specifically immunoreactive with the selected antigen and not with other proteins. This selection may be achieved by subtracting out antibodies that cross-react with other molecules. A variety of immunoassay formats may be used to select antibodies specifically immunoreactive with a particular protein. For example, solid-phase ELISA immunoassays are routinely used to select antibodies specifically immunoreactive with a protein (see, e.g., Harlow & Lane, Using Antibodies, A Laboratory Manual (1998), which is incorporated herein in its entirety and for all purposes, for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity).

[0115] A "ligand" refers to an agent, e.g., a polypeptide or other molecule, capable of binding to a receptor or antibody, antibody variant, antibody region or fragment thereof.

[0116] Techniques for conjugating therapeutic agents to antibodies are well known (see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery" in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review" in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982), which are incorporated herein in their entirety and for all purposes). As used herein, the term "antibody-drug conjugate" or "ADC" refers to a therapeutic agent conjugated or otherwise covalently bound to to an antibody.

[0117] The term "Ephrin B2 protein" or "Ephrin B2" as used herein, unless otherwise indicated, includes any of the recombinant or naturally-occurring forms of Ephrin B2, also known as EphrinB2, EPH-related receptor tyrosine kinase ligand 5, LERK-5, HTK ligand, HTK-L, or variants or homologs thereof that maintain Ephrin B2 activity (e.g. within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to Ephrin B2). In some aspects, the variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (*e.g.* a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring Ephrin B2 protein. In embodiments, the Ephrin B2 protein is a mammalian Ephrin B2 protein. In embodiments, the Ephrin B2 protein is a mouse Ephrin B2 protein or a rat Ephrinb B2 protein. In embodiments, the Ephrin B2 protein is a primate Ephrin B2 protein. In embodiments, the Ephrin B2 protein is a cynomolgus Ephrin B2 protein. In embodiments, the Ephrin B2 protein is a human Ephrin B2 protein. In embodiments, the Ephrin B2 protein is substantially identical to the protein identified by SEQ ID NO:79. In embodiments, the Ephrin B2 protein includes the extracellular domain (ECD) of Ephrin B2. In embodiments, the Ephrin B2 protein is the extracellular domain of Ephrin B2. In embodiments, the extracellular domain includes a sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 95%, 95%, 96%, 97%, 98%, 99%, or 100% to SEQ ID NO:85. In embodiments, the extracellular domain includes

SEQ ID NO:85. In embodiments, the extracellular domain is SEQ ID NO:85. In embodiments, the extracellular domain includes residues corresponding to positions 197-219 of SEQ ID NO:79. In embodiments, the Ephrin B2 protein is substantially identical to the protein identified by the UniProt reference number P52799 or a variant or homolog having substantial identity thereto.

[0118] For specific proteins described herein, the named protein includes any of the protein's naturally occurring forms, variants or homologs that maintain the protein activity (e.g., within at least 50%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% activity compared to the native protein). In some embodiments, variants or homologs have at least 90%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity across the whole sequence or a portion of the sequence (e.g. a 50, 100, 150 or 200 continuous amino acid portion) compared to a naturally occurring form. In other embodiments, the protein is the protein as identified by its NCBI sequence reference. In other embodiments, the protein is the protein as identified by its NCBI sequence reference, homolog or functional fragment thereof.

[0119] The term "gene" means the segment of DNA involved in producing a protein; it includes regions preceding and following the coding region (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons). The leader, the trailer as well as the introns include regulatory elements that are necessary during the transcription and the translation of a gene. Further, a "protein gene product" is a protein expressed from a particular gene.

[0120] The terms "plasmid", "vector" or "expression vector" refer to a nucleic acid molecule that encodes for genes and/or regulatory elements necessary for the expression of genes. Expression of a gene from a plasmid can occur in cis or in trans. If a gene is expressed in cis, the gene and the regulatory elements are encoded by the same plasmid. Expression in trans refers to the instance where the gene and the regulatory elements are encoded by separate plasmids.

[0121] The terms "transfection", "transduction", "transfecting" or "transducing" can be used interchangeably and are defined as a process of introducing a nucleic acid molecule or a protein to a cell. Nucleic acids are introduced to a cell using non-viral or viral-based methods. The nucleic acid molecules may be gene sequences encoding complete proteins or functional portions thereof. Non-viral methods of transfection include any appropriate transfection method that does not use viral DNA or viral particles as a delivery system to introduce the nucleic acid molecule into the cell. Exemplary non-viral transfection methods include calcium phosphate transfection, liposomal

transfection, nucleofection, sonoporation, transfection through heat shock, magnetifection and electroporation. In some embodiments, the nucleic acid molecules are introduced into a cell using electroporation following standard procedures well known in the art. For viral-based methods of transfection any useful viral vector may be used in the methods described herein. Examples for viral vectors include, but are not limited to retroviral, adenoviral, lentiviral and adeno-associated viral vectors. In some embodiments, the nucleic acid molecules are introduced into a cell using a retroviral vector following standard procedures well known in the art. The terms "transfection" or "transduction" also refer to introducing proteins into a cell from the external environment. Typically, transduction or transfection of a protein relies on attachment of a peptide or protein capable of crossing the cell membrane to the protein of interest. *See, e.g.*, Ford *et al.* (2001) *Gene Therapy* 8:1-4 and Prochiantz (2007) *Nat. Methods* 4:119-20., which is incorporated herein in its entirety and for all purposes.

[0122] A "label" or a "detectable moiety" is a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical, or other physical means. For example, useful labels include 32P, fluorescent dyes, electron-dense reagents, enzymes (e.g., as commonly used in an ELISA), biotin, digoxigenin, or haptens and proteins or other entities which can be made detectable, e.g., by incorporating a radiolabel into a peptide or antibody specifically reactive with a target peptide. Any appropriate method known in the art for conjugating an antibody to the label may be employed, e.g., using methods described in Hermanson, Bioconjugate Techniques 1996, Academic Press, Inc., San Diego., which is incorporated herein in its entirety and for all purposes.

[0123] "Contacting" is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. antibodies and antigens) to become sufficiently proximal to react, interact, or physically touch. It should be appreciated; however, that the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0124] The term "contacting" may include allowing two species to react, interact, or physically touch, wherein the two species may be, for example, a pharmaceutical composition as provided herein and a cell. In embodiments contacting includes, for example, allowing an antibody as described herein to interact with a cell (e.g. an Ephrin B2-expressing cell). In embodiments contacting includes, for example, allowing an antibody as described herein to physically interact

with a Ephrin B2 protein or a fragment thereof. In embodiments, the contacting occurs *in vitro*. In embodiments, the contacting occurs *in vivo*. In embodiments, the contacting occurs in a subject. In embodiments, the subject is a healthy subject. In embodiments, the subject is a subject having fibrosis.

[0125] A "cell" as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaryotic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include, but are not limited to, yeast cells and cells derived from plants and animals, for example mammalian, insect (*e.g.*, spodoptera) and human cells. In embodiments, the cell is a fibroblast. In embodiments, the cell is an endothelial cell. In embodiments, the cell is an Ephrin B2-expressing cell.

[0126] The term "recombinant" when used with reference, *e.g.*, to a cell, nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all. Transgenic cells and plants are those that express a heterologous gene or coding sequence, typically as a result of recombinant methods.

[0127] The term "isolated", when applied to a nucleic acid or protein, denotes that the nucleic acid or protein is essentially free of other cellular components with which it is associated in the natural state. It can be, for example, in a homogeneous state and may be in either a dry or aqueous solution. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid chromatography. A protein that is the predominant species present in a preparation is substantially purified.

[0128] The term "heterologous" when used with reference to portions of a nucleic acid indicates that the nucleic acid comprises two or more subsequences that are not found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having

two or more sequences from unrelated genes arranged to make a new functional nucleic acid, e.g., a promoter from one source and a coding region from another source. Similarly, a heterologous protein indicates that the protein comprises two or more subsequences that are not found in the same relationship to each other in nature (e.g., a fusion protein).

[0129] The term "exogenous" refers to a molecule or substance (*e.g.*, a compound, nucleic acid or protein) that originates from outside a given cell or organism. For example, an "exogenous promoter" as referred to herein is a promoter that does not originate from the cell or organism it is expressed by. Conversely, the term "endogenous" or "endogenous promoter" refers to a molecule or substance that is native to, or originates within, a given cell or organism.

[0130] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to protein activity means negatively affecting (e.g., decreasing) the function of the protein. In some embodiments, inhibition refers to reduction of a disease or symptoms of disease (e.g., fibrosis (e.g. lung fibrosis, skin fibrosis, etc.)). Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein (e.g. Ephrin B2 protein). Similarly an "inhibitor" is a compound or protein that inhibits a receptor or another protein, *e.g.*, by binding, partially or totally blocking, decreasing, preventing, delaying, inactivating, desensitizing, or down-regulating activity (e.g., a receptor activity or a protein activity).

[0131] As defined herein, the term "inhibition", "inhibit", "inhibiting" and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein (e.g. Ephrin B2 protein) relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of Ephrin B2 relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease (e.g. fibrosis). In embodiments, inhibition refers to a reduction in the activity of Ephrin B2. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of Ephrin B2. In embodiments, inhibition refers to a reduction of activity of Ephrin B2 resulting from a direct interaction (e.g. an inhibitor binds to Ephrin B2). In embodiments, inhibition refers to a reduction of activity of Ephrin B2 from an

indirect interaction (e.g. an inhibitor binds to a protein that activates Ephrin B2, thereby preventing target protein activation).

[0132] Thus, the terms "inhibitor," "repressor" or "antagonist" or "downregulator" interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein (e.g. Ephrin B2 protein). The antagonist can decrease Ephrin B2 expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, Ephrin B2 expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist.

[0133] The term "expression" includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (*e.g.*, ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, *etc.*).

[0134] "Biological sample" or "sample" refer to materials obtained from or derived from a subject or patient. A biological sample includes sections of tissues such as biopsy and autopsy samples, and frozen sections taken for histological purposes. Such samples include bodily fluids such as blood and blood fractions or products (e.g., serum, plasma, platelets, red blood cells, and the like), sputum, tissue, cultured cells (e.g., primary cultures, explants, and transformed cells) stool, urine, immune cells, hematopoietic cells, fibroblasts, macrophages, T cells, etc. A biological sample is typically obtained from a eukaryotic organism, such as a mammal such as a primate e.g., chimpanzee or human; cow; dog; cat; a rodent, e.g., guinea pig, rat, mouse; rabbit; or a bird; reptile; or fish. In embodiments the biological sample is bronchoalveolar lavage fluid (BALF). In embodiments, the biological sample is tissue, for example, tissue derived from the lungs, liver, heart, kidney or skin of a subject.

[0135] A "control" or "standard control" refers to a sample, measurement, or value that serves as a reference, usually a known reference, for comparison to a test sample, measurement, or value. For example, a test sample can be taken from a patient suspected of having a given disease (e.g. fibrosis) and compared to a known normal (non-diseased) individual (e.g. a standard control subject). In embodiments, the control is a biological sample taken from a subject who does not have fibrosis. A

standard control can also represent an average measurement or value gathered from a population of similar individuals (e.g. standard control subjects) that do not have a given disease (i.e. standard control population), e.g., healthy individuals with a similar medical background, same age, weight, etc. A standard control value can also be obtained from the same individual, e.g. from an earlier-obtained sample from the patient prior to disease onset. For example, a control can be devised to compare therapeutic benefit based on pharmacological data (*e.g.*, half-life) or therapeutic measures (*e.g.*, comparison of side effects). Controls are also valuable for determining the significance of data. For example, in embodiments, a control may be a test sample that does not include an anti-Ephrin B2 antibody as provided herein. In embodiments, a control may be a subject who is not administered an Ephrin B2 antibody provided herein. In embodiments, if values for a given parameter are widely variant in controls, variation in test samples will not be considered as significant. One of skill will recognize that standard controls can be designed for assessment of any number of parameters (e.g. disease symptoms, disease progression, RNA levels, protein levels, specific cell types, specific bodily fluids, specific tissues, etc).

[0136] One of skill in the art will understand which standard controls are most appropriate in a given situation and be able to analyze data based on comparisons to standard control values. Standard controls are also valuable for determining the significance (e.g. statistical significance) of data. For example, if values for a given parameter are widely variant in standard controls, variation in test samples will not be considered as significant.

[0137] "Patient" or "subject in need thereof" refers to a living organism suffering from or prone to a disease (e.g. fibrosis) or condition that can be treated by administration of a composition or pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

[0138] The terms "disease" or "condition" refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be fibrosis. Fibrosis is a condition which may be characterized by an abnormal accumulation of a collagen matrix following injury or inflammation which alters the structure and function of various tissues. In embodiments, the fibrosis is in the gut, kidney, liver, lung, heart, bone or bone marrow, or skin.

[0139] The term "associated" or "associated with" in the context of a substance or substance activity or function associated with a disease (e.g. a protein associated disease (*e.g.,* fibrosis associated with Ephrin B2 activity)) means that the disease (e.g. fibrosis) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, fibrosis associated with Ephrin B2 activity or function or a Ephrin B2 associated disease (*e.g.* fibrosis (e.g. lung fibrosis, skin fibrosis, etc.)), may be treated with a Ephrin B2 modulator or Ephrin B2 inhibitor, in the instance where increased Ephrin B2 activity or function (e.g. signaling pathway activity) causes the disease (*e.g.,* fibrosis). For example, a fibrotic disorder associated with Ephrin B2 activity may be treated with an Ephrin B2 modulator or Ephrin B2 inhibitor, in the instance where increased Ephrin B2 activity or function (e.g. signaling pathway activity) causes the disease.

[0140] The term "signaling pathway" as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propagated to other signaling pathway components.

[0141] The term "aberrant" as used herein refers to different from normal. When used to describe enzymatic activity, aberrant refers to activity that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by using a method as described herein), results in reduction of the disease or one or more disease symptoms.

[0142] A "therapeutic agent" as referred to herein, is a composition useful in treating or preventing fibrosis (e.g. lung fibrosis, skin fibrosis, etc.). In embodiments, the therapeutic agent is an anti-fibrotic agent. For example, an anti-fibrotic agent may refer to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having the ability to inhibit or slow the rate of fibrosis or scarring. In embodiments, an anti-fibrotic agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating fibrosis.

[0143] As used herein, "treating" or "treatment of" a condition, disease or disorder or symptoms associated with a condition, disease or disorder refers to an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of condition, disorder or disease, stabilization of the state of condition, disorder or disease, prevention of development of condition, disorder or disease, prevention of spread of condition, disorder or disease, delay or slowing of condition, disorder or disease progression, delay or slowing of condition, disorder or disease onset, amelioration or palliation of the condition, disorder or disease state, and remission, whether partial or total. "Treating" can also mean prolonging survival of a subject beyond that expected in the absence of treatment. "Treating" can also mean inhibiting the progression of the condition, disorder or disease, slowing the progression of the condition, disorder or disease temporarily, although in some instances, it involves halting the progression of the condition, disorder or disease permanently. As used herein the terms treatment, treat, or treating refers to a method of reducing the effects of one or more symptoms of a disease or condition characterized by expression of the protease or symptom of the disease or condition characterized by expression of the protease. Thus in the disclosed method, treatment can refer to a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% reduction in the severity of an established disease, condition, or symptom of the disease or condition. For example, a method for treating a disease is considered to be a treatment if there is a 10% reduction in one or more symptoms of the disease in a subject as compared to a control. Thus the reduction can be a 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or any percent reduction in between 10% and 100% as compared to native or control levels. It is understood that treatment does not necessarily refer to a cure or complete ablation of the disease, condition, or symptoms of the disease or condition. Further, as used herein, references to decreasing, reducing, or inhibiting include a change of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater as compared to a control level and such terms can include but do not necessarily include complete elimination.

[0144] The terms "dose" and "dosage" are used interchangeably herein. A dose refers to the amount of active ingredient given to an individual at each administration. The dose will vary depending on a number of factors, including the range of normal doses for a given therapy, frequency of administration; size and tolerance of the individual; severity of the condition; risk of side effects; and the route of administration. One of skill will recognize that the dose can be

modified depending on the above factors or based on therapeutic progress. The term "dosage form" refers to the particular format of the pharmaceutical or pharmaceutical composition, and depends on the route of administration. For example, a dosage form can be in a liquid form for nebulization, e.g., for inhalants, in a tablet or liquid, e.g., for oral delivery, or a saline solution, e.g., for injection.

[0145] By "therapeutically effective amount" as used herein is meant any amount that produces effects for which it is administered (e.g. treating or preventing a disease). By "therapeutically effective dose" as used herein is meant a specific amount of a substance (such as an antibody disclosed herein) administered to a subject at one time or over a specified period. A "therapeutically effective amount" may comprise one or more "therapeutically effective dose(s)" required to achieve the desired therapeutic effect. The exact dose and formulation will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, Pharmaceutical Dosage Forms (vols. 1-3, 1992); Lloyd, The Art, Science and Technology of Pharmaceutical Compounding (1999); Remington: The Science and Practice of Pharmacy, 20th Edition, Gennaro, Editor (2003), and Pickar, Dosage Calculations (1999), which are incorporated herein in their entirety and for all purposes). For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%. Therapeutic efficacy can also be expressed as "-fold" increase or decrease. For example, a therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a standard control. A therapeutically effective dose or amount may ameliorate one or more symptoms of a disease. A therapeutically effective dose or amount may prevent or delay the onset of a disease or one or more symptoms of a disease when the effect for which it is being administered is to treat a person who is at risk of developing the disease.

[0146] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.,* a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal. Parenteral administration includes, *e.g.,* intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches,

etc. By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies, for example, an anti-fibrotic agent. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0147] As used herein, the term "pharmaceutically acceptable" is used synonymously with "physiologically acceptable" and "pharmacologically acceptable". A pharmaceutical composition will generally comprise agents for buffering and preservation in storage, and can include buffers and carriers for appropriate delivery, depending on the route of administration.

[0148] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

ANTI-EPHRIN B2 ANTIBODIES

[0149] Provided herein are, *inter alia*, antibodies (e.g., humanized antibodies, monoclonal antibodies) and antibody fragments (e.g., Fab domains, scFvs), which bind Ephrin B2 with high efficiency and specificity. In embodiments, the antibodies and antibody compositions provided herein include novel variable heavy chain domain sequences. In embodiments, the antibodies provided herein have been identified to bind the extracellular domain (ECD) of the Ephrin B2 protein. Antibodies described herein including embodiments thereof are useful for binding Ephrin B2 with high effectivity and affinity and inhibit Ephrin B2 activity in cells expressing Ephrin B2. The antibodies provided herein including embodiments thereof, may be used for diagnostic and therapeutic purposes in Ephrin B2-related fibrotic disorders. In embodiments, the antibodies provided herein including embodiments thereof, have an ability to suppress collagen formation

and/or inhibit expression of inflammatory cytokines and therefore are capable of inhibiting or slowing fibrosis (e.g. lung fibrosis, skin fibrosis, etc.).

[0150] Exemplary anti-Ephrin B2 antibodies provided herein are referred to by names (e.g., Ab25, Ab51, Ab11, Ab18, B11-QTS, and B11-DTS).

[0151] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:66, a CDR H2 as set forth in SEQ ID NO:67, and a CDR H3, wherein said CDR H3 is a variant of SEQ ID NO:68; wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:69, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:70; and wherein the variant of SEQ ID NO:68 includes the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4, position 6, position 10, and position 11 relative to SEQ ID NO:68. In embodiments, the CDR L2 is LSG.

[0152] In embodiments, the variant of SEQ ID NO:68 includes the sequence of SEQ ID NO:68 including a substitution at a position corresponding to position 4 relative to SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes the sequence of SEQ ID NO:68 including a substitution at a position corresponding to position 6 relative to SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes the sequence of SEQ ID NO:68 including a substitution at a position corresponding to position 10 relative to SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes the sequence of SEQ ID NO:68 including a substitution at a position corresponding to position 11 relative to SEQ ID NO:68.

[0153] In embodiments, the variant of SEQ ID NO:68 includes one substitution. In embodiments, the variant of SEQ ID NO:68 includes two substitutions. In embodiments, the variant of SEQ ID NO:68 includes three substitutions. In embodiments, the variant of SEQ ID NO:68 includes four substitutions.

[0154] In embodiments, the variant of SEQ ID NO:68 includes a I4S, I4A, I4G, I4P, I4R, I4K, I4C, or I4M substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4S substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4A substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the

variant of SEQ ID NO:68 includes a I4G substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4P substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4R substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4K substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4C substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4M substitution at the position corresponding to position 4 of SEQ ID NO:68.

[0155] In embodiments, the variant of SEQ ID NO:68 includes a G6N, G6K, or G6R substitution at the position corresponding to position 6 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a G6N at the position corresponding to position 6 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a G6K substitution at the position corresponding to position 6 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a G6R substitution at the position corresponding to position 6 of SEQ ID NO:68.

[0156] In embodiments, the variant of SEQ ID NO:68 includes a G10K or G10R substitution at the position corresponding to position 10 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a G10K substitution at the position corresponding to position 10 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a G10R substitution at the position corresponding to position 10 of SEQ ID NO:68.

[0157] In embodiments, the variant of SEQ ID NO:68 includes an F11L, F11V, or F11I substitution at the position corresponding to position 11 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes an F11L substitution at the position corresponding to position 11 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes an F11V substitution at the position corresponding to position 11 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes an F11I substitution at the position corresponding to position 11 of SEQ ID NO:68.

[0158] In embodiments, the variant of SEQ ID NO:68 includes a I4G substitution at the position corresponding to position 4 of SEQ ID NO:68, a G6K substitution at the position corresponding to position 6 of SEQ ID NO:68, an G10R substitution at the position corresponding to position 10 of

SEQ ID NO:68, and a F11V substitution at the position corresponding to position 11 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 is SEQ ID NO:3.

[0159] In embodiments, the variant of SEQ ID NO:68 includes a a I4S substitution at the position corresponding to position 4 of SEQ ID NO:68, an G10K substitution at the position corresponding to position 10 of SEQ ID NO:68, and a F11L substitution at the position corresponding to position 11 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 is SEQ ID NO:88.

[0160] As described above, a "light chain variable (VL) domain" as provided herein refers to the variable region of the light chain of an antibody, an antibody variant or fragment thereof. Likewise, the "heavy chain variable (VH) domain" as provided herein refers to the variable region of the heavy chain of an antibody, an antibody variant or fragment thereof. The light chain variable domain and the heavy chain variable domain together form the paratope, which binds an antigen (epitope). The paratope or antigen-binding site is formed at the N-terminus of an antibody, an antibody variant or fragment thereof. In embodiments, the light chain variable (VL) domain includes CDR L1, CDR L2, CDR L3 and FR L1, FR L2, FR L3 and FR L4 (framework regions) of an antibody light chain. In embodiments, the heavy chain variable (VH) domain includes CDR H1, CDR H2, CDR H3 and FR H1, FR H2, FR H3 and FR H4 (framework regions) of an antibody heavy chain. In embodiments, the light chain variable (VL) domain and a light chain constant (CL) domain form part of an antibody light chain. In embodiments, the heavy chain variable (VH) domain and a heavy chain constant (CH1) domain form part of an antibody heavy chain. In embodiments, the heavy chain variable (VH) domain and one or more heavy chain constant (CH1, CH2, or CH3) domains form part of an antibody heavy chain. Thus, in embodiments, the light chain variable (VL) domain forms part of an antibody. In embodiments, the heavy chain variable (VH) domain forms part of an antibody. In embodiments, the light chain variable (VL) domain forms part of a therapeutic antibody. In embodiments, the heavy chain variable (VH) domain forms part of a therapeutic antibody. In embodiments, the light chain variable (VL) domain forms part of a human antibody. In embodiments, the heavy chain variable (VH) domain forms part of a human antibody. In embodiments, the light chain variable (VL) domain forms part of a humanized antibody. In embodiments, the heavy chain variable (VH) domain forms part of a humanized antibody. In embodiments, the light chain variable (VL) domain forms part of a chimeric antibody. In embodiments, the heavy chain variable (VH) domain forms part of a chimeric antibody. In

embodiments, the light chain variable (VL) domain forms part of an antibody fragment. In embodiments, the heavy chain variable (VH) domain forms part of an antibody fragment. In embodiments, the light chain variable (VL) domain forms part of an antibody variant. In embodiments, the heavy chain variable (VH) domain forms part of an antibody variant. In embodiments, the light chain variable (VL) domain forms part of a Fab. In embodiments, the heavy chain variable (VH) domain forms part of a Fab. In embodiments, the light chain variable (VL) domain forms part of a scFv. In embodiments, the heavy chain variable (VH) domain forms part of a scFv.

[0161] In embodiments, the heavy chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:12. In embodiments, said heavy chain variable domain includes SEQ ID NO:12. In embodiments, said heavy chain variable domain is SEQ ID NO:12.

[0162] In embodiments, the light chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a

sequence having at least 93% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:13. In embodiments, said light chain variable domain includes SEQ ID NO:13. In embodiments, said light chain variable domain is SEQ ID NO:13.

[0163] In embodiments, the heavy chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 90% identity to SEQ ID NO: 98. In embodiments, the heavy chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:98. In embodiments, said heavy chain variable domain includes SEQ ID NO:98. In embodiments, said heavy chain variable domain is SEQ ID NO:98.

[0164] In embodiments, the light chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 91% identity to

SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:99. In embodiments, said light chain variable domain includes SEQ ID NO:99. In embodiments, said light chain variable domain is SEQ ID NO:99.

[0165] In embodiments, the heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:66, a CDR H2 as set forth in SEQ ID NO:67, and a CDR H3, wherein said CDR H3 is a variant of SEQ ID NO:68, wherein the variant of SEQ ID NO:68 includes the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4, position 6, position 10, and position 11 relative to SEQ ID NO:68, has at least 80% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 81% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 82% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 83% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 84% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 85% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 86% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 87% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 88% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 89% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 90% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 91% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 92% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 93% sequence identity to SEQ

ID NO:51. In embodiments, the heavy chain variable domain has at least 94% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 95% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 96% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 97% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 98% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 99% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain includes a glutamine or an aspartic acid at a position relative to position 73 of SEQ ID NO:51

[0166] In embodiments, the light chain variable domain including a CDR L1 as set forth in SEQ ID NO:69, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:70, has at least 80% sequence identity to SEQ ID NO:52. In embodiments, the :light chain variable domain has at least 81% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 82% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 83% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 84% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 85% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 86% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 87% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 88% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 89% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 90% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 91% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 92% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 93% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 94% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 95% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 96% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 97% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 98% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has

at least 99% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain includes SEQ ID NO:52. In embodiments, the light chain variable domain is SEQ ID NO:52. In embodiments, the light chain variable domain is not SEQ ID NO:52.

[0167] The antibody or a sequence of the antibody may be selected from any combination of antibodies or antibody sequences provided herein. For example, the heavy chain variable domain may be selected from a combination of heavy chain variable domains provided herein and/or the light chain variable domain may be selected from a combination of light chain variable domains provided herein. For the antibody provided herein, in embodiments, CDRs such as light chain CDRs or heavy chain CDRs may be selected from a combination of CDRs provided herein.

[0168] In embodiments, the heavy chain variable domain includes a sequence having less than 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:77. In embodiments, the heavy chain variable domain includes a sequence having less than 90% identity to SEQ ID NO:77. In embodiments, the heavy chain variable domain includes a sequence having less than 91% identity to SEQ ID NO:77. In embodiments, the heavy chain variable domain includes a sequence having less than 92% identity to SEQ ID NO:77. In embodiments, the heavy chain variable domain includes a sequence having less than 93% identity to SEQ ID NO:77. In embodiments, the heavy chain variable domain includes a sequence having less than 94% identity to SEQ ID NO:77. In embodiments, the heavy chain variable domain includes a sequence having less than 95% identity to SEQ ID NO:77. In embodiments, the heavy chain variable domain includes a sequence having less than 96% identity to SEQ ID NO:77. In embodiments, the heavy chain variable domain includes a sequence having less than 97% identity to SEQ ID NO:77. In embodiments, the heavy chain variable domain includes a sequence having less than 98% identity to SEQ ID NO:77. In embodiments, the heavy chain variable domain includes a sequence having less than 99% identity to SEQ ID NO:77. In embodiments, the heavy chain variable domain includes a sequence having less than 100% identity to SEQ ID NO:77. In embodiments, said heavy chain variable domain does not include SEQ ID NO:77. In embodiments, said heavy chain variable domain is not SEQ ID NO:77. As described above, in embodiments, the antibody provided herein may include a heavy chain variable domain including a substitution at a position corresponding to position 73 of SEQ ID NO:77. In embodiments, the substitution is a N73Q substitution. In embodiments, the substitution is a N73D substitution.

[0169] In embodiments, the light chain variable domain includes a sequence having less than 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:78. In embodiments, the light chain variable domain includes a sequence having less than 90% identity to SEQ ID NO:78. In embodiments, the light chain variable domain includes a sequence having less than 91% identity to SEQ ID NO:78. In embodiments, the light chain variable domain includes a sequence having less than 92% identity to SEQ ID NO:78. In embodiments, the light chain variable domain includes a sequence having less than 93% identity to SEQ ID NO:78. In embodiments, the light chain variable domain includes a sequence having less than 94% identity to SEQ ID NO:78. In embodiments, the light chain variable domain includes a sequence having less than 95% identity to SEQ ID NO:78. In embodiments, the light chain variable domain includes a sequence having less than 96% identity to SEQ ID NO:78. In embodiments, the light chain variable domain includes a sequence having less than 97% identity to SEQ ID NO:78. In embodiments, the light chain variable domain includes a sequence having less than 98% identity to SEQ ID NO:78. In embodiments, the light chain variable domain includes a sequence having less than 99% identity to SEQ ID NO:78. In embodiments, the light chain variable domain includes a sequence having less than 100% identity to SEQ ID NO:78. In embodiments, said light chain variable domain does not include SEQ ID NO:78. In embodiments, said light chain variable domain is not SEQ ID NO:78.

[0170] In an aspect is provided an anti-Ephrin B2 antibody, wherein the antibody includes a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes a variant of SEQ ID NO:51 and wherein the light chain domain includes SEQ ID NO:52, wherein the variant of SEQ ID NO:51 includes the sequence of SEQ ID NO:51 including at least one substitution thereto at positions corresponding to position 100, position 102, position 106, and position 107 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes one substitution. In embodiments, the variant of SEQ ID NO:51 includes two substitutions. In embodiments, the variant of SEQ ID NO:51 includes three substitutions. In embodiments, the variant of SEQ ID NO:51 includes four substitutions.

[0171] In embodiments, the variant of SEQ ID NO:51 includes a I100S, I100A, I100G, I100P, I100R, I4K, I4C, or I4M substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100S substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51

includes a I100A substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100G substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100P substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100R substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100K substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100C substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100M substitution at the position corresponding to position 100 of SEQ ID NO:51.

[0172] In embodiments, the variant of SEQ ID NO:51 includes a G102N, G102K, or G102R substitution at the position corresponding to position 102 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a G102N at the position corresponding to position 102 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a G102K substitution at the position corresponding to position 102 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a G102R substitution at the position corresponding to position 102 of SEQ ID NO:51.

[0173] In embodiments, the variant of SEQ ID NO:51 includes a G106K or G106R substitution at the position corresponding to position 106 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a G106K substitution at the position corresponding to position 106 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a G106R substitution at the position corresponding to position 106 of SEQ ID NO:51.

[0174] In embodiments, the variant of SEQ ID NO:51 includes a F107L, F107V, or F107I substitution at the position corresponding to position 107 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes an F107L substitution at the position corresponding to position 107 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes an F107V substitution at the position corresponding to position 107 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes an F107I substitution at the position corresponding to position 107 of SEQ ID NO:51.

[0175] In embodiments, the variant of SEQ ID NO:51 includes a I100G substitution at the position corresponding to position 100 of SEQ ID NO:51, a G102K substitution at the position corresponding to position 102 of SEQ ID NO:51, an G106R substitution at the position corresponding to position 106 of SEQ ID NO:51, and a F1107V substitution at the position corresponding to position 107 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 is SEQ ID NO:12.

[0176] In embodiments, the variant of SEQ ID NO:51 includes a a I100S substitution at the position corresponding to position 100 of SEQ ID NO:51, an G106K substitution at the position corresponding to position 106 of SEQ ID NO:51, and a F107L substitution at the position corresponding to position 107 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 is SEQ ID NO:98.

[0177] In embodiments, the antibody is an IgG. In embodiments, the antibody is an IgG1, IgG2, IgG3, or IgG4. In embodiments, the antibody is an IgG1. In embodiments, the antibody is an IgG2. In embodiments, the antibody is an IgG3. In embodiments, the antibody is an IgG4.

[0178] In embodiments, the antibody is a humanized antibody or a chimeric antibody. In embodiments, the antibody is a humanized antibody. In embodiments, the antibody is a chimeric antibody.

[0179] As described above, in embodiments, the antibody may be a fragment of an antibody. In embodiments, the antibody includes a Fab fragment. In embodiments, the antibody is a single-chain variable fragment (scFv). In embodiments, the light chain variable domain and the heavy chain variable domain form part of an scFv. In embodiments, the antibody includes a fragment crystallizable (Fc) domain. In embodiments, the antibody is a single domain antibody. In embodiments, the single domain antibody includes a light chain variable domain. In embodiments, the single domain antibody includes a heavy chain variable domain.

[0180] The antibodies provided herein may include one or more glycosylation sites within the IgG heavy chain. For example, the glycosylation site may be within the variable heavy domain of the antibody. In embodiments, the glycosylation site corresponds to Asn73 of SEQ ID NO:77. In embodiments, the antibodies provided herein include one or more modifications that remove a potential glycosylation site. In embodiments, the antibody includes a modification at a position

corresponding to position 73 of SEQ ID NO:77. In embodiments, the modification is a N73Q substitution. In embodiments, the modification is a N73D substitution.

[0181] In embodiments, the Fc domain of the antibody includes one or more glycosylation sites. In embodiments, the Fc domain may include one or more modifications wherein one or more one or more carbohydrate moiety is added, substituted, deleted or modified. For example, substitution of a residue with asparagine-X-serine or asparagine-X-threonine motif may create a potential site for enzymatic attachment of carbohydrate moieties and may, therefore, be used to regulate glycosylation of an antibody. In embodiments, the one or more glycosylation sites may be involved in or enhance binding of the antibody to an Fc receptor (e.g. FcγRI, FcγRII, FcγRII). Thus, in embodiments, the presence of one or more glycosylation sites in the antibody may enhance, for example, antibody dependent cellular cytotoxicity (ADCC) and/or complement-dependent cytotoxicity (CDC). In embodiments, the Fc domain includes one or more modifications to decrease binding to an Fc receptor. In embodiments, the Fc domain may include one or more modifications wherein one or more one glycosylation site is modified or deleted. In embodiments, the one or more modifications includes removal of a glycosylation site.

[0182] In embodiments, the antibodies provided herein including embodiments thereof may include a modified Fc domain that does not elicit an antibody dependent cellular cytotoxicity (ADCC). In embodiments, the antibodies provided herein including embodiments thereof may include a modified Fc domain that does not elicit complement dependent cytotoxicity (CDC). In embodiments, the Fc domain includes an effector cell inhibiting substitution. In the presence of an effector cell inhibiting substitution the binding of the Fc domain to the effector cell ligand decreases activation of an effector cell relative to the absence of said substitution. In embodiments, the binding of the Fc domain to the effector cell ligand results in substantially no activation of an effector cell relative to the absence of said substitution.

[0183] In embodiments, the antibody is capable of binding a Ephrin B2 protein. In embodiments, the Ephrin B2 protein is a mammalian Ephrin B2 protein. In embodiments, the Ephrin B2 protein is a primate Ephrin B2 protein. In embodiments, the Ephrin B2 protein is a cynomolgus Ephrin B2 protein, a mouse Ephrin B2 protein, a rat Ephrin B2 protein, or a human Ephrin B2 protein. In embodiments, the Ephrin B2 protein is a human Ephrin B2 protein. In embodiments, the Ephrin B2 protein includes the sequence of SEQ ID NO:79. In embodiments, the Ephrin B2 protein includes

the extracellular domain of the Ephrin B2 protein. In embodiments, the Ephrin B2 protein is the extracellular domain of the Ephrin B2 protein. In embodiments, the extracellular domain includes residues corresponding to positions 1-229 of SEQ ID NO:79. In embodiments, the extracellular domain includes SEQ ID NO:100. In embodiments, the extracellular domain includes SEQ ID NO:85. In embodiments, the extracellular domain is SEQ ID NO:85.

[0184] In embodiments, the antibody is capable of binding the extracellular domain of the Ephrin B2 protein. In embodiments, the extracellular domain of the Ephrin B2 protein includes residues corresponding to positions 26-229 of SEQ ID NO:79.otIn embodiments, the antibody is capable of binding residues within the extracellular domain of Ephrin B2. In embodiments, the extracellular domain includes a glutamic acid at a position corresponding to position 69, an asparagine corresponding to position 70, a threonine corresponding to position 71, a leucine corresponding to position 73, an asparagine corresponding to position 75, a lysine corresponding to position 84, a serine corresponding to position 93, a leucine corresponding to position 96, a tryptophan corresponding to position 97, a glycine corresponding to position 98, a glutamic acid corresponding to position 100, a glutamine corresponding to position 102 of SEQ ID NO:85, or a combination thereof. In embodiments, the extracellular domain includes a glutamic acid at a position corresponding to position 69, an asparagine corresponding to position 70, a threonine corresponding to position 71, a leucine corresponding to position 73, an asparagine corresponding to position 75, a lysine corresponding to position 84, a serine corresponding to position 93, a leucine corresponding to position 96, a tryptophan corresponding to position 97, a glycine corresponding to position 98, a glutamic acid corresponding to position 100, and a glutamine corresponding to position 102 of SEQ ID NO:85. In embodiments, the extracellular domain includes a glutamic acid at a position corresponding to position 69, an asparagine corresponding to position 70, and a threonine corresponding to position 71 of SEQ ID NO:85.

[0185] The ability of an antibody to bind a specific epitope (e.g., a Ephrin B2 protein, the extracellular domain of Ephrin B2 protein) can be described by the equilibrium dissociation constant (K_D). The equilibrium dissociation constant (K_D) as defined herein is the ratio of the dissociation rate (K-off) and the association rate (K-on) of an antibody to a Ephrin B2 protein. It is described by the following formula: K_D = K-off/K-on.

[0186] The anti-Ephin B2 antibodies provided herein including embodiments thereof exhibit high affinity binding and specificity. In embodiments, the anti-Ephin B2 antibodies have the benefit of being cross-reactive towards human and non-human primate Ephrin B2 (e.g, cynomolgus Ephrin B2), thereby facilitating production and pre-clinical testing. Thus, in embodiments, the antibody binds to human Ephrin B2 or cynomolgus Ephrin B2.

[0187] In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 1 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 1.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 2 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 2.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 3 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 3.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 4 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 4.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 5.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 6 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 6.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 7 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 7.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 8 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 8.5

nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 9 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 9.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 11 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 11.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 12 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 12.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 13 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 13.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 14 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 14.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 15 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 15.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 16 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 16.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 17 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 17.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 18 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 18.5 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant

(K_D) from about 19 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 19.5 nM to about 20 nM.

[0188] In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 19.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 19 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 18.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 18 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 17.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 17 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 16.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 16 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 15.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 15 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 14.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 14 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 13.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 13 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 12.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 12 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 11.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 11 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10.5 nM. In embodiments, the antibody binds the

Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 9.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 9 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 8.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 8 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 7.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 7 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 6.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 6 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 5.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 4.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 4 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 3.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 3 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 2.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 2 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 1.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 1 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about .5 nM.

[0189] In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 0.01, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12,5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, or 20 nM.

[0190] In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.9 nM to 1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 1.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 2.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.4

nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 4.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 5.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 6.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein

with a K_D from about 6.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 7.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 8.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.9 nM to about 10 nM. In embodiments, the antibody binds the

Ephrin B2 protein with a K_D from about 9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 9.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.9 nM to about 10 nM.

[0191] In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about about 9.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.2 nM. In

embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.4 nM. In embodiments, the antibody

binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.6 nM. In embodiments, the antibody binds the Ephrin B2

protein with a K_D from about 0.01 nM to about 2.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.1 nM.

[0192] In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3,

7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D of less than about 1 nM.

[0193] For the antibody provided herein, in embodiments, the K_D may be determined using a variety of methods known in the art. In embodiments, the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS). In embodiments, the K_D is determined by BLI. In embodiments, the K_D is determined by Biacore™. In embodiments, the K_D is determined by SERS.

[0194] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:66, a CDR H2 as set forth in SEQ ID NO:67 and a CDR H3, wherein said CDR H3 is a variant of SEQ ID NO:68; wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:69, a CDR L2 includes LGS, and a CDR L3 as set forth in SEQ ID NO:70; and wherein the variant of SEQ ID NO:68 includes the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4 and position 7 relative to SEQ ID NO:68. In embodiments, the CDR L2 is LSG.

[0195] In embodiments, the variant of SEQ ID NO:68 includes the sequence of SEQ ID NO:68 including a substitution thereto at a position corresponding to position 4 relative to SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes the sequence of SEQ ID NO:68 including a substitution thereto at a position corresponding to position 7 relative to SEQ ID NO:68.

[0196] In embodiments, the variant of SEQ ID NO:68 includes one substitution. In embodiments, the variant of SEQ ID NO:68 includes two substitutions.

[0197] In embodiments, the variant of SEQ ID NO:68 includes a I4L, I4K, I4Y, I4V, I4M, I4T, I4F, I4A, I4Q, I4S, I4G, I4R, I4W, I4H, or I4N substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4L substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4K substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4Y substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68

includes a I4V substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4M substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4T substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4F substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4A substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4Q substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4S substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4G substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4R substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4W substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4H substitution at the position corresponding to position 4 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a I4N substitution at the position corresponding to position 4 of SEQ ID NO:68.

[0198] In embodiments, the variant of SEQ ID NO:68 includes a T7Y, T7F, or T7S at the position corresponding to position 7 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a T7Y at the position corresponding to position 7 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a T7F at the position corresponding to position 7 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 includes a T7S at the position corresponding to position 7 of SEQ ID NO:68.

[0199] In embodiments, the variant of SEQ ID NO:68 includes an I4M substitution at the position corresponding to position 4 of SEQ ID NO:68 and a T7Y substitution at the position corresponding to position 7 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 is SEQ ID NO:16.

[0200] In embodiments, the variant of SEQ ID NO:68 includes an I4L substitution at the position corresponding to position 4 of SEQ ID NO:68 and a T7Y substitution at the position corresponding to position 7 of SEQ ID NO:68. In embodiments, the variant of SEQ ID NO:68 is SEQ ID NO:29.

[0201] In embodiments, the heavy chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:25. In embodiments, said heavy chain variable domain includes SEQ ID NO:25. In embodiments, said heavy chain variable domain is SEQ ID NO:25.

[0202] In embodiments, the light chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:26. In embodiments, said

light chain variable domain includes SEQ ID NO:26. In embodiments, said light chain variable domain is SEQ ID NO:26.

[0203] In embodiments, the heavy chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:38. In embodiments, said heavy chain variable domain includes SEQ ID NO:38. In embodiments, said heavy chain variable domain is SEQ ID NO:38.

[0204] In embodiments, the light chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a

sequence having at least 98% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:39. In embodiments, said light chain variable domain includes SEQ ID NO:39. In embodiments, said light chain variable domain is SEQ ID NO:39.

[0205] In embodiments, the heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:66, a CDR H2 as set forth in SEQ ID NO:67, and a CDR H3, wherein said CDR H3 is a variant of SEQ ID NO:68, wherein the variant of SEQ ID NO:68 includes the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4 and position 7 relative to SEQ ID NO:68, has at least 80% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 81% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 82% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 83% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 84% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 85% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 86% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 87% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 88% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 89% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 90% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 91% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 92% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 93% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 94% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 95% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 96% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 97% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 98% sequence identity to SEQ ID NO:51. In embodiments, the heavy chain variable domain has at least 99% sequence identity to SEQ ID NO:51.

[0206] In embodiments, the light chain variable domain including a CDR L1 as set forth in SEQ ID NO:69, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:70, has at least 80% sequence identity to SEQ ID NO:52. In embodiments, the :light chain variable domain has at least 81% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 82% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 83% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 84% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 85% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 86% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 87% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 88% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 89% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 90% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 91% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 92% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 93% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 94% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 95% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 96% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 97% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 98% sequence identity to SEQ ID NO:52. In embodiments, the light chain variable domain has at least 99% sequence identity to SEQ ID NO:52.

[0207] In embodiments, the antibody includes a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes a variant of SEQ ID NO:51 and wherein the light chain domain includes SEQ ID NO:52, wherein the variant of SEQ ID NO:51 includes the sequence of SEQ ID NO:51 including at least one substitution thereto at positions corresponding to position 100 and position 103 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes one substitution. In embodiments, the variant of SEQ ID NO:51 includes two substitutions.

[0208] In embodiments, the variant of SEQ ID NO:51 includes the sequence of SEQ ID NO:51 including a substitution thereto at a position corresponding to position 100 relative to SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes the sequence of SEQ ID NO:51 including a substitution thereto at a position corresponding to position 103 relative to SEQ ID NO:51.

[0209] In embodiments, the variant of SEQ ID NO:51 includes one substitution. In embodiments, the variant of SEQ ID NO:51 includes two substitutions.

[0210] In embodiments, the variant of SEQ ID NO:51 includes a I100L, I100K, I100Y, I100V, I100M, I100T, I100F, I100A, I100Q, I100S, I100G, I100R, I100W, I100H, or I100N substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100L substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100K substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100Y substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100V substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100M substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100T substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100F substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100A substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100Q substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100S substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100G substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100R substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100W substitution at the position corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100H substitution at the position

corresponding to position 100 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a I100N substitution at the position corresponding to position 100 of SEQ ID NO:51.

[0211] In embodiments, the variant of SEQ ID NO:51 includes a T103Y, T103F, or T103S at the position corresponding to position 103 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a T103Y at the position corresponding to position 103 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a T103F at the position corresponding to position 103 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 includes a T103S at the position corresponding to position 103 of SEQ ID NO:51.

[0212] In embodiments, the variant of SEQ ID NO:51 includes an I100L substitution at the position corresponding to position 100 of SEQ ID NO:51 and a T103Y substitution at the position corresponding to position 103 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 is SEQ ID NO:38.

[0213] In embodiments, the variant of SEQ ID NO:51 includes an I100M substitution at the position corresponding to position 100 of SEQ ID NO:51 and a T103Y substitution at the position corresponding to position 103 of SEQ ID NO:51. In embodiments, the variant of SEQ ID NO:51 is SEQ ID NO:25.

[0214] In embodiments, the antibody is an IgG. In embodiments, the antibody is an IgG1, IgG2, IgG3, or IgG4. In embodiments, the antibody is an IgG1. In embodiments, the antibody is an IgG2. In embodiments, the antibody is an IgG3. In embodiments, the antibody is an IgG4.

[0215] In embodiments, the antibody is a humanized antibody or a chimeric antibody. In embodiments, the antibody is a humanized antibody. In embodiments, the antibody is a chimeric antibody.

[0216] As described above, in embodiments, the antibody may be a fragment of an antibody. In embodiments, the antibody includes a Fab fragment. In embodiments, the antibody is a a single-chain variable fragment (scFv). In embodiments, the antibody includes a fragment crystallizable (Fc) domain.

[0217] In embodiments, the antibody is capable of binding a Ephrin B2 protein. In embodiments, the antibody is capable of binding the extracellular domain of the Ephrin B2 protein. In

embodiments, the antibody is capable of binding residues within the extracellular domain of Ephrin B2. In embodiments, the extracellular domain includes residues corresponding to positions 26-229 of SEQ ID NO:79. In embodiments, the extracellular domain includes residues corresponding to positions 197-218 of SEQ ID NO:79. In embodiments, the antibody binds the Ephrin B2 extracellular domain including residues corresponding to positions 197-218 of SEQ ID NO:79 with higher affinity relative to the extracellular domain lacking said residues. For example, in embodiments, the antibody binds the Ephrin B2 extracellular domain including residues corresponding to positions 197-218 of SEQ ID NO:79 with at least 1-, 2-, 3-, 4- 5- 6-, 7-, 8-, 9-, 10-, 20-, 30-, 40-, 50-, 60-, 70-, 80-, 90-, 100-, 200-, 300-, 400-, 500-, 600-, 700-, 800-, 900-, or 100-fold higher affinity relative to an Ephrin B2 extracellular domain lacking said residues. In embodiments, the antibody does not substantially bind an Ephrin B2 extracellular domain lacking residues corresponding to positions 197-218 of SEQ ID NO:79. In embodiments, an antibody does not substantially bind to the extracellular domain of Ephrin B2 when use of conventional methods and compositions well known and used in the art to detect the interaction of an antibody to an epitope (e.g., immunofluorescence, Western Blot analysis, FACS analysis, Octet,) does not reveal a detectable level of binding relative to a standard control (e.g., an antibody known in the art to bind to the extracellular domain of Ephrin B2).

[0218] In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.9 nM to 1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 1.1 nM to about 10 nM. In embodiments, the

antibody binds the Ephrin B2 protein with a K_D from about 1.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 1.9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 2.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 2.9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 4.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 4.9 nM to about 10 nM. In embodiments, the antibody

binds the Ephrin B2 protein with a K_D from about 5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 5.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 5.9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 6.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 6.9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 7.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D

from about 7.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 7.9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 8.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 8.9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 9.1 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.2 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.3 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.4 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.5 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.6 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.7 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.8 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 9.9 nM to about 10 nM.

[0219] In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about about 9.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.5 nM. In embodiments, the antibody binds the

Ephrin B2 protein with a K_D from about 0.01 nM to about 9.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.7 nM. In embodiments, the antibody binds the Ephrin B2 protein

with a K_D from about 0.01 nM to about 6.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from

about 0.01 nM to about 3.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 1.1 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to

about 0.9 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.8 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.7 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.6 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.5 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.4 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.3 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.2 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D from about 0.01 nM to about 0.1 nM.

[0220] In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10 nM.

[0221] In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 1.496 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D of 1.496 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 1.259 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D of 1.259 nM.

[0222] For the antibody provided herein, in embodiments, the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0223] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 set forth in SEQ ID NO:3; wherein the light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:5. In embodiments, the CDR L2 is LSG.

[0224] In embodiments, the heavy chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:12. In embodiments, the heavy chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:12. In embodiments, said heavy chain variable domain includes SEQ ID NO:12. In embodiments, said heavy chain variable domain is SEQ ID NO:12.

[0225] In embodiments, the light chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:13. In embodiments, the light chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:13. In embodiments, said

light chain variable domain includes SEQ ID NO:13. In embodiments, said light chain variable domain is SEQ ID NO:13.

[0226] In embodiments, the antibody is an IgG. In embodiments, the antibody is an IgG1, IgG2, IgG3, or IgG4. In embodiments, the antibody is an IgG1. In embodiments, the antibody is an IgG2. In embodiments, the antibody is an IgG3. In embodiments, the antibody is an IgG4.

[0227] In embodiments, the antibody is a humanized antibody or a chimeric antibody. In embodiments, the antibody is a humanized antibody. In embodiments, the antibody is a chimeric antibody.

[0228] In embodiments, the antibody may be a fragment of an antibody. In embodiments, the antibody includes a Fab fragment. In embodiments, the antibody is a a single-chain variable fragment (scFv). In embodiments, the antibody includes a fragment crystallizable (Fc) domain.

[0229] In embodiments, the antibody is capable of binding a Ephrin B2 protein. In embodiments, the antibody is capable of binding the extracellular domain of the Ephrin B2 protein. In embodiments, the extracellular domain of the Ephrin B2 protein includes residues corresponding to positions 26-229 of SEQ ID NO:79. In embodiments, the antibody is capable of binding residues within the extracellular domain of Ephrin B2. In embodiments, the extracellular domain includes the sequence of SEQ ID NO:100. In embodiments, the extracellular domain includes the sequence of SEQ ID NO:85. In embodiments, the extracellular domain includes a glutamic acid at a position corresponding to position 69, an asparagine corresponding to position 70, a threonine corresponding to position 71, a leucine corresponding to position 73, an asparagine corresponding to position 75, a lysine corresponding to position 84, a serine corresponding to position 93, a leucine corresponding to position 96, a tryptophan corresponding to position 97, a glycine corresponding to position 98, a glutamic acid corresponding to position 100, a glutamine corresponding to position 102 of SEQ ID NO:85, or a combination thereof. In embodiments, the extracellular domain includes a glutamic acid at a position corresponding to position 69, an asparagine corresponding to position 70, a threonine corresponding to position 71, a leucine corresponding to position 73, an asparagine corresponding to position 75, a lysine corresponding to position 84, a serine corresponding to position 93, a leucine corresponding to position 96, a tryptophan corresponding to position 97, a glycine corresponding to position 98, a glutamic acid corresponding to position 100, and a glutamine corresponding to position 102 of SEQ ID NO:85. In embodiments, the extracellular domain includes a glutamic acid

at a position corresponding to position 69, an asparagine corresponding to position 70, and a threonine corresponding to position 71 of SEQ ID NO:85.

[0230] In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10 nM.

[0231] In embodiments, the antibody binds the Ephrin B2 protein with a K_D of less than about 1 nM. In embodiments, the antibody is antibody Ab25 and binds a Ephrin B2 protein with a K_D of 0.01 nM to about 10 nM. In embodiments, the antibody Ab25 binds a Ephrin B2 protein with a K_D of 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10 nM. In embodiments, the antibody is antibody Ab25 and binds a Ephrin B2 protein with a K_D of less than about 1 nM.

[0232] For the antibody provided herein, in embodiments, the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0233] In one embodiment, the antibody has a heavy chain variable domain of SEQ ID NO:12 and a light chain variable domain of SEQ ID NO:13. In one embodiment, the antibody includes a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2; a CDR H3 as set forth in SEQ ID NO:3; and a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:5. In one further embodiment, the antibody is antibody Ab25.

[0234] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes a CDR H1 as set forth in SEQ ID NO:14, a CDR H2 as set forth in SEQ ID NO:15 and a CDR H3 set forth in SEQ ID NO:16; wherein said light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:17, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:18. In embodiments, the CDR L2 is LSG.

[0235] In embodiments, the heavy chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:25. In embodiments, the heavy chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:25. In embodiments, said heavy chain variable domain includes SEQ ID NO:25. In embodiments, said heavy chain variable domain is SEQ ID NO:25.

[0236] In embodiments, the light chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:26. In embodiments, the light chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:26. In embodiments, said

light chain variable domain includes SEQ ID NO:26. In embodiments, said light chain variable domain is SEQ ID NO:26.

[0237] In embodiments, the antibody is an IgG. In embodiments, the antibody is an IgG1, IgG2, IgG3, or IgG4. In embodiments, the antibody is an IgG1. In embodiments, the antibody is an IgG2. In embodiments, the antibody is an IgG3. In embodiments, the antibody is an IgG4.

[0238] In embodiments, the antibody is a humanized antibody or a chimeric antibody. In embodiments, the antibody is a humanized antibody. In embodiments, the antibody is a chimeric antibody.

[0239] As described above, in embodiments, the antibody may be a fragment of an antibody. In embodiments, the antibody includes a Fab fragment. In embodiments, the antibody is a a single-chain variable fragment (scFv). In embodiments, the antibody includes a fragment crystallizable (Fc) domain.

[0240] In embodiments, the antibody is capable of binding a Ephrin B2 protein. In embodiments, the antibody is capable of binding the extracellular domain of the Ephrin B2 protein. In embodiments, the antibody is capable of binding residues within the extracellular domain of Ephrin B2. In embodiments, the extracellular domain of the Ephrin B2 protein includes residues corresponding to positions 26-229 of SEQ ID NO:79. In embodiments, the extracellular domain of the Ephrin B2 protein includes residues corresponding to positions 197-218 of SEQ ID NO:79.

[0241] In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10 nM.

[0242] In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 1.496. In embodiments, the antibody is antibody Ab51 and binds a Ephrin B2 protein with a K_D of 0.01 nM to about 10 nM. In embodiments, the antibody Ab51 binds a Ephrin B2 protein with a K_D of 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5,

9, 9.5, or 10 nM. In embodiments, the antibody is antibody Ab51 and binds a Ephrin B2 protein with a K_D of about 1.496.

[0243] For the antibody provided herein, in embodiments, the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0244] In one embodiment, the antibody has a heavy chain variable domain of SEQ ID NO:25 and a light chain variable domain of SEQ ID NO:26. In one embodiment, the antibody includes a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:14, a CDR H2 as set forth in SEQ ID NO:15; a CDR H3 as set forth in SEQ ID NO:16; and a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:17, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:18. In one further embodiment, the antibody is antibody Ab51.

[0245] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes a CDR H1 as set forth in SEQ ID NO:27, a CDR H2 as set forth in SEQ ID NO:28 and a CDR H3 set forth in SEQ ID NO:29; wherein said light chain variable domain includes: a CDR L1 as set forth in SEQ ID NO:30, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:31. In embodiments, the CDR L2 is LSG.

[0246] In embodiments, the heavy chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:38. In embodiments, the heavy chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:38. In embodiments, said

heavy chain variable domain includes SEQ ID NO:38. In embodiments, said heavy chain variable domain is SEQ ID NO:38.

[0247] In embodiments, the light chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:39. In embodiments, the light chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:39. In embodiments, said light chain variable domain includes SEQ ID NO:39. In embodiments, said light chain variable domain is SEQ ID NO:39.

[0248] In embodiments, the antibody is an IgG. In embodiments, the antibody is an IgG1 or an IgG2. In embodiments, the antibody is an IgG1. In embodiments, the antibody is an IgG2.

[0249] In embodiments, the antibody is a humanized antibody or a chimeric antibody. In embodiments, the antibody is a humanized antibody. In embodiments, the antibody is a chimeric antibody.

[0250] In embodiments, the antibody may be a fragment of an antibody. In embodiments, the antibody includes a Fab fragment. In embodiments, the antibody is a single-chain variable fragment (scFv). In embodiments, the antibody includes a fragment crystallizable (Fc) domain.

[0251] In embodiments, the antibody is capable of binding a Ephrin B2 protein. In embodiments, the antibody is capable of binding the extracellular domain of the Ephrin B2 protein. In embodiments, the antibody is capable of binding residues within the extracellular domain of Ephrin

B2. In embodiments, the extracellular domain of the Ephrin B2 protein includes residues corresponding to positions 26-229 of SEQ ID NO:79. In embodiments, the extracellular domain of the Ephrin B2 protein includes residues corresponding to positions 197-218 of SEQ ID NO:79.

[0252] In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10 nM.

[0253] In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 1.259 nM. In embodiments, the antibody is antibody Ab11 and binds a Ephrin B2 protein with a K_D of 0.01 nM to about 10 nM. In embodiments, the antibody Ab11 binds a Ephrin B2 protein with a K_D of 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10 nM. In embodiments, the antibody is antibody Ab11 and binds a Ephrin B2 protein with a K_D of about 1.259 nM.

[0254] For the antibody provided herein, in embodiments, the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0255] In one embodiment, the antibody has a heavy chain variable domain of SEQ ID NO:38 and a light chain variable domain of SEQ ID NO:39. In one embodiment, the antibody includes a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:27, a CDR H2 as set forth in SEQ ID NO:28; a CDR H3 as set forth in SEQ ID NO:29; and a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:30, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:31. In one further embodiment, the antibody is antibody Ab11.

[0256] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes: a CDR H1 as set forth in SEQ ID NO:86, a CDR H2 as set forth in SEQ ID NO:87 and a CDR H3 set forth in SEQ ID NO:88; wherein the light chain variable domain includes: a CDR L1 as set forth in

SEQ ID NO:89, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:90. In embodiments, the CDR L2 is LSG.

[0257] In embodiments, the heavy chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 98% identity to SEQ ID NO:98. In embodiments, the heavy chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:98. In embodiments, said heavy chain variable domain includes SEQ ID NO:98. In embodiments, said heavy chain variable domain is SEQ ID NO:98.

[0258] In embodiments, the light chain variable domain includes a sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 90% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 91% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 92% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 93% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 94% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 95% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 96% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 97% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a

sequence having at least 98% identity to SEQ ID NO:99. In embodiments, the light chain variable domain includes a sequence having at least 99% identity to SEQ ID NO:99. In embodiments, said light chain variable domain includes SEQ ID NO:99. In embodiments, said light chain variable domain is SEQ ID NO:99.

[0259] In embodiments, the antibody is an IgG. In embodiments, the antibody is an IgG1, IgG2, IgG3, or IgG4. In embodiments, the antibody is an IgG1. In embodiments, the antibody is an IgG2. In embodiments, the antibody is an IgG3. In embodiments, the antibody is an IgG4.

[0260] In embodiments, the antibody is a humanized antibody or a chimeric antibody. In embodiments, the antibody is a humanized antibody. In embodiments, the antibody is a chimeric antibody.

[0261] In embodiments, the antibody may be a fragment of an antibody. In embodiments, the antibody includes a Fab fragment. In embodiments, the antibody is a a single-chain variable fragment (scFv). In embodiments, the antibody includes a fragment crystallizable (Fc) domain.

[0262] In embodiments, the antibody is capable of binding a Ephrin B2 protein. In embodiments, the antibody is capable of binding the extracellular domain of the Ephrin B2 protein. In embodiments, the extracellular domain of the Ephrin B2 protein includes residues corresponding to positions 26-229 of SEQ ID NO:79. In embodiments, the antibody is capable of binding residues within the extracellular domain of Ephrin B2.

[0263] In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, or 10 nM.

[0264] In embodiments, the antibody is antibody Ab18 and binds a Ephrin B2 protein with a K_D of 0.01 nM to about 10 nM. In embodiments, the antibody Ab18 binds a Ephrin B2 protein with a K_D of 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, or 10 nM.

[0265] For the antibody provided herein, in embodiments, the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0266] In one embodiment, the antibody has a heavy chain variable domain of SEQ ID NO:98 and a light chain variable domain of SEQ ID NO:99. In one embodiment, the antibody includes a heavy chain variable domain including a CDR H1 as set forth in SEQ ID NO:86, a CDR H2 as set forth in SEQ ID NO:87; a CDR H3 as set forth in SEQ ID NO:88; and a light chain variable domain including a CDR L1 as set forth in SEQ ID NO:89, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:90. In one further embodiment, the antibody is antibody Ab18.

[0267] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes SEQ ID NO:51; wherein said light chain variable domain includes SEQ ID NO:52. In embodiments, the heavy chain variable domain is SEQ ID NO:51, and the light chain variable domain is SEQ ID NO:52.

[0268] In an aspect is provided an anti-Ephrin B2 antibody including a heavy chain variable domain and a light chain variable domain, wherein the heavy chain variable domain includes SEQ ID NO:64; wherein said light chain variable domain includes SEQ ID NO:65. In embodiments, the heavy chain variable domain is SEQ ID NO:64, and the light chain variable domain is SEQ ID NO:65.

[0269] In embodiments, the antibody is an IgG. In embodiments, the antibody is an IgG1, IgG2, IgG3, or IgG4. In embodiments, the antibody is an IgG1. In embodiments, the antibody is an IgG2. In embodiments, the antibody is an IgG3. In embodiments, the antibody is an IgG4.

[0270] In embodiments, the antibody is a humanized antibody or a chimeric antibody. In embodiments, the antibody is a humanized antibody. In embodiments, the antibody is a chimeric antibody.

[0271] In embodiments, the antibody may be a fragment of an antibody. In embodiments, the antibody includes a Fab fragment. In embodiments, the antibody is a single-chain variable fragment (scFv). In embodiments, the antibody includes a fragment crystallizable (Fc) domain.

[0272] In embodiments, the antibody is capable of binding a Ephrin B2 protein. In embodiments, the antibody is capable of binding the extracellular domain of the Ephrin B2 protein. In embodiments, the antibody is capable of binding residues within the extracellular domain of Ephrin B2. In embodiments, the extracellular domain of the Ephrin B2 protein includes residues corresponding to positions 26-229 of SEQ ID NO:79. In embodiments, the extracellular domain of the Ephrin B2 protein includes residues corresponding to positions 197-218 of SEQ ID NO:79. In embodiments, the antibody binds the Ephrin B2 extracellular domain including residues corresponding to positions 197-218 of SEQ ID NO:79 with higher affinity relative to the extracellular domain lacking said residues. For example, in embodiments, the antibody binds the Ephrin B2 extracellular domain including residues corresponding to positions 197-218 of SEQ ID NO:79 with at least 1-, 2-, 3-, 4- 5- 6-, 7-, 8-, 9-, 10-, 20-, 30-, 40-, 50-, 60-, 70-, 80-, 90-, 100-, 200-, 300-, 400-, 500-, 600-, 700-, 800-, 900-, or 100-fold higher affinity relative to an Ephrin B2 extracellular domain lacking said residues. In embodiments, the antibody does not substantially bind an Ephrin B2 extracellular domain lacking residues corresponding to positions 197-218 of SEQ ID NO:79.

[0273] In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 15 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 20 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 25 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 30 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 35 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 40 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 45 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 50 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 55 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 60 nM to about 200 nM. In

embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 65 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 70 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 75 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 80 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 85 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 90 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 95 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 100 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 105 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 110 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 115 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 120 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 125 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 130 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 135 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 140 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 145 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 150 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 155 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 160 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 165 nM to about 200 nM. In

embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 170 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 175 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 180 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 185 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 190 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 195 nM to about 200 nM.

[0274] In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 1 nM to about about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 5 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 15 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 20 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 25 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 30 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 35 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 40 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 45 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 50 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 55 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 60 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 65 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 70 nM to about 200 nM. In embodiments, the

antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 75 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 80 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 85 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 90 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 95 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 100 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 105 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 110 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 115 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 120 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 125 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 130 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 135 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 140 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 145 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 150 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 155 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 160 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 165 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 170 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 175 nM to about 200 nM. In

embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 180 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 185 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 190 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 195 nM to about 200 nM.

[0275] In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 195 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 190 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 185 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 180 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 175 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 170 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 165 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 160 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 155 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 150 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 145 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 140 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 135 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 130 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 125 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 120 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10

nM to about 115 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 110 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 105 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 100 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 95 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 90 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 85 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 80 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 75 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 70 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 65 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 60 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 55 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 50 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 45 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 40 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 35 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 30 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 25 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 20 nM. In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 15 nM.

[0276] In embodiments, the antibody binds the Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 200 nM. In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 230, 235, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 200 nM.

[0277] In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 81.5 nM. In embodiments, the antibody is antibody B11-QTS and binds a Ephrin B2 protein with a K_D of 10 to 200 nM. In embodiments, the antibody B11-QTS binds a Ephrin B2 protein with a K_D of 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 230, 235, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 200 nM. In embodiments, the antibody is antibody B11-QTS and binds a Ephrin B2 protein with a K_D of about 81.5 nM.

[0278] In embodiments, the antibody binds the Ephrin B2 protein with a K_D of about 141 nM. In embodiments, the antibody is antibody B11-DTS and binds a Ephrin B2 protein with a K_D of 10 to 200 nM. In embodiments, the antibody B11-DTS binds a Ephrin B2 protein with a K_D of 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 230, 235, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 200 nM. In embodiments, the antibody is antibody B11-DTS and binds a Ephrin B2 protein with a K_D of about 141 nM.

[0279] For the antibody provided herein, in embodiments, the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0280] In one embodiment, the antibody has a heavy chain variable domain of SEQ ID NO:51 and a light chain variable domain of SEQ ID NO:52. In one further embodiment, the antibody is antibody B11-QTS.

[0281] In one embodiment, the antibody has a heavy chain variable domain of SEQ ID NO:64 and a light chain variable domain of SEQ ID NO:65. In one further embodiment, the antibody is antibody B11-DTS.

[0282] In an aspect is provided an anti-Ephrin B2 antibody, wherein the anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a

CDR H3 set forth in SEQ ID NO:3; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:5.

[0283] In an aspect is provided an anti-Ephrin B2 antibody, where the anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:14, a CDR H2 as set forth in SEQ ID NO:15 and a CDR H3 set forth in SEQ ID NO:16; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:17, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:18.

[0284] In an aspect is provided an anti-Ephrin B2 antibody, where the anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:27, a CDR H2 as set forth in SEQ ID NO:28 and a CDR H3 set forth in SEQ ID NO:29; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:30, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:31.

[0285] In an aspect is provided an anti-Ephrin B2 antibody, where the anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody including a heavy chain variable domain including: a CDR H1 as set forth in SEQ ID NO:86, a CDR H2 as set forth in SEQ ID NO:87 and a CDR H3 set forth in SEQ ID NO:88; and a light chain variable domain including: a CDR L1 as set forth in SEQ ID NO:89, a CDR L2 including LGS, and a CDR L3 as set forth in SEQ ID NO:90.

[0286] Some aspects herein relate to or include an anti-Ephrin B2 antibody that includes a CDR (e.g. CDR H3) that is a variant of SEQ ID NO:68. The variant may include 1, 2, 3, 4, or more substitutions relative to SEQ ID NO:68. An example of such a variant may include the amino acid sequence of SEQ ID NO:3. The 1, 2, 3, 4, or more substitutions may be at positions corresponding to position 4, position 6, position 10, and/or position 11 relative to SEQ ID NO:68. Some aspects herein relate to or include an anti-Ephrin B2 antibody that includes a CDR (e.g. CDR H3) comprising the sequence of SEQ ID NO:3, or a variant thereof that includes 1, 2, or 3 amino acid substitutions. In embodiments, a variant of SEQ ID NO:3 is not identical to SEQ ID NO:68. Some aspects herein relate to or include an anti-Ephrin B2 antibody that includes a CDR (e.g. CDR H3) including the sequence of SEQ ID NO:3. Such CDRs may be included in an antibody with other CDRs (e.g. with other CDRs including LC CDR1, LC CDR2, LC CDR3, HC CDR1, and/or HC CDR2). The substitutions may include any substitution or combination of substitutions provided herein.

[0287] Some aspects herein relate to or include an anti-Ephrin B2 antibody that includes a CDR (e.g. CDR H3) that is a variant of SEQ ID NO:73. The variant may include 1, 2, 3, 4, or more substitutions relative to SEQ ID NO:73. An example of such a variant may include the amino acid sequence of SEQ ID NO:8. The 1, 2, 3, 4, or more substitutions may be at positions corresponding to position 2, position 4, position 8, and/or position 9 relative to SEQ ID NO:73. Some aspects herein relate to or include an anti-Ephrin B2 antibody that includes a CDR (e.g. CDR H3) including the sequence of SEQ ID NO:8, or a variant thereof that includes 1, 2, or 3 amino acid substitutions. In embodiments, a variant of SEQ ID NO:8 is not identical to SEQ ID NO:73. Some aspects herein relate to or include an anti-Ephrin B2 antibody that includes a CDR (e.g. CDR H3) including the sequence of SEQ ID NO:8. Such CDRs may be included in an antibody with other CDRs (e.g. with other CDRs including LC CDR1, LC CDR2, LC CDR3, HC CDR1, and/or HC CDR2). A substitution provided herein may be included in the CDR. The substitutions may include any substitution or combination of substitutions provided herein.

[0288] For the anti-Ephrin B2 antibodies provided herein, in embodiments, the antibody is attached to a therapeutic agent. In embodiments, the antibody is attached to a diagnostic agent. In embodiments, the diagnostic agent is a detectable moiety.

NUCLEIC ACID COMPOSITIONS

[0289] The compositions provided herein include nucleic acid molecules encoding the anti-Ephrin B2 antibodies or fragments thereof provided herein including embodiments thereof. The antibodies encoded by the isolated nucleic acid are described in detail throughout this application (including the description above and in the examples section). Thus, in an aspect, an isolated nucleic acid encoding an antibody as provided herein including embodiments thereof is provided.

[0290] In embodiments, the isolated nucleic acid encodes a variable heavy chain domain or a variable light chain domain provided herein. In embodiments, the isolated nucleic acid encodes a variable heavy chain domain. In embodiments, the isolated nucleic acid encodes a variable light chain domain.

[0291] In embodiments, the isolated nucleic acid may be provided in a vector, such as an expression vector. Thus, in another aspect a vector including the isolated nucleic acid provided herein including embodiments thereof is provided. In embodiments, the vector is an expression vector capable of directing the expression of nucleic acids to which they are operatively linked. The

term "operably linked" means that the nucleotide sequence of interest is linked to regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence. The regulatory sequence may include, for example, promoters, enhancers, and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are well known in the art and are described, for example, in Goeddel; Gene Expression Technology: Methods in Enzymology 185, Academic Press, San Diego, CA (1990)., which is incorporated herein in its entirety and for all purposes.

METHODS

[0292] The compositions (e.g., the anti-Ephrin B2 antibodies) provided herein, including embodiments thereof, are contemplated as providing effective treatments for diseases such as fibrosis (e.g., liver fibrosis, lung fibrosis, etc.). Thus, in an aspect is provided a method of treating fibrosis in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of the anti-Ephrin B2 antibody provided herein including embodiments thereof.

[0293] For the methods provided herein, in embodiments, the subject has been identified as having a disease or condition as provided herein including embodiments thereof. In embodiments, the subject has been identified as having fibrosis. Thus, in embodiments, the method includes administering a composition including an antibody provided herein including embodiments thereof to a subject that has been identified as having the disease. In embodiments, the method includes identifying the subject as having the disease. In embodiments, the method includes identifying the subject as having the fibrosis.

[0294] In embodiments, the subject has been identified as at risk of having a disease or condition as provided herein including embodiments thereof. In embodiments, the subject has been identified as at risk of having fibrosis. In embodiments, the method includes administering a composition including an antibody provided herein including embodiments thereof to a subject that has been identified as at risk of having a disease. In embodiments, the subject is at risk of having the disease. In embodiments, the subject is at risk of having the fibrosis. In embodiments, the method includes identifying the subject as at risk having the disease. In embodiments, the method includes identifying the subject as at risk of having the fibrosis.

[0295] For the methods provided herein, in embodiments, the fibrosis is skin fibrosis, lung fibrosis, cardiac fibrosis, liver fibrosis, kidney fibrosis, gut fibrosis, or cystic fibrosis. In embodiments, the fibrosis is skin fibrosis. In embodiments, the fibrosis is lung fibrosis. In embodiments, the fibrosis is cardiac fibrosis. In embodiments, the fibrosis is liver fibrosis. In embodiments, the fibrosis is kidney fibrosis. In embodiments, the fibrosis is gut fibrosis. In embodiments, the fibrosis is cystic fibrosis.

[0296] In embodiments, the fibrosis is skin fibrosis. In embodiments, the subject has systemic sclerosis, keloids, hypertrophic scars, or a combination thereof. In embodiments, the subject has systemic sclerosis. In embodiments, the subject has keloids. In embodiments, the subject has hypertrophic scars. In embodiments, the skin fibrosis is associated with or caused by systemic sclerosis, keloids, or hypertrophic scars. In embodiments, the skin fibrosis is associated with or caused by systemic sclerosis. In embodiments, the skin fibrosis is associated with or caused by keloids. In embodiments, the skin fibrosis is associated with or caused by hypertrophic scars.

[0297] In embodiments, the fibrosis is lung fibrosis. In embodiments, subject has interstitial lung disease. In embodiments, the interstitial lung disease causes pulmonary fibrosis in the subject. For example, when the interstitial lung disease causes scarring of lung tissue, the subject has pulmonary lung fibrosis. The interstitial lung disease and/or pulmonary fibrosis may, in embodiments, be idiopathic, autoimmune-associated, connective-tissue disease-associated, environmental, occupational, radiation-induced, or drug-induced. In embodiments, the interstitial lung disease and/or pulmonary fibrosis may be associated with a viral infection or lymphangioleiomyomatosis. In embodiments, the interstitial lung disease and/or pulmonary fibrosis may be genetic.

[0298] In embodiments, the interstitial lung disease is non-specific interstitial pneumonia, rheumatoid arthritis interstitial lung disease, hypersensitivity pneumonitis, berylliosis, respiratory bronchiolitis interstitial lung disease, desquamative interstitial pneumonitis, sarcoidosis, acute interstitial pneumonitis, cryptogenic-organizing pneumonitis, lymphocytic interstitial pneumonitis, or pleuroparenchymal fibroelastosis. In embodiments, the interstitial lung disease is non-specific interstitial pneumonia. In embodiments, the interstitial lung disease is rheumatoid arthritis interstitial lung disease. In embodiments, the interstitial lung disease is hypersensitivity pneumonitis. In embodiments, the interstitial lung disease is berylliosis. In embodiments, the interstitial lung disease is respiratory bronchiolitis interstitial lung disease. In embodiments, the interstitial lung disease is

desquamative interstitial pneumonitis. In embodiments, the interstitial lung disease is sarcoidosis. In embodiments, the interstitial lung disease is acute interstitial pneumonitis. In embodiments, the interstitial lung disease is cryptogenic-organizing pneumonitis. In embodiments, the interstitial lung disease is lymphocytic interstitial pneumonitis. In embodiments, the interstitial lung disease is pleuroparenchymal fibroelastosis.

[0299] In embodiments, the lung fibrosis is idiopathic pulmonary fibrosis, systemic sclerosis associated pulmonary fibrosis, progressive pulmonary fibrosis, pulmonary fibrosis associated with Sjogrens Syndrome., pneumoconiosis, asbestosis, silicosis, radiation-induced pulmonary fibrosis, drug-induced pulmonary fibrosis, COVID-19-related pulmonary fibrosis, pulmonary fibrosis following acute respiratory distress syndrome, pulmonary fibrosis associated with lymphangioleiomyomatosis, familial pulmonary fibrosis, pulmonary fibrosis associated with Hermansky Pudlak syndrome, or pulmonary fibrosis associated with dyskeratosis congenita. In embodiments, the lung fibrosis is idiopathic pulmonary fibrosis, systemic sclerosis associated pulmonary fibrosis, or progressive pulmonary fibrosis.

[0300] In embodiments, the lung fibrosis is idiopathic pulmonary fibrosis. In embodiments, the lung fibrosis is systemic sclerosis associated pulmonary fibrosis. In embodiments, the lung fibrosis is progressive pulmonary fibrosis. In embodiments, the lung fibrosis is pulmonary fibrosis associated with Sjogrens Syndrome. In embodiments, the lung fibrosis is pneumoconiosis. In embodiments, the lung fibrosis is asbestosis. In embodiments, the lung fibrosis is silicosis. In embodiments, the lung fibrosis is radiation-induced pulmonary fibrosis. In embodiments, the lung fibrosis is drug-induced pulmonary fibrosis. In embodiments, the lung fibrosis is COVID-19-related pulmonary fibrosis. In embodiments, the lung fibrosis is pulmonary fibrosis following acute respiratory distress syndrome. In embodiments, the lung fibrosis is pulmonary fibrosis associated with lymphangioleiomyomatosis. In embodiments, the lung fibrosis is familial pulmonary fibrosis. In embodiments, the lung fibrosis is pulmonary fibrosis associated with Hermansky Pudlak syndrome. In embodiments, the lung fibrosis is pulmonary fibrosis associated with dyskeratosis congenita.

[0301] In embodiments, the fibrosis is cardiac fibrosis. In embodiments, the subject has chronic heart failure or has previously had a myocardial infarction. In embodiments, the subject has chronic heart failure. In embodiments, the subject has previously had a myocardial infarction. In

embodiments, the cardiac fibrosis is caused by or associated with the chronic heart failure or myocardial infarction. In embodiments, the cardiac fibrosis is caused by or associated with the chronic heart failure. In embodiments, the cardiac fibrosis is caused by or associated with the myocardial infarction.

[0302] In embodiments, the fibrosis is liver fibrosis. In embodiments, the subject has nonalcoholic fatty liver disease, metabolic dysfunction-associated steatohepatitis, cirrhosis, primary biliary cholangitis, or primary sclerosing cholangitis. In embodiments, the subject has nonalcoholic fatty liver disease. In embodiments, the subject has metabolic dysfunction-associated steatohepatitis, cirrhosis. In embodiments, the subject has primary biliary cholangitis. In embodiments, the subject has primary sclerosing cholangitis. In embodiments, the liver fibrosis is caused by or associated with the nonalcoholic fatty liver disease, metabolic dysfunction-associated steatohepatitis, cirrhosis, primary biliary cholangitis, or primary sclerosing cholangitis. In embodiments, the liver fibrosis is caused by or associated with the nonalcoholic fatty liver disease. In embodiments, the liver fibrosis is caused by or associated with the metabolic dysfunction-associated steatohepatitis. In embodiments, the liver fibrosis is caused by or associated with the cirrhosis. In embodiments, the liver fibrosis is caused by or associated with the primary biliary cholangitis. In embodiments, the liver fibrosis is caused by or associated with the primary sclerosing cholangitis.

[0303] In embodiments, the fibrosis is kidney fibrosis. In embodiments, the subject has chronic kidney disease or diabetic nephropathy. In embodiments, the subject has chronic kidney disease. In embodiments, the subject has diabetic nephropathy. In embodiments, the kidney fibrosis is caused by or associated with the chronic kidney disease or diabetic nephropathy. In embodiments, the kidney fibrosis is caused by or associated with the chronic kidney disease. In embodiments, the kidney fibrosis is caused by or associated with the diabetic nephropathy.

[0304] In embodiments, the fibrosis is gut fibrosis. In embodiments, the subject has Crohn's disease or fibrostenotic inflammatory bowel disease. In embodiments, the subject has Crohn's disease. In embodiments, the subject has fibrostenotic inflammatory bowel disease. In embodiments, the gut fibrosis is caused by or associated with the Crohn's disease or fibrostenotic inflammatory bowel disease. In embodiments, the gut fibrosis is caused by or associated with the Crohn's disease. In embodiments, the gut fibrosis is caused by or associated with the fibrostenotic inflammatory bowel disease.

[0305] In embodiments, the fibrosis is autoimmune-associated. For example, in embodiments, the subject has an auto-immune disorder that causes over-production of collagen, leading to fibrosis.

[0306] In another aspect is provided a method of inhibiting migration of an Ephrin B2 expressing cell, the method including contacting the cell with an anti- Ephrin B2 antibody provided herein including embodiments thereof.

[0307] In embodiments, the cell is a fibroblast or an endothelial cell. In embodiments, the cell is a fibroblast. In embodiments, the cell is an endothelial cell.

P EMBODIMENTS

[0308] P Embodiment 1. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:66, a CDR H2 as set forth in SEQ ID NO:67, and a CDR H3, wherein said CDR H3 is a variant of SEQ ID NO:68; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:69, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:70; and wherein said variant of SEQ ID NO:68 comprises the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4, position 6, position 10, and position 11 relative to SEQ ID NO:68.

[0309] P Embodiment 2. The antibody of P embodiment 1, wherein the variant of SEQ ID NO:68 includes one substitution.

[0310] P Embodiment 3. The antibody of P embodiment 1, wherein the variant of SEQ ID NO:68 includes two substitutions.

[0311] P Embodiment 4. The antibody of P embodiment 1, wherein the variant of SEQ ID NO:68 includes three substitutions.

[0312] P Embodiment 5. The antibody of P embodiment 1, wherein the variant of SEQ ID NO:68 includes four substitutions.

[0313] P Embodiment 6. The antibody of any one of P embodiments 1 to 5, wherein the variant of SEQ ID NO:68 comprises a I4S, I4A, I4G, I4P, I4R, I4K, I4C, or I4M substitution at the position corresponding to position 4 of SEQ ID NO:68.

[0314] P Embodiment 7. The antibody of any one of P embodiments 1 to 6, wherein the variant of SEQ ID NO:68 comprises a G6N, G6K, or G6R substitution at the position corresponding to position 6 of SEQ ID NO:68.

[0315] P Embodiment 8. The antibody of any one of P embodiments 1 to 7, wherein the variant of SEQ ID NO:68 comprises a G10K or G10R substitution at the position corresponding to position 10 of SEQ ID NO:68.

[0316] P Embodiment 9. The antibody of any one of P embodiments 1 to 8, wherein the variant of SEQ ID NO:68 comprises an F11L, F11V, or F11I substitution at the position corresponding to position 11 of SEQ ID NO:68.

[0317] P Embodiment 10. The antibody of any one of P embodiments 1 to 9, wherein the variant of SEQ ID NO:68 comprises a I4G substitution at the position corresponding to position 4 of SEQ ID NO:68, a G6K substitution at the position corresponding to position 6 of SEQ ID NO:68, an G10R substitution at the position corresponding to position 10 of SEQ ID NO:68, and a F11V substitution at the position corresponding to position 11 of SEQ ID NO:68.

[0318] P Embodiment 11. The antibody of any one of P embodiments 1 to 10, wherein the variant of SEQ ID NO:68 is SEQ ID NO:3.

[0319] P Embodiment 12. The antibody of any one of P embodiments 1 to 11, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:12.

[0320] P Embodiment 13. The antibody of P embodiment 12, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:12.

[0321] P Embodiment 14. The antibody of P embodiment 13, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:12.

[0322] P Embodiment 15. The antibody of P embodiment 14, wherein said heavy chain variable domain comprises SEQ ID NO:12.

[0323] P Embodiment 16. The antibody of any one of P embodiments 1 to 15, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:13.

[0324] P Embodiment 17. The antibody of P embodiment 16, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:13.

[0325] P Embodiment 18. The antibody of P embodiment 17, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:13.

[0326] P Embodiment 19. The antibody of P embodiment 18, wherein said light chain variable domain comprises SEQ ID NO:13.

[0327] P Embodiment 20. The antibody of any one of P embodiments 1 to 19, wherein said antibody is an IgG.

[0328] P Embodiment 21. The antibody of any one of P embodiments 1 to 20, wherein said antibody is a humanized antibody or a chimeric antibody.

[0329] P Embodiment 22. The antibody of any one of P embodiments 1 to 21, wherein said antibody comprises a Fab fragment.

[0330] P Embodiment 23. The antibody of any one of P embodiments 1 to 21, wherein said antibody is a single-chain variable fragment (scFv).

[0331] P Embodiment 24. The antibody of any one of P embodiments 1 to 23, wherein said antibody is capable of binding an Ephrin B2 protein.

[0332] P Embodiment 25. The antibody of P embodiment 24, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0333] P Embodiment 26. The antibody of P embodiment 24 or 25, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

[0334] P Embodiment 27. The antibody of any one of P embodiments 24 to 26, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of less than about 1 nM.

[0335] P Embodiment 28. The antibody of P embodiment 26 or 27, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0336] P Embodiment 29. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:66, a CDR H2 as set forth in SEQ ID NO:67 and a CDR H3, wherein said CDR H3 is a variant of SEQ ID NO:68; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:69, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:70; and wherein said variant of SEQ ID NO:68 comprises the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4 and position 7 relative to SEQ ID NO:68.

[0337] P Embodiment 30. The antibody of P embodiment 29, wherein the variant of SEQ ID NO:68 includes one substitution.

[0338] P Embodiment 31. The antibody of P embodiment 29, wherein the variant of SEQ ID NO:68 includes two substitutions.

[0339] P Embodiment 32. The antibody of any one of P embodiments 29 to 31, wherein the variant of SEQ ID NO:68 comprises a I4L, I4K, I4Y, I4V, I4M, I4T, I4F, I4A, I4Q, I4S, I4G, I4R, I4W, I4H, or I4N substitution at the position corresponding to position 4 of SEQ ID NO:68.

[0340] P Embodiment 33. The antibody of any one of P embodiments 29 to 32, wherein the variant of SEQ ID NO:68 comprises a T7Y, T7F, or T7S at the position corresponding to position 7 of SEQ ID NO:68.

[0341] P Embodiment 34. The antibody of any one of P embodiments 29 to 33, wherein the variant of SEQ ID NO:68 comprises an I4M substitution at the position corresponding to position 4 of SEQ ID NO:68 and a T7Y substitution at the position corresponding to position 7 of SEQ ID NO:68.

[0342] P Embodiment 35. The antibody of any one of P embodiments 29 to 34, wherein the variant of SEQ ID NO:68 is SEQ ID NO:16.

[0343] P Embodiment 36. The antibody of any one of P embodiments 29 to 33, wherein the variant of SEQ ID NO:68 comprises an I4L substitution at the position corresponding to position 4 of SEQ ID NO:68 and a T7Y substitution at the position corresponding to position 7 of SEQ ID NO:68.

[0344] P Embodiment 37. The antibody of any one of P embodiments 29 to 33 or 36, wherein the CDR H3 is SEQ ID NO:29.

[0345] P Embodiment 38. The antibody of any one of P embodiments 29 to 35, wherein the heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:25.

[0346] P Embodiment 39. The antibody of P embodiment 38, wherein the heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:25.

[0347] P Embodiment 40. The antibody of P embodiment 39, wherein the heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:25.

[0348] P Embodiment 41. The antibody of P embodiment 40, wherein the heavy chain variable domain comprises SEQ ID NO:25.

[0349] P Embodiment 42. The antibody of any one of P embodiments 29 to 35 or 38 to 41, wherein the light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:26.

[0350] P Embodiment 43. The antibody of P embodiment 42, wherein the light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:26.

[0351] P Embodiment 44. The antibody of P embodiment 43, wherein the light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:26.

[0352] P Embodiment 45. The antibody of P embodiment 44, wherein the light chain variable domain comprises SEQ ID NO:26.

[0353] P Embodiment 46. The antibody of any one of P embodiments 29 to 33, 36 or 37, wherein the heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:38.

[0354] P Embodiment 47. The antibody of P embodiment 46, wherein the heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:38.

[0355] P Embodiment 48. The antibody of P embodiment 47, wherein the heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:38.

[0356] P Embodiment 49. The antibody of P embodiment 48, wherein the heavy chain variable domain comprises SEQ ID NO:38.

[0357] P Embodiment 50. The antibody of any one of P embodiments 29 to 33, 36, 37, or 46 to 49, wherein the light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:39.

[0358] P Embodiment 51. The antibody of P embodiment 50, wherein the light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:39.

[0359] P Embodiment 52. The antibody of P embodiment 51, wherein the light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:39.

[0360] P Embodiment 53. The antibody of P embodiment 52, wherein the light chain variable domain comprises SEQ ID NO:39.

[0361] P Embodiment 54. The antibody of any one of P embodiments 24 to 53, wherein said antibody is an IgG.

[0362] P Embodiment 55. The antibody of any one of P embodiments 24 to 54, wherein said antibody is a humanized antibody or a chimeric antibody.

[0363] P Embodiment 56. The antibody of any one of P embodiments 24 to 55, wherein said antibody comprises a Fab fragment.

[0364] P Embodiment 57. The antibody of any one of P embodiments 24 to 55, wherein said antibody is a single-chain variable fragment (scFv).

[0365] P Embodiment 58. The antibody of any one of P embodiments 24 to 57, wherein said antibody is capable of binding an Ephrin B2 protein.

[0366] P Embodiment 59. The antibody of P embodiment 58, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0367] P Embodiment 60. The antibody of P embodiment 59, wherein the extracellular domain of said Ephrin B2 protein comprises residues corresponding to positions 197-218 of SEQ ID NO:79.

[0368] P Embodiment 61. The antibody of any one of P embodiments 58 to 60, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

[0369] P Embodiment 62. The antibody of any one of P embodiments 58 to 61, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 1.496 nM.

[0370] P Embodiment 63. The antibody of any one of P embodiments 58 to 61, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 1.259 nM.

[0371] P Embodiment 64. The antibody of any one of P embodiments 61 to 63, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0372] P Embodiment 65. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 set forth in SEQ ID NO:3; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:5.

[0373] P Embodiment 66. The antibody of P embodiment 65, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:12.

[0374] P Embodiment 67. The antibody of P embodiment 66, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:12.

[0375] P Embodiment 68. The antibody of P embodiment 67, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:12.

[0376] P Embodiment 69. The antibody of P embodiment 68, wherein said heavy chain variable domain comprises SEQ ID NO:12.

[0377] P Embodiment 70. The antibody of any one of P embodiments 65 to 69, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:13.

[0378] P Embodiment 71. The antibody of P embodiment 70, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:13.

[0379] P Embodiment 72. The antibody of P embodiment 71, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:13.

[0380] P Embodiment 73. The antibody of P embodiment 72, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:13.

[0381] P Embodiment 74. The antibody of P embodiment 73, wherein said light chain variable domain comprises SEQ ID NO:13.

[0382] P Embodiment 75. The antibody of any one of P embodiments 65 to 74, wherein said antibody is an IgG.

[0383] P Embodiment 76. The antibody of any one of P embodiments 65 to 75, wherein said antibody comprises a Fab fragment.

[0384] P Embodiment 77. The antibody of any one of P embodiments 65 to 75, wherein said antibody is a single-chain variable fragment (scFv).

[0385] P Embodiment 78. The antibody of any one of P embodiments 65 to 77, wherein said antibody is capable of binding an Ephrin B2 protein.

[0386] P Embodiment 79. The antibody of P embodiment 78, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0387] P Embodiment 80. The antibody of any one of P embodiments 78 or 79, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

[0388] P Embodiment 81. The antibody of any one of P embodiments 78 to 80, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of less than about 1 nM.

[0389] P Embodiment 82. The antibody of P embodiment 80 or 81, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0390] P Embodiment 83. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:14, a CDR H2 as set forth in SEQ ID NO:15 and a CDR H3 set forth in SEQ ID NO:16; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:17, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:18.

[0391] P Embodiment 84. The antibody of P embodiment 83, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:25.

[0392] P Embodiment 85. The antibody of P embodiment 84, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:25.

[0393] P Embodiment 86. The antibody of P embodiment 85, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:25.

[0394] P Embodiment 87. The antibody of P embodiment 86, wherein said heavy chain variable domain comprises SEQ ID NO:25.

[0395] P Embodiment 88. The antibody of any one of P embodiments 83 to 87, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:26.

[0396] P Embodiment 89. The antibody P embodiment 88, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:26.

[0397] P Embodiment 90. The antibody P embodiment 89, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:26.

[0398] P Embodiment 91. The antibody P embodiment 90, wherein said light chain variable domain comprises SEQ ID NO:26.

[0399] P Embodiment 92. The antibody of any one of P embodiments 83 to 91, wherein said antibody is an IgG.

[0400] P Embodiment 93. The antibody of any one of P embodiments 83 to 92, wherein said antibody is a humanized antibody or a chimeric antibody.

[0401] P Embodiment 94. The antibody of any one of P embodiments 83 to 93, wherein said antibody comprises a Fab fragment

[0402] P Embodiment 95. The antibody of any one of P embodiments 83 to 93, wherein said antibody is a single-chain variable fragment (scFv).

[0403] P Embodiment 96. The antibody of any one of P embodiments 83 to 95, wherein said antibody is capable of binding an Ephrin B2 protein.

[0404] P Embodiment 97. The antibody of P embodiment 96, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0405] P Embodiment 98. The antibody of P embodiment 97, wherein the extracellular domain of said Ephrin B2 protein comprises residues corresponding to positions 197-218 of SEQ ID NO:79.

[0406] P Embodiment 99. The antibody of any one of P embodiments 96 to 98, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

[0407] P Embodiment 100. The antibody of P embodiment 99, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 1.496 nM.

[0408] P Embodiment 101. The antibody of P embodiment 99 or 100, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0409] P Embodiment 102. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:27, a CDR H2 as set forth in SEQ ID NO:28 and a CDR H3 set forth in SEQ ID NO:29; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:30, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:31.

[0410] P Embodiment 103. The antibody of P embodiment 102, wherein the heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:38.

[0411] P Embodiment 104. The antibody of P embodiment 103, wherein the heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:38.

[0412] P Embodiment 105. The antibody of P embodiment 104, wherein the heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:38.

[0413] P Embodiment 106. The antibody of P embodiment 102, wherein the heavy chain variable domain comprises SEQ ID NO:38.

[0414] P Embodiment 107. The antibody of any one of P embodiments 102 to 106, wherein the light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:39.

[0415] P Embodiment 108. The antibody of P embodiment 107, wherein the light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:39.

[0416] P Embodiment 109. The antibody of P embodiment 108, wherein the light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:39.

[0417] P Embodiment 110. The antibody of P embodiment 109, wherein the light chain variable domain comprises SEQ ID NO:39.

[0418] P Embodiment 111. The antibody of any one of P embodiments 106 to 110, wherein said antibody is an IgG.

[0419] P Embodiment 112. The antibody of any one of P embodiments 106 to 111, wherein said antibody is a humanized antibody or a chimeric antibody.

[0420] P Embodiment 113. The antibody of any one of P embodiments 106 to 112, wherein said antibody comprises a Fab fragment.

[0421] P Embodiment 114. The antibody of any one of P embodiments 106 to 112, wherein said antibody is a single-chain variable fragment (scFv).

[0422] P Embodiment 115. The antibody of any one of P embodiments 106 to 114, wherein said antibody is capable of binding an Ephrin B2 protein.

[0423] P Embodiment 116. The antibody of P embodiment 115, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0424] P Embodiment 117. The antibody of P embodiment 116, wherein the extracellular domain of said Ephrin B2 protein comprises residues corresponding to positions 197-218 of SEQ ID NO:79.

[0425] P Embodiment 118. The antibody of any one of P embodiments 115 to 117, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

[0426] P Embodiment 119. The antibody of any one of P embodiments 115 to 118, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 1.259 nM.

[0427] P Embodiment 120. The antibody of P embodiment 118 or 119, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0428] P Embodiment 121. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:86, a CDR H2 as set forth in SEQ ID NO:87 and a CDR H3 set forth in SEQ ID NO:88; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:89, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:90

[0429] P Embodiment 122. The antibody of P embodiment 121, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:98.

[0430] P Embodiment 123. The antibody of P embodiment 122, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:98.

[0431] P Embodiment 124. The antibody of P embodiment 123, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:98.

[0432] P Embodiment 125. The antibody of P embodiment 124, wherein said heavy chain variable domain comprises SEQ ID NO:98.

[0433] P Embodiment 126. The antibody of any one of P embodiments 121 to 125, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:99.

[0434] P Embodiment 127. The antibody of P embodiment 126, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:99.

[0435] P Embodiment 128. The antibody of P embodiment 127, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:99.

[0436] P Embodiment 129. The antibody of P embodiment 128, wherein said light chain variable domain comprises SEQ ID NO:99.

[0437] P Embodiment 130. The antibody of any one of P embodiments 121 to 129, wherein said antibody is an IgG.

[0438] P Embodiment 131. The antibody of any one of P embodiments 121 to 130, wherein said antibody comprises a Fab fragment.

[0439] P Embodiment 132. The antibody of any one of P embodiments 121 to 131, wherein said antibody is a single-chain variable fragment (scFv).

[0440] P Embodiment 133. The antibody of any one of P embodiments 121 to 132, wherein said antibody is capable of binding an Ephrin B2 protein.

[0441] P Embodiment 134. The antibody of P embodiment 133, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0442] P Embodiment 135. The antibody of P embodiment 133 or 134, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

[0443] P Embodiment 136. The antibody of P embodiment 135, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0444] P Embodiment 137. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises SEQ ID NO:51; and wherein said light chain variable domain comprises SEQ ID NO:52.

[0445] P Embodiment 138. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises SEQ ID NO:64; and wherein said light chain variable domain comprises SEQ ID NO:65.

[0446] P Embodiment 139. The antibody of P embodiment 137 or 138, wherein said antibody is an IgG.

[0447] P Embodiment 140. The antibody of any one of P embodiments 137 to 139, wherein said antibody is a humanized antibody or a chimeric antibody.

[0448] P Embodiment 141. The antibody of any one of P embodiments 137 to 140, wherein said antibody comprises a Fab fragment.

[0449] P Embodiment 142. The antibody of any one of P embodiments 137 to 140, wherein said antibody is a single-chain variable fragment (scFv).

[0450] P Embodiment 143. The antibody of any one of P embodiments 137 to 142, wherein said antibody is capable of binding an Ephrin B2 protein.

[0451] P Embodiment 144. The antibody of P embodiment 143, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0452] P Embodiment 145. The antibody of P embodiment 144, wherein the extracellular domain of said Ephrin B2 protein comprises residues corresponding to positions 197-218 of SEQ ID NO:79.

[0453] P Embodiment 146. The antibody of any one of P embodiments 143 to 145, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 200 nM.

[0454] P Embodiment 147. The antibody of any one of P embodiments 143 to 146, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 81.5 nM.

[0455] P Embodiment 148. The antibody of any one of P embodiments 143 to 146, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 141 nM.

[0456] P Embodiment 149. The antibody of any one of P embodiments 148 to 148, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0457] P Embodiment 150. The antibody of any one of P embodiments 1 to 149, wherein said antibody is attached to a therapeutic agent.

[0458] P Embodiment 151. The antibody of any one of P embodiments 1 to 149, wherein said antibody is attached to a diagnostic agent.

[0459] P Embodiment 152. A method of treating fibrosis in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of an antibody of any one of P embodiments 1 to 151.

[0460] P Embodiment 153. The method of P embodiment 152, wherein said fibrosis is lung fibrosis or skin fibrosis.

[0461] P Embodiment 154. A method of inhibiting migration of an Ephrin-B2 expressing cell, the method comprising contacting said cell with the anti-Ephrin B2 antibody of any one of P embodiments 1 to 151.

EMBODIMENTS

[0462] Embodiment 1. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:66, a CDR H2 as set forth in SEQ ID NO:67, and a CDR H3, wherein said CDR H3 is a variant of SEQ ID NO:68; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:69, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:70; and wherein said variant of SEQ ID NO:68 comprises the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4, position 6, position 10, and position 11 relative to SEQ ID NO:68.

[0463] Embodiment 2. The antibody of Embodiment 1, wherein the variant of SEQ ID NO:68 includes one substitution.

[0464] Embodiment 3. The antibody of Embodiment 1, wherein the variant of SEQ ID NO:68 includes two substitutions.

[0465] Embodiment 4. The antibody of Embodiment 1, wherein the variant of SEQ ID NO:68 includes three substitutions.

[0466] Embodiment 5. The antibody of Embodiment 1, wherein the variant of SEQ ID NO:68 includes four substitutions.

[0467] Embodiment 6. The antibody of any one of Embodiments 1 to 5, wherein the variant of SEQ ID NO:68 comprises a I4S, I4A, I4G, I4P, I4R, I4K, I4C, or I4M substitution at the position corresponding to position 4 of SEQ ID NO:68.

[0468] Embodiment 7. The antibody of any one of Embodiments 1 to 6, wherein the variant of SEQ ID NO:68 comprises a G6N, G6K, or G6R substitution at the position corresponding to position 6 of SEQ ID NO:68.

[0469] Embodiment 8. The antibody of any one of Embodiments 1 to 7, wherein the variant of SEQ ID NO:68 comprises a G10K or G10R substitution at the position corresponding to position 10 of SEQ ID NO:68.

[0470] Embodiment 9. The antibody of any one of Embodiments 1 to 8, wherein the variant of SEQ ID NO:68 comprises an F11L, F11V, or F11I substitution at the position corresponding to position 11 of SEQ ID NO:68.

[0471] Embodiment 10. The antibody of any one of Embodiments 1 to 9, wherein the variant of SEQ ID NO:68 comprises a I4G substitution at the position corresponding to position 4 of SEQ ID NO:68, a G6K substitution at the position corresponding to position 6 of SEQ ID NO:68, an G10R substitution at the position corresponding to position 10 of SEQ ID NO:68, and a F11V substitution at the position corresponding to position 11 of SEQ ID NO:68.

[0472] Embodiment 11. The antibody of any one of Embodiments 1 to 10, wherein the variant of SEQ ID NO:68 is SEQ ID NO:3.

[0473] Embodiment 12. The antibody of any one of Embodiments 1 to 9, wherein the variant of SEQ ID NO:68 comprises a I4S substitution at the position corresponding to position 4 of SEQ ID NO:68, an G10K substitution at the position corresponding to position 10 of SEQ ID NO:68, and a F11L substitution at the position corresponding to position 11 of SEQ ID NO:68.

[0474] Embodiment 13. The antibody of any one of Embodiments 1 to 10 or 12, wherein the variant of SEQ ID NO:68 is SEQ ID NO:88.

[0475] Embodiment 14. The antibody of any one of Embodiments 1 to 11, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:12.

[0476] Embodiment 15. The antibody of Embodiment 14, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:12.

[0477] Embodiment 16. The antibody of Embodiment 15, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:12.

[0478] Embodiment 17. The antibody of Embodiment 16, wherein said heavy chain variable domain comprises SEQ ID NO:12.

[0479] Embodiment 18. The antibody of any one of Embodiments 1 to 11 and 14 to 17, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:13.

[0480] Embodiment 19. The antibody of Embodiment 18, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:13.

[0481] Embodiment 20. The antibody of Embodiment 19, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:13.

[0482] Embodiment 21. The antibody of Embodiment 20, wherein said light chain variable domain comprises SEQ ID NO:13.

[0483] Embodiment 22. The antibody of any one of Embodiments 1 to 9, 12 or 13, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:98.

[0484] Embodiment 23. The antibody of Embodiment 22, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:98.

[0485] Embodiment 24. The antibody of Embodiment 23, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:98.

[0486] Embodiment 25. The antibody of Embodiment 24, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:98.

[0487] Embodiment 26. The antibody of Embodiment 25, wherein said heavy chain variable domain comprises SEQ ID NO:98.

[0488] Embodiment 27. The antibody of any one of Embodiments 1 to 9, 12, 13 or 22 to 26, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:99.

[0489] Embodiment 28. The antibody of Embodiment 27, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:99.

[0490] Embodiment 29. The antibody of Embodiment 28, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:99.

[0491] Embodiment 30. The antibody of Embodiment 29, wherein said light chain variable domain comprises SEQ ID NO:99.

[0492] Embodiment 31. The antibody of any one of Embodiments 1 to 30, wherein said antibody is an IgG.

[0493] Embodiment 32. The antibody of any one of Embodiments 1 to 31, wherein said antibody is a humanized antibody or a chimeric antibody.

[0494] Embodiment 33. The antibody of any one of Embodiments 1 to 32, wherein said antibody comprises a Fab fragment.

[0495] Embodiment 34. The antibody of any one of Embodiments 1 to 32, wherein said antibody is a single-chain variable fragment (scFv).

[0496] Embodiment 35. The antibody of any one of Embodiments 1 to 34, wherein said antibody is capable of binding an Ephrin B2 protein.

[0497] Embodiment 36. The antibody of Embodiment 35, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0498] Embodiment 37. The antibody of Embodiment 36, wherein said extracellular domain comprises the sequence of SEQ ID NO:100.

[0499] Embodiment 38. The antibody of Embodiment 36 or 37, wherein said extracellular domain comprises the sequence of SEQ ID NO:85.

[0500] Embodiment 39. The antibody of any one of Embodiments 36 to 38, wherein the extracellular domain comprises a glutamic acid at a position corresponding to position 69, an asparagine corresponding to position 70, and a threonine corresponding to position 71 of SEQ ID NO:85.

[0501] Embodiment 40. The antibody of any one of Embodiments 35 to 39, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

[0502] Embodiment 41. The antibody of any one of Embodiments 35 to 40, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of less than about 1 nM.

[0503] Embodiment 42. The antibody of Embodiment 40 or 41, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0504] Embodiment 43. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:66, a CDR H2 as set forth in SEQ ID NO:67 and a CDR H3, wherein said CDR H3 is a variant of SEQ ID NO:68; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:69, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:70; and wherein said variant of SEQ ID NO:68 comprises the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4 and position 7 relative to SEQ ID NO:68.

[0505] Embodiment 44. The antibody of Embodiment 43, wherein the variant of SEQ ID NO:68 includes one substitution.

[0506] Embodiment 45. The antibody of Embodiment 43, wherein the variant of SEQ ID NO:68 includes two substitutions.

[0507] Embodiment 46. The antibody of any one of Embodiments 43 to 45, wherein the variant of SEQ ID NO:68 comprises a I4L, I4K, I4Y, I4V, I4M, I4T, I4F, I4A, I4Q, I4S, I4G, I4R, I4W, I4H, or I4N substitution at the position corresponding to position 4 of SEQ ID NO:68.

[0508] Embodiment 47. The antibody of any one of Embodiments 43 to 46, wherein the variant of SEQ ID NO:68 comprises a T7Y, T7F, or T7S at the position corresponding to position 7 of SEQ ID NO:68.

[0509] Embodiment 48. The antibody of any one of Embodiments 43 to 47, wherein the variant of SEQ ID NO:68 comprises an I4M substitution at the position corresponding to position 4 of SEQ ID NO:68 and a T7Y substitution at the position corresponding to position 7 of SEQ ID NO:68.

[0510] Embodiment 49. The antibody of any one of Embodiments 43 to 48, wherein the variant of SEQ ID NO:68 is SEQ ID NO:16.

[0511] Embodiment 50. The antibody of any one of Embodiments 43 to 47, wherein the variant of SEQ ID NO:68 comprises an I4L substitution at the position corresponding to position 4 of SEQ ID NO:68 and a T7Y substitution at the position corresponding to position 7 of SEQ ID NO:68.

[0512] Embodiment 51. The antibody of any one of Embodiments 43 to 47 or 50, wherein the variant of SEQ ID NO:68 is SEQ ID NO:29.

[0513] Embodiment 52. The antibody of any one of Embodiments 43 to 49, wherein the heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:25.

[0514] Embodiment 53. The antibody of Embodiment 52, wherein the heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:25.

[0515] Embodiment 54. The antibody of Embodiment 53, wherein the heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:25.

[0516] Embodiment 55. The antibody of embodiment 54, wherein the heavy chain variable domain comprises SEQ ID NO:25.

[0517] Embodiment 56. The antibody of any one of Embodiments 43 to 49 or 52 to 55, wherein the light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:26.

[0518] Embodiment 57. The antibody of Embodiment 56, wherein the light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:26.

[0519] Embodiment 58. The antibody of Embodiment 57, wherein the light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:26.

[0520] Embodiment 59. The antibody of Embodiment 58, wherein the light chain variable domain comprises SEQ ID NO:26.

[0521] Embodiment 60. The antibody of any one of Embodiments 43 to 47, 50 or 51, wherein the heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:38.

[0522] Embodiment 61. The antibody of Embodiment 60, wherein the heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:38.

[0523] Embodiment 62. The antibody of Embodiment 61, wherein the heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:38.

[0524] Embodiment 63. The antibody of Embodiment 62, wherein the heavy chain variable domain comprises SEQ ID NO:38.

[0525] Embodiment 64. The antibody of any one of Embodiments 43 to 47, 50, 51, or 60 to 63, wherein the light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:39.

[0526] Embodiment 65. The antibody of Embodiment 64, wherein the light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:39.

[0527] Embodiment 66. The antibody of Embodiment 65, wherein the light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:39.

[0528] Embodiment 67. The antibody of Embodiment 66, wherein the light chain variable domain comprises SEQ ID NO:39.

[0529] Embodiment 68. The antibody of any one of Embodiments 43 to 67, wherein said antibody is an IgG.

[0530] Embodiment 69. The antibody of any one of Embodiments 43 to 68, wherein said antibody is a humanized antibody or a chimeric antibody.

[0531] Embodiment 70. The antibody of any one of Embodiments 43 to 69, wherein said antibody comprises a Fab fragment.

[0532] Embodiment 71. The antibody of any one of Embodiments 43 to 69, wherein said antibody is a single-chain variable fragment (scFv).

[0533] Embodiment 72. The antibody of any one of Embodiments 43 to 71, wherein said antibody is capable of binding an Ephrin B2 protein.

[0534] Embodiment 73. The antibody of Embodiment 72, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0535] Embodiment 74. The antibody of Embodiment 73, wherein the extracellular domain of said Ephrin B2 protein comprises residues corresponding to positions 197-218 of SEQ ID NO:79.

[0536] Embodiment 75. The antibody of any one of Embodiments 72 to 74, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

[0537] Embodiment 76. The antibody of any one of Embodiments 72 to 75, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 1.496 nM.

[0538] Embodiment 77. The antibody of any one of Embodiments 72 to 75, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 1.259 nM.

[0539] Embodiment 78. The antibody of any one of Embodiments 75 to 77, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0540] Embodiment 79. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 set forth in SEQ ID NO:3; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:5.

[0541] Embodiment 80. The antibody of Embodiment 79, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:12.

[0542] Embodiment 81. The antibody of Embodiment 80, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:12.

[0543] Embodiment 82. The antibody of Embodiment 81, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:12.

[0544] Embodiment 83. The antibody of Embodiment 82, wherein said heavy chain variable domain comprises SEQ ID NO:12.

[0545] Embodiment 84. The antibody of any one of Embodiments 79 to 83, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:13.

[0546] Embodiment 85. The antibody of Embodiment 84, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:13.

[0547] Embodiment 86. The antibody of Embodiment 85, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:13.

[0548] Embodiment 87. The antibody of Embodiment 86, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:13.

[0549] Embodiment 88. The antibody of Embodiment 87, wherein said light chain variable domain comprises SEQ ID NO:13.

[0550] Embodiment 89. The antibody of any one of Embodiments 79 to 88, wherein said antibody is an IgG.

[0551] Embodiment 90. The antibody of any one of Embodiments 79 to 89, wherein said antibody comprises a Fab fragment.

[0552] Embodiment 91. The antibody of any one of Embodiments 79 to 89, wherein said antibody is a single-chain variable fragment (scFv).

[0553] Embodiment 92. The antibody of any one of Embodiments 79 to 91, wherein said antibody is capable of binding an Ephrin B2 protein.

[0554] Embodiment 93. The antibody of Embodiment 92, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0555] Embodiment 94. The antibody of Embodiment 93, wherein said extracellular domain comprises the sequence of SEQ ID NO:100.

[0556] Embodiment 95. The antibody of Embodiment 93 or 94, wherein said extracellular domain comprises the sequence of SEQ ID NO:85.

[0557] Embodiment 96. The antibody of any one of Embodiments 93 to 95, wherein the extracellular domain comprises a glutamic acid at a position corresponding to position 69, an asparagine corresponding to position 70, and a threonine corresponding to position 71 of SEQ ID NO:85.

[0558] Embodiment 97. The antibody of any one of Embodiments 92 to 96, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

[0559] Embodiment 98. The antibody of any one of Embodiments 92 to 97, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of less than about 1 nM.

[0560] Embodiment 99. The antibody of Embodiment 97 or 98, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0561] Embodiment 100. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:14, a CDR H2 as set forth in SEQ ID NO:15 and a CDR H3 set forth in SEQ ID NO:16; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:17, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:18.

[0562] Embodiment 101. The antibody of Embodiment 100, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:25.

[0563] Embodiment 102. The antibody of Embodiment 101, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:25.

[0564] Embodiment 103. The antibody of Embodiment 102, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:25.

[0565] Embodiment 104. The antibody of Embodiment 103, wherein said heavy chain variable domain comprises SEQ ID NO:25.

[0566] Embodiment 105. The antibody of any one of Embodiments 100 to 104, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:26.

[0567] Embodiment 106. The antibody Embodiment 105, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:26.

[0568] Embodiment 107. The antibody Embodiment 106, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:26.

[0569] Embodiment 108. The antibody Embodiment 107, wherein said light chain variable domain comprises SEQ ID NO:26.

[0570] Embodiment 109. The antibody of any one of Embodiments 100 to 108, wherein said antibody is an IgG.

[0571] Embodiment 110. The antibody of any one of Embodiments 100 to 109, wherein said antibody is a humanized antibody or a chimeric antibody.

[0572] Embodiment 111. The antibody of any one of Embodiments 100 to 110, wherein said antibody comprises a Fab fragment.

[0573] Embodiment 112. The antibody of any one of Embodiments 100 to 110, wherein said antibody is a single-chain variable fragment (scFv).

[0574] Embodiment 113. The antibody of any one of Embodiments 100 to 112, wherein said antibody is capable of binding an Ephrin B2 protein.

[0575] Embodiment 114. The antibody of embodiment 113, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0576] Embodiment 115. The antibody of embodiment 114, wherein the extracellular domain of said Ephrin B2 protein comprises residues corresponding to positions 197-218 of SEQ ID NO:79.

[0577] Embodiment 116. The antibody of any one of Embodiments 113 to 115, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

[0578] Embodiment 117. The antibody of Embodiment 116, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 1.496 nM.

[0579] Embodiment 118. The antibody of Embodiment 116 or 117, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0580] Embodiment 119. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1 as set forth in SEQ ID NO:27, a CDR H2 as set forth in SEQ ID NO:28 and a CDR H3 set forth in SEQ ID NO:29; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:30, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:31

[0581] Embodiment 120. The antibody of Embodiment 119, wherein the heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:38.

[0582] Embodiment 121. The antibody of Embodiment 120, wherein the heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:38.

[0583] Embodiment 122. The antibody of Embodiment 121, wherein the heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:38.

[0584] Embodiment 123. The antibody of Embodiment 119, wherein the heavy chain variable domain comprises SEQ ID NO:38.

[0585] Embodiment 124. The antibody of any one of Embodiments 119 to 123, wherein the light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:39.

[0586] Embodiment 125. The antibody of Embodiment 124, wherein the light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:39.

[0587] Embodiment 126. The antibody of Embodiment 125, wherein the light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:39.

[0588] Embodiment 127. The antibody of Embodiment 126, wherein the light chain variable domain comprises SEQ ID NO:39.

[0589] Embodiment 128. The antibody of any one of Embodiments 123 to 127, wherein said antibody is an IgG.

[0590] Embodiment 129. The antibody of any one of Embodiments 123 to 128, wherein said antibody is a humanized antibody or a chimeric antibody.

[0591] Embodiment 130. The antibody of any one of Embodiments 123 to 129, wherein said antibody comprises a Fab fragment.

[0592] Embodiment 131. The antibody of any one of Embodiments 123 to 129, wherein said antibody is a single-chain variable fragment (scFv).

[0593] Embodiment 132. The antibody of any one of Embodiments 123 to 131, wherein said antibody is capable of binding an Ephrin B2 protein.

[0594] Embodiment 133. The antibody of Embodiment 132, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0595] Embodiment 134. The antibody of Embodiment 133, wherein the extracellular domain of said Ephrin B2 protein comprises residues corresponding to positions 197-218 of SEQ ID NO:79.

[0596] Embodiment 135. The antibody of any one of Embodiments 132 to 134, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

[0597] Embodiment 136. The antibody of any one of Embodiments 132 to 135, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 1.259 nM.

[0598] Embodiment 137. The antibody of Embodiment 135 or 136, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0599] Embodiment 138. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises: a CDR H1

as set forth in SEQ ID NO:86, a CDR H2 as set forth in SEQ ID NO:87 and a CDR H3 set forth in SEQ ID NO:88; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:89, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:90.

[0600] Embodiment 139. The antibody of Embodiment 138, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:98.

[0601] Embodiment 140. The antibody of Embodiment 139, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:98.

[0602] Embodiment 141. The antibody of Embodiment 140, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:98.

[0603] Embodiment 142. The antibody of Embodiment 141, wherein said heavy chain variable domain comprises SEQ ID NO:98.

[0604] Embodiment 143. The antibody of any one of Embodiments 138 to 142, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:99.

[0605] Embodiment 144. The antibody of Embodiment 143, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:99.

[0606] Embodiment 145. The antibody of Embodiment 144, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:99.

[0607] Embodiment 146. The antibody of Embodiment 145, wherein said light chain variable domain comprises SEQ ID NO:99.

[0608] Embodiment 147. The antibody of any one of Embodiments 138 to 146, wherein said antibody is an IgG.

[0609] Embodiment 148. The antibody of any one of Embodiments 138 to 147, wherein said antibody comprises a Fab fragment.

[0610] Embodiment 149. The antibody of any one of Embodiments 138 to 148, wherein said antibody is a single-chain variable fragment (scFv).

[0611] Embodiment 150. The antibody of any one of Embodiments 138 to 149, wherein said antibody is capable of binding an Ephrin B2 protein.

[0612] Embodiment 151. The antibody of Embodiment 150, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0613] Embodiment 152. The antibody of Embodiment 150 or 151, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

[0614] Embodiment 153. The antibody of Embodiment 152, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0615] Embodiment 154. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises SEQ ID NO:51; and wherein said light chain variable domain comprises SEQ ID NO:52.

[0616] Embodiment 155. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain, wherein said heavy chain variable domain comprises SEQ ID NO:64; and wherein said light chain variable domain comprises SEQ ID NO:65

[0617] Embodiment 156. The antibody of embodiment 154 or 155, wherein said antibody is an IgG.

[0618] Embodiment 157. The antibody of any one of Embodiments 154 to 156, wherein said antibody is a humanized antibody or a chimeric antibody.

[0619] Embodiment 158. The antibody of any one of Embodiments 154 to 157, wherein said antibody comprises a Fab fragment.

[0620] Embodiment 159. The antibody of any one of Embodiments 154 to 157, wherein said antibody is a single-chain variable fragment (scFv).

[0621] Embodiment 160. The antibody of any one of Embodiments 154 to 159, wherein said antibody is capable of binding an Ephrin B2 protein.

[0622] Embodiment 161. The antibody of Embodiment 160, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

[0623] Embodiment 162. The antibody of Embodiment 161, wherein the extracellular domain of said Ephrin B2 protein comprises residues corresponding to positions 197-218 of SEQ ID NO:79.

[0624] Embodiment 163. The antibody of any one of Embodiments 160 to 162, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 200 nM.

[0625] Embodiment 164. The antibody of any one of Embodiments 160 to 163, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 81.5 nM.

[0626] Embodiment 165. The antibody of any one of Embodiments 160 to 163, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 141 nM.

[0627] Embodiment 166. The antibody of any one of Embodiments 165 to 165, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

[0628] Embodiment 167. An anti-Ephrin B2 antibody, wherein said anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody comprising a heavy chain variable domain comprising: a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 set forth in SEQ ID NO:3; and a light chain variable domain comprising: a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:5

[0629] Embodiment 168. An anti-Ephrin B2 antibody, wherein said anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody comprising a heavy chain variable domain comprising: a CDR H1 as set forth in SEQ ID NO:14, a CDR H2 as set forth in SEQ ID NO:15 and a CDR H3 set forth in SEQ ID NO:16; and a light chain variable domain comprising: a CDR L1 as set forth in SEQ ID NO:17, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:18

[0630] Embodiment 169. An anti-Ephrin B2 antibody, wherein said anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody comprising a heavy chain variable domain comprising: a CDR H1 as set forth in SEQ ID NO:27, a CDR H2 as set forth in SEQ ID NO:28 and

a CDR H3 set forth in SEQ ID NO:29; and a light chain variable domain comprising: a CDR L1 as set forth in SEQ ID NO:30, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:31

[0631] Embodiment 170. An anti-Ephrin B2 antibody, wherein said anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody comprising a heavy chain variable domain comprising: a CDR H1 as set forth in SEQ ID NO:86, a CDR H2 as set forth in SEQ ID NO:87 and a CDR H3 set forth in SEQ ID NO:88; wherein said light chain variable domain comprises: a CDR L1 as set forth in SEQ ID NO:89, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:90

[0632] Embodiment 171. The antibody of any one of Embodiments 1 to 170, wherein said antibody is attached to a therapeutic agent.

[0633] Embodiment 172. The antibody of any one of Embodiments 1 to 170, wherein said antibody is attached to a diagnostic agent.

[0634] Embodiment 173. A method of treating fibrosis in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of an antibody of any one of Embodiments 1 to 172.

[0635] Embodiment 174. The method of Embodiment 173, wherein said fibrosis is skin fibrosis, lung fibrosis, cardiac fibrosis, liver fibrosis, kidney fibrosis, gut fibrosis, or cystic fibrosis.

[0636] Embodiment 175. The method of Embodiment 173 or 174, wherein said fibrosis is skin fibrosis.

[0637] Embodiment 176. The method of Embodiment 175, wherein said subject has systemic sclerosis, keloids, hypertrophic scars, or a combination thereof.

[0638] Embodiment 177. The method of Embodiment 176, wherein said subject has systemic sclerosis.

[0639] Embodiment 178. The method of Embodiment 173 or 174, wherein said fibrosis is lung fibrosis.

[0640] Embodiment 179. The method of Embodiment 178, wherein the subject has interstitial lung disease.

[0641] Embodiment 180. The method of Embodiment 179, wherein the interstitial lung disease is non-specific interstitial pneumonia, rheumatoid arthritis interstitial lung disease, hypersensitivity pneumonitis, berylliosis, respiratory bronchiolitis interstitial lung disease, desquamative interstitial pneumonitis, sarcoidosis, acute interstitial pneumonitis, cryptogenic-organizing pneumonitis, lymphocytic interstitial pneumonitis, or pleuroparenchymal fibroelastosis.

[0642] Embodiment 181. The method of any one of Embodiments 178 to 180, wherein the lung fibrosis is idiopathic pulmonary fibrosis, systemic sclerosis associated pulmonary fibrosis, progressive pulmonary fibrosis, pulmonary fibrosis associated with Sjogrens Syndrome., pneumoconiosis, asbestosis, silicosis, radiation-induced pulmonary fibrosis, drug-induced pulmonary fibrosis, COVID-19-related pulmonary fibrosis, pulmonary fibrosis following acute respiratory distress syndrome, pulmonary fibrosis associated with lymphangioleiomyomatosis, familial pulmonary fibrosis, pulmonary fibrosis associated with Hermansky Pudlak syndrome, or pulmonary fibrosis associated with dyskeratosis congenita.

[0643] Embodiment 182. The method of Embodiment 181, wherein the lung fibrosis is idiopathic pulmonary fibrosis, systemic sclerosis associated pulmonary fibrosis, or progressive pulmonary fibrosis.

[0644] Embodiment 183. The method of Embodiment 182, wherein the lung fibrosis is idiopathic pulmonary fibrosis.

[0645] Embodiment 184. The method of Embodiment 182, wherein the lung fibrosis is systemic sclerosis associated pulmonary fibrosis.

[0646] Embodiment 185. The method of Embodiment 173 or 174, wherein said fibrosis is cardiac fibrosis.

[0647] Embodiment 186. The method of Embodiment 185, wherein said subject has chronic heart failure or has previously had a myocardial infarction.

[0648] Embodiment 187. The method of Embodiment 173 or 174, wherein said fibrosis is liver fibrosis.

[0649] Embodiment 188. The method of Embodiment 187, wherein said subject has nonalcoholic fatty liver disease, metabolic dysfunction-associated steatohepatitis, cirrhosis, primary biliary cholangitis, or primary sclerosing cholangitis.

[0650] Embodiment 189. The method of Embodiment 173 or 174, wherein said fibrosis is kidney fibrosis.

[0651] Embodiment 190. The method of Embodiment 189, wherein said subject has chronic kidney disease or diabetic nephropathy.

[0652] Embodiment 191. The method of Embodiment 173 or 174, wherein said fibrosis is gut fibrosis.

[0653] Embodiment 192. The method of Embodiment 191, wherein said subject has Crohn's disease or fibrostenotic inflammatory bowel disease.

[0654] Embodiment 193. The method of Embodiment 173 or 174, wherein said fibrosis is cystic fibrosis.

[0655] Embodiment 194. A method of inhibiting migration of an Ephrin-B2 expressing cell, the method comprising contacting said cell with the anti-Ephrin B2 antibody of any one of Embodiments 1 to 172.

[0656] Embodiment 195. The antibody according to any one of Embodiments 1-172 for use in a method of treating fibrosis in a subject in need thereof.

[0657] Embodiment 196. The antibody for use according to Embodiment 195, wherein said fibrosis is skin fibrosis, lung fibrosis, cardiac fibrosis, liver fibrosis, kidney fibrosis, gut fibrosis, or cystic fibrosis.

[0658] Embodiment 197. The antibody for use according to Embodiment 195 or 196, wherein said fibrosis is skin fibrosis.

[0659] Embodiment 198. The antibody for use according to Embodiment 197, wherein said subject has systemic sclerosis, keloids, hypertrophic scars, or a combination thereof.

[0660] Embodiment 199. The antibody for use according to Embodiment 198, wherein said subject has systemic sclerosis.

[0661] Embodiment 200. The antibody for use according to Embodiment 195 or 196, wherein said fibrosis is lung fibrosis.

[0662] Embodiment 201. The antibody for use according to Embodiment 200, wherein the subject has interstitial lung disease.

[0663] Embodiment 202. The antibody for use according to Embodiment 201, wherein the interstitial lung disease is non-specific interstitial pneumonia, rheumatoid arthritis interstitial lung disease, hypersensitivity pneumonitis, berylliosis, respiratory bronchiolitis interstitial lung disease, desquamative interstitial pneumonitis, sarcoidosis, acute interstitial pneumonitis, cryptogenic-organizing pneumonitis, lymphocytic interstitial pneumonitis, or pleuroparenchymal fibroelastosis.

[0664] Embodiment 203. The antibody for use according to any one of Embodiments 200 to 202, wherein the lung fibrosis is idiopathic pulmonary fibrosis, systemic sclerosis associated pulmonary fibrosis, progressive pulmonary fibrosis, pulmonary fibrosis associated with Sjogrens Syndrome., pneumoconiosis, asbestosis, silicosis, radiation-induced pulmonary fibrosis, drug-induced pulmonary fibrosis, COVID-19-related pulmonary fibrosis, pulmonary fibrosis following acute respiratory distress syndrome, pulmonary fibrosis associated with lymphangioleiomyomatosis, familial pulmonary fibrosis, pulmonary fibrosis associated with Hermansky Pudlak syndrome, or pulmonary fibrosis associated with dyskeratosis congenita.

[0665] Embodiment 204. The antibody for use according to Embodiment 203, wherein the lung fibrosis is idiopathic pulmonary fibrosis, systemic sclerosis associated pulmonary fibrosis, or progressive pulmonary fibrosis.

[0666] Embodiment 205. The antibody for use according to Embodiment 204, wherein the lung fibrosis is idiopathic pulmonary fibrosis.

[0667] Embodiment 206. The antibody for use according to Embodiment 204, wherein the lung fibrosis is systemic sclerosis associated pulmonary fibrosis.

[0668] Embodiment 207. The antibody for use according to Embodiment 195 or 196, wherein said fibrosis is cardiac fibrosis.

[0669] Embodiment 208. The antibody for use according to Embodiment 207, wherein said subject has chronic heart failure or has previously had a myocardial infarction.

[0670] Embodiment 209. The antibody for use according to Embodiment 195 or 196, wherein said fibrosis is liver fibrosis.

[0671] Embodiment 210. The antibody for use according to Embodiment 209, wherein said subject has nonalcoholic fatty liver disease, metabolic dysfunction-associated steatohepatitis, cirrhosis, primary biliary cholangitis, or primary sclerosing cholangitis.

[0672] Embodiment 211. The antibody for use according to Embodiment 195 or 196, wherein said fibrosis is kidney fibrosis.

[0673] Embodiment 212. The antibody for use according to Embodiment 211, wherein said subject has chronic kidney disease or diabetic nephropathy.

[0674] Embodiment 213. The antibody for use according to Embodiment 195 or 196, wherein said fibrosis is gut fibrosis.

[0675] Embodiment 214. The antibody for use according to Embodiment 213, wherein said subject has Crohn's disease or fibrostenotic inflammatory bowel disease.

[0676] Embodiment 215. The antibody for use according to Embodiment 195 or 196, wherein said fibrosis is cystic fibrosis.

[0677] Embodiment 216. The antibody according to any one of Embodiments 1-172 for use in a method of inhibiting migration of an Ephrin-B2 expressing cell, the method comprising contacting said cell with the anti-Ephrin B2 antibody of any one of Embodiments 1 to 172.

[0678] Embodiment 216. An *in vitro* method for inhibiting migration of an Ephrin-B2 expressing cell, the method comprising contacting said cell with the anti-Ephrin B2 antibody of any one of Embodiments 1 to 172.

EXAMPLES

Example 1: Generation of anti-Ephrin B2 antibodies

[0679] The anti-Human Ephrin B2 single-chain variable fragment (scFv) B11 was previously described in US Patent US 9,062,109 B2, which is incorporated herein in its entirety and for all purposes. In embodiments, the anti-Ephrin B2 antibody and fragments thereof may be referred to as B11-NTS. To test the B11 molecule as a full-length IgG, the light and heavy chain variable regions

were synthesized in frame with human kappa and human IgG1 constant region sequence. These constructs were synthesized, transfected in mammalian expression systems, and affinity purified at Genscript.

[0680] Upon reviewing the B11 sequence for potential development liabilities, a consensus N-glycosylation site was identified in the heavy chain variable region. The removal of this N-glycosylation site could impact binding to EphrinB2 so 2 variants of the B11 heavy chain, B11-QTS and B11-DTS, each containing a single residue substitution for the asparagine in the first position of the N-glycosylation site, were synthesized and expressed as full length IgG1 antibodies. The parent B11-NTS and the two variant antibodies B11-QTS and B11- DTS were compared for binding to human EphrinB2 by Biacore SPR.

[0681] Recombinant EphrinB2 ECD (6His-HuEphrinB2-(26-229)-hIgG1-Fc) was immobilized on CM5 chips by standard amine coupling conjugation chemistry procedures. After the amine coupling reaction, the remaining active coupling sites on the chip surface were blocked with 1 mol/L ethanolamine hydrochloride. The binding assay was performed at 25°C in HBS-EP+ buffer PH 7.4 starting with an injection of the antibodies over the antigen coated surface for the association phase and followed by an injection of running buffer for the dissociation phase. The binding data given in FIG.s 1A-1D demonstrates that the removal of the N-glycosylation site by either of the two mutations tested results in little impact to binding to human EphrinB2.

Example 2: Generating anti-Ephrin B2 antibodies by affinity maturation

[0682] The affinity of the B11 antibody to human EphrinB2 was increased by utilizing saturation mutagenesis of CDR residues together with phage display panning methods. The B11-QTS VH and VL sequences were amplified by PCR and joined with a (G4S)3 linker to convert to a scFv which was subsequently cloned into ChemPartner's phagemid vector. CDR residues were randomized by PCR mutagenesis using NNK primers. Six separate libraries were generated, two with single CDR mutations and four with pairs of CDRs containing mutations. Library details are provided in FIG 2. Prior to panning, the 2 single CDR libraries were combined as one library and the 4 dual CDR libraries were combined as a second library.

[0683] The initial goal of the affinity maturation of B11 was to increase the binding affinity to Ephrin B2, while also preserving the unique epitope of the parent B11 antibody. Among previously known anti-Ephrin B2 antibodies used in this study, B11 is the only antibody to demonstrate a

reliance on residues 197 to 218 (SEQ ID NO:84) (numbering relative to SEQ ID NO:79) of the Ephrin B2 extracellular domain (ECD) (SEQ ID NO:85) , just upstream of the transmembrane domain. This distinction is illustrated in FIG. 3A where B11 binds to recombinant Ephrin B2 ECD with a deletion spanning residues 182 to 194 (numbering relative to SEQ ID NO:79) (6His-HuEphrinB2-ECD-Del-182-194-hIgG1-Fc) but does not bind to recombinant Ephrin B2 ECD with a deletion spanning residues 197 to 218 (numbering relative to SEQ ID NO:79) (6His-HuEphrinB2-ECD-Del-197-218-hIgG1-Fc). Meanwhile, the EB2-P01-A05 antibody can bind both constructs similarly (FIG. 3B).

[0684] The phage library panning scheme was therefore designed to pull out antibodies with increased binding affinity to the full Ephrin B2 ECD (e.g. residues 26-229 of SEQ ID NO:79), while maintaining low to no binding to the Ephrin B2 ECD deletion construct (6His-HuEphrinB2-ECD-Del-197-218-hIgG1-Fc). The two phage libraries were subjected to 3 rounds of panning, beginning with high to low concentration competition of the Ephrin B2 ECD residue 197-218 deletion construct in the first 2 rounds followed by increasing competition stringency by the full length Ephrin B2 ECD in the second and third rounds. This competition strategy drives the output towards both increased affinity and epitope specificity.

[0685] Surprisingly, the output observed from both the single CDR library and the dual CDR library was heavily enriched for clones derived from HC CDR3 mutated libraries. By the third round of panning virtually all of the clones output from the dual CDR library were derived from the H1&H3 or H3&L3 mutant libraries. Further, most of these dual CDR mutant clones displayed increased affinity for both the full length Ephrin B2 ECD construct and the Ephrin B2 ECD construct with the residues 197-218 deletion, with few clones that preserved the B11-like binding dependency on Ephrin B2 ECD residues 197-218.

[0686] The output from the single CDR library was not only heavily enriched for HC CDR3 mutations, but further revealed key heavy chain CDR3 residue positions capable of tuning both affinity and B11-like epitope specificity. The phage library derived scFvs were screened by ELISAs for binding to both the full length Ephrin B2 ECD and Ephrin B2 ECD with residues 197-218 deleted. Clones which demonstrate increased binding to full length Ephrin B2 compared with the parent B11, but preserve the low binding of the parent antibody to the deletions construct are given in FIG.s 4A-4B. Across this set of clones, variability of residues within the heavy chain CDR3,

specifically I100 and T103 relative to the variable heavy chain domain of SEQ ID NO:51 (or residues I96 and T99, as defined by Kabat numbering), reveal the key role these positions hold for tuning the affinity and epitope specificity of the parent B11 antibody (FIG.s 4A-4B). The T103 mutations, largely restricted to either Tyrosine or Phenylalanine for clones tested suggests a critical role for these closely related aromatic residue substitutions in preserving the B11 epitope while enhancing affinity. Conversely, residue I100 can be substituted by a variety of amino acids, suggesting that this position plays a key role in fine tuning the affinity of these clones.

[0687] A second set of clones given in FIG.s 5A-5B reveal that heavy chain mutations which pair I100 substitutions with F107 substitutions relative to the variable heavy chain domain of SEQ ID NO:51 (or residues I96 and F100 of the antibody in accordance with Kabat numbering) instead of T103 substitutions lead to high affinity clones to both the full EphrinB2 ECD and the residue 197-218 deletion construct. Once again there are a number of mutations observed in the tuning I100 position, but now the F107 mutations are restricted to valine, leucine, or isoleucine. This suggests a critical role for the substation of the phenylalanine at residue position F107 with the structurally related hydrophobic residues valine, leucine or isoleucine for increasing the B11 affinity to both EphrinB2 constructs. In addition to the critical I100 and F107 positions in this set, residues G102 and G106 relative to SEQ ID NO:51 (e.g. G98 and G100B in accordance with Kabat numbering), appear to contribute additional affinity tuning by adding either positively charged lysine or arginine residues to these positions. Together the heavy chain CDR3 residue mutation in both sets of clones provide compelling evidence of the critical role for specific residue positions in modulating the affinity and specificity of the parent B11 antibody.

Example 3: Characterization of affinity matured anti-Ephrin B2 antibodies

[0688] The phage derived affinity matured anti-EphrinB2 variable region sequences were provided to CROs to generate and express recombinant, full length antibodies for further characterization and testing. The increased binding affinity and preservation of the unique B11 epitope was evaluated by direct binding ELISAs. The human EphrinB2 deletion constructs (6HIS-huEphrinB2-Del-182-194-huIgG1-Fc and 6HIS-huEphrinB2-Del-197-218-huIgG1-Fc) were coated on the ELISA plates (Immulon-2HB plate; Thermo Scientific), followed by incubation with the test antibodies, and finally detected with anti-human IgG Fc gamma-HRP (Jackson Immunoresearch). The results given in FIG. 6A demonstrate that the affinity matured antibodies bound the 6HIS-

huEphrinB2-Del-182-194-huIgG1-Fc construct with greater than 3-fold shifts in EC50s compared to parental B11-QTS. In the ELISA with the 6HIS-huEphrinB2-Del-197-218-huIgG1-Fc construct however, most of the antibodies display low to no binding, reflecting a preservation of the B11-like epitope (FIG. 6B). The EC50 of the Ab25 antibody to both constructs was very similar reflecting the epitope shift from B11 towards high affinity binding to the EphrinB2 ECD independent of residues 197-218.

[0689] The affinity matured antibodies were further characterized by Octet BLI to better understand binding kinetics and affinity enhancements over the parental B11-QTS antibody (FIG.s 7A-7D). Prior to setting up the experiment, the SA biosensors were pre-equilibrated in assay buffer (0.5% BSA in PBS with 0.05% Tween-20) for 15 mins at RT. Pre-equilibrated biosensors were dipped in kinetic buffer for 60 seconds to ensure all biosensors were activated and behaving in a similar manner. Next, the antigen was immobilized on Streptavidin (SA) biosensors at a concentration of 5 ug/mL for 180 seconds. After antigen immobilization, the biosensors were dipped in wells with assay buffer for 120 seconds to establish the baseline step and remove non-specific binding. Association was performed for 300 seconds with the B11-QTS and the affinity-matured variants plated in an 8 point, 2-fold serial dilution series starting at either 20nM or 200nM as the highest concentration. Finally, the dissociation step was performed in wells with assay buffer for 300 seconds. The data were analyzed using Octet analysis software version 13. The kinetic model used was 1:1 interaction model, with global fit parameters. The results in FIG.s 7A-7D demonstrate increased affinities of greater than 10-fold over the parental B11-QTS antibody with the novel affinity matured antibodies ranging from single digit nM to sub-nM K_D binding to the Ephrin B2 ECD.

[0690] The affinity matured antibodies were evaluated for binding to EphrinB2 on the cell surface by flow cytometry methods. HEK293 cells were stably transfected with an Ephrin B2 expression plasmid and subsequently selected for clones expressing high levels of Ephrin B2. To perform the flow cytometry analysis, the cultured EphrinB2 overexpressing cells were wash 3 times with 3 mL Flow Cytometry Staining Buffer (eBiosicience). Cells were then resuspended in Flow Cytometry Staining Buffer at $1X10^6$ cells/mL, filtered through a cell strainer (Fisher) and the 10mL of cells were pre-incubated with 100uL of Human Fc Receptor Binding (eBiosicience) for 20 minutes on ice. Cells were then pelleted, resuspended in the serial diluted test and control antibodies (10 nM to

0.6 pM in PBS), and incubated for 1 hour on ice. The cells were then washed twice in 200 µl Flow Cytometry Staining Buffer, resuspended in anti-human Fc-AF647 secondary antibody (Southern Biotech) and incubated for 1 hour, protected from light. The cells were then washed twice in 200 µl Flow Cytometry Staining Buffer and fixed with 100 µl of IC fixation buffer and 100 µl of staining buffer before analyzing on an Attune flow cytometer. The results given in FIG. 8 show high affinity, sub-nM EC50 binding to the EphrinB2 overexpressing cells. Even though the EC50s for each of the antibodies tested are relatively similar, the antibodies, like Ab25, which bind recombinant EphrinB2 ECD independent of residues 197-218 appear to bind at a greater magnitude than antibodies like Ab11 which preserve the B11 epitope dependence on residues 197-218. This suggests that the observed epitope dependency on the membrane proximal EphrinB2 residues 197-218 for recombinant constructs may reflect a structural distinction for how these two groups of affinity matured B11 antibodies access and bind EphrinB2 expressed on cells.

Example 4: Suppression of EphB4 phosphorylation by anti-Ephrin B2 antibodies

[0691] Thus, we evaluated the ability of anti-EphrinB2 antibodies to suppress Eph receptor phosphorylation (pEphB). Human umbilical vein endothelial cells (HUVECs) were stimulated with recombinant human EphrinB2-Fc (0.75 µg/mL) for 1 hour in the absence/presence of monoclonal anti-EphrinB2 antibodies or an isotype control (10 µg/mL) with pEphB4 then evaluated in cell lysates by ELISA. Ab90, Ab18 and Ab25 reduced pEphB4 to a level equivalent to that of unstimulated cells (PBS only; FIG. 9A). The human isotype control (IgG) antibody did not reduce pEphB4. Further, HUVECs were treated with recombinant EphrinB2-Fc (0.75µg/mL) for 1 hour and 9 point, 3-fold serial dilution of Ab25 or isotype control IgG from 66.7nM (10µg/mL). The IC_{50} of Ab25 is 1.2 nM, as determined by a 4-PL non-linear regression curve fit using GraphPad PRISM. (FIG. 9B).

Example 5: Anti-Ephrin B2 antibodies immunoprecipitate soluble EphrinB2 from cell culture supernatant and normal human serum

[0692] ADAM10 has been identified as a sheddase on lung fibroblasts, releasing EphrinB2 from the cell surface (sEphrinB2). sEphrinB2 in turn has been shown to be a profibrotic mediator by its ability to drive myofibroblast formation *in vitro* and fibrosis *in vivo* (Lagares et al 2017; Su et al. 2017). The ADAM10/sEphrinB2 pathway has further been characterized in the lungs of individuals

with pulmonary fibrosis, as indicated by a marked increase in sEphrinB2 in the BAL fluid of IPF patients in comparison to healthy volunteers (Lagares et al. 2017).

[0693] To evaluate the ability of monoclonal anti-EphrinB2 antibodies to bind to sEphrinB2 in biological matrices, Dynabeads (7.5 mg) were separately coupled to 37.5 µg of antibodies Ab25, B11-QTS, Ab11, Ab51, Ab18 or an isotype control (IgG). Culture supernatant (5 mL) from CHO cells stably overexpressing EphrinB2 (CHO-OE) was incubated with antibody-coupled beads for 2 hrs rotating at 4°C (FIG. 10A). Alternatively, antibody-coupled beads were incubated with 10 mL of supernatant from colon cancer cell line Colo205 overnight rotating at 4°C (FIG. 10B). Immune complexes were washed and immunoprecipitated proteins eluted from the Dynabeads. Following elution, proteins were separated by SDS-PAGE (NuPage 4–12% Bis-Tris gel), transferred to a PVDF membrane and blotted with a polyclonal goat anti-EphrinB2 antibody. Recombinant EphrinB2 (100 ng) was loaded on the same gel as a reference for the eluted proteins (FIG. 10A). Supernatants from parental CHO cells, CHO-OE, and Colo205 (without IP) were similarly analyzed by Western blot to demonstrate the relative amounts of EphrinB2 present in the input supernatants (FIG. 10C). EphrinB2 was detected by chemiluminescence using an iBright imager, following incubation with an HRP-conjugated anti-goat secondary antibody and HRP substrate.

[0694] All evaluated antibodies immunoprecipitated (IP) sEphrinB2 from CHO-OE supernatants (FIG. 10A) with the higher affinity antibodies Ab25 and Ab18 the most efficient. Ab25 and Ab18 were also able to IP sEphrinB2 from Colo205 supernatants (FIG. 10B).

[0695] Ab25 or an isotype control antibody (IgG, negative control) were coupled to Dynabeads and incubated with 5mL of gender-pooled normal human serum overnight rotating at 4°C. Conditions for elution and Western Blot were as described above. Ab25 immunoprecipitated sEphrinB2 from human serum while a control IgG did not (FIG. 10D)

Example 6: Chemotaxis/migration of primary human umbilical vascular endothelial cells

[0696] Endothelial cells have been proposed to play a prominent role in fibrosis through a number of mechanisms including endothelial-mesenchymal transition (EndoMT), angiogenesis and secretion of inflammatory and pro-fibrotic factors including TGFβ (Romano et al., Rheumatology 2024; Sun et al., Seminars in Cell Dev Biol 2020; Leach et al., Am J Respir Cell Mol Bio 2013). This EndoMT transition further results in the acquisition of migratory and invasive capabilities of the

newly transformed cell, thus enhancing its pathogenesis and potential to exacerbate fibrosis (Ciszewski et al., Int Jour Mol Sci 2021).

[0697] An assay to evaluate HUVEC cell chemotaxis/migration was established using transwell plates in combination with the Incucyte S3 Live-Cell Analysis System. Primary HUVEC cells were starved for 2hrs (no FBS) and then added to the upper chamber of a 96-well transwell assay plate at 1K cells per well. FBS was added to lower chamber of the transwell as a chemoattractant at 10%, 2% or no FBS. Images of both the upper and lower side of the transwell membrane were then captured every 2 hours using the Incucyte System. The "Phase Area Bottom Normalized to Initial Top Value" metric was used for calculating chemotaxis. This method takes the total masked cell area on the basal side of the membrane (bottom) and normalizes it to the masked area on the apical side of the membrane (top) from the first scan (0h), representing the number of cells that have migrated from the apical to the basal side of the transwell. More HUVEC cells migrated to the basal (lower) side of the transwell when 10% FBS was provided as a chemoattractant compared to 2% FBS or no FBS (FIG.s 11A-11B).

Example 7: Inhibition of human umbilical vascular endothelial cell chemotaxis/migration by anti-EphrinB2 antibodies

[0698] The Ephrin protein family has been implicated in fibrosis with elevated levels of both its receptors and ligands demonstrated in mouse models of fibrosis as well as human patient samples with various fibrotic indications (Mekala et al., Jour Cell Comm and Signaling 2023; Wu et al., Curr Rheumatol 2020; Darling and Lamb Front Immunol 2019; Su et al., Circ Res 2017; Lagares et al, Nat Med 2017). More specifically, targeting EphrinB2 has been shown to impact cell migration and morphology using an scFv against EphrinB2 (Abengozar et al., Blood 2012).

[0699] To evaluate the ability of full-length monoclonal anti-EphrinB2 antibodies to modulate the chemotaxis/migration phenotype, B11-QTS, Ab11, Ab51 or Ab25 were added at 10 or 100 μg/mL to the HUVEC cells in the upper chambers of a 96-well transwell plate with 10% FBS provided in the lower chamber as a chemoattractant. Cell chemotaxis/migration was evaluated as for FIG.s 12A-12C with quantitation at 24 hrs and 40 hrs shown (FIG.s 11A-11B). Significant migration occurs without any antibody and 10% FBS as a chemoattractant (FIG.s 11A-11B). All monoclonal anti-EphrinB2 antibodies decrease chemotaxis/migration at 10 and 100 μg/mL. While not statistically different, a dose-dependent trend is observed with increased inhibition at the higher

antibody concentration (FIG.s 11A-11B). Treatment with a polyclonal anti-EphrinB2 antibody (R&D AF496) reduces chemotaxis/migration in a dose-dependent manner at 10 and 100 μg/mL (FIG.s 11A-11B). IgG antibody treatment at 10 and 100 μg/mL does not significantly alter chemotaxis rates compared to wells receiving no antibody (FIG.s 11A-11B). These trends emerge by 24 hrs (FIG. 11A) and remain evident at 40 hrs (FIG. 11B).

Example 8: Inhibition of human umbilical vascular endothelial cell chemotaxis/migration by anti-EphrinB2 antibody AB25

[0700] Monoclonal anti-EphrinB2 antibody Ab25 and polyclonal anti-EphrinB2 antibody AF496 reduce HUVEC chemotaxis migration at both 10 and 100 μg/mL relative to no antibody. Non-specific IgG antibody does not significantly inhibit chemotaxis/cell migration even at the highest concentration (100 μg/mL). FIG.s 13A-13D provides the full timecourse demonstrating inhibition of HUVEC chemotaxis/migration by anti-EphrinB2 antibodies, including Ab25 at 10 and 100 μg/mL under all conditions tested (10%, 2%, no FBS), which is comparable to inhibition with a polyclonal anti-EphrinB2 antibody at 100 μg/mL (R&D AF496).

Example 9: In vivo studies showing therapeutic effects of anti-EphrinB2 antibodies in bleomycin model of lung injury and fibrosis

[0701] To induce lung fibrosis, 1.5 U/kg Bleomycin (Bleo) was administered via oropharyngeal route in male C57bl/6 mice. Mice received vehicle (PBS) or 10mg/kg of antibodies every three days from day 7 through day 21 after bleo instillation. All dosing was given i.p. in volumes equal to 200uL/injection.

[0702] At day 21, lung tissues were harvested. Fibrosis was measured by quantifying collagen content in the lung by hydroxyproline (FIG. 14A).

[0703] Anti-EphrinB2 antibodies suppressed lung fibrosis. Bleo induced an increase in hydroxyproline content in the lung when compared to control group. Anti-EphrinB2 antibodies led to the following % reduction in hydroxyproline compared to vehicle group (B11-QTS: 55%; Ab11: 42%; Ab25:63%; Ab51: 87%) (FIG. 14B).

[0704] The anti-EphrinB2 antibodies used in this study were expressed with human IgG constant regions.

[0705] The results show that anti-EphrinB2 antibodies are effective for suppressing lung fibrosis.

Example 10: In vivo studies showing effects of anti-EphrinB2 antibodies on pro-inflammatory cytokines in a model of lung injury and fibrosis

[0706] To induce lung fibrosis, 1.5 U/kg Bleomycin (Bleo) was administered via oropharyngeal route in male C57bl/6 mice. Mice were treated with vehicle (PBS) or antibodies once a week or every three days from day 7 through day 21 after bleo instillation. All dosing was given i.p. in volumes equal to 200uL/injection.

[0707] At day 21, bronchoalveolar lavage fluid (BALF) and whole blood were harvested. Plasma was obtained from whole blood collected with anti-coagulant Ethylenediaminetetraacetic acid (EDTA). Pro-inflammatory cytokines were measured using Meso Scale Discovery (MSD) kits.

[0708] Bleo induced an increase in plasma pro-inflammatory cytokines when compared to no bleo control group (IFNγ: 0.73 vs 0.33; IL-6: 28.1 vs 10.3; KC/GRO: 83.2 vs 35.3 pg/ml). Anti-EphrinB2 antibodies significantly decreased levels of plasma pro-inflammatory cytokines IFNγ, IL-6 and KC/GRO when compared to vehicle group (FIG. 15A).

[0709] Bleo induced an increase in BALF pro-inflammatory cytokines when compared to no bleo control group (IL-5: 1.4 vs 0.2; IL-6: 111.4 vs 4.8; KC/GRO: 22.4 vs 6.4; TNFα: 3.9 vs 0.9 pg/ml). Anti-EphrinB2 antibodies significantly decreased levels of BALF pro-inflammatory cytokines IL-5, IL-6, KC/GRO and TNFα (FIG. 15B).

[0710] These results show that anti-EphrinB2 antibodies are effective for suppressing bleo-induced pro-inflammatory cytokines in the BALF and plasma.

Example 11: In vivo studies showing therapeutic effects of anti-EphrinB2 antibodies in scleroderma model of skin fibrosis

[0711] A 21-day model of scleroderma was induced by subcutaneous bleomycin injections (5 days/week for 2 weeks) in the back dorsal skin of female C57BL/6 mice. Mice were treated with vehicle (PBS) or 10mg/kg anti-EphrinB2 antibodies every three days from day 7 to day 21. All dosing was given i.p. in volumes equal to 200uL/injection. Alk5 inhibitor was used as reference control and dosed orally twice-a-day at 30mg/kg/dose.

[0712] At day 21, skin was harvested. Skin fibrosis was measured by quantifying collagen content by hydroxyproline and dermal thickness by histology.

[0713] Anti-EphrinB2 antibodies suppressed skin fibrosis. Bleo induced an increase in collagen content in the skin, as shown by increased hydroxyproline production when compared to the control group (38.71 ± 1.8 vs. 26.11 ± 1.3 ug/mg of skin). Anti-EphrinB2 antibodies led to a reduction in hydroxyproline when compared to vehicle group (B11-QTS: 34.20 ± 1.7; Ab11: 32.47 ± 1.4; Ab51: 35.14 ± 1.2; Ab25: 30.13 ± 1.1 vs 38.71 ± 1.8 ug/mg of skin) (FIG. 16A).

[0714] Skin tissue was paraffin-embedded, and blocks were sectioned. Sections were stained with Masson's Trichrome (MT). Images were evaluated by a board-certified veterinary pathologist and dermal measurements (μm) were performed using MT-stained skin slides in five sites and averaged for each sample.

[0715] Representative photomicrographs of skin tissue stained with Masson's Trichrome are illustrated in (FIG. 16C).

[0716] Bleomycin injection was associated with a significant increase in thickness compared to no bleomycin control (281.7 ± 8.6 vs 178.9 ± 14.72 μm). Anti-EphrinB2 antibody Ab25 led to significant reduction in dermal thickness compared to vehicle group (246.5 ± 8.6 vs 281.7 ± 8.6 μm) (FIG. 16B). Dermal thickness reduction by Ab25 was similar to ALK5i reference control (246.5 ± 8.6 vs 246.5 ± 6.3).

[0717] The results demonstrate that anti-EphrinB2 antibodies are potent suppressors of skin fibrosis.

Example 12: Ephrin B2-EphB receptor competition ELISA

[0718] Ab25 was further characterized for its ability to block ephrinB2-EphB receptor interactions. Wells in a 96-well microtiter plate were coated with recombinant human ephrinB2 followed by co-incubation of biotinylated human EphB2 (FIG. 17A), biotinylated human EphB3 (FIG. 17B), and biotinylated human EphB4 (FIG. 17AC) with competing or blocking antibody AB25 or the non-targeting control. Streptavidin-HRP was used to detect bound EphB receptors. Optical density was measured at 450 nm. The IC_{50} values were determined using best-fit values from non-linear four-parameter logistic regression using GraphPad Prism. The data illustrated in FIG.s 17A-17C show that AB25 blocks ephrinB2-EphB receptors in a dose-response manner.

Example 13: Assessing binding of anti-Ephrin B2 to human, cynomolgus, and rat Ephrin B2

[0719] Octet Bio-Layer Interference (BLI) was done to assess binding of anti-Ephrin B2 antibody Ab25 to different species of EphrinB2, including human, cynomolgus, mouse, and rat ephrinB2.

[0720] Prior to setting up the experiment, the anti-human Fc (AHC) biosensors were pre-equilibrated in assay buffer (0.5% BSA in PBS with 0.05% Tween-20) for 15 mins at room temperature. Pre-equilibrated biosensors were conditioned in assay buffer for 60 seconds to ensure all biosensors were activated and behaving in a comparable manner. Next, test antibody Ab25 was immobilized on AHC biosensors at a concentration of 5 ug/mL for 180 seconds. After antibody immobilization, the biosensors were dipped in wells with assay buffer for 120 seconds to establish the baseline step and remove non-specific binding. Association was performed for 300 seconds in wells with human ephrinB2 antigens plated in an 8 point, 2-fold serial dilution series starting at 20nM as the highest concentration. Finally, the dissociation step was performed in wells with assay buffer for 400 seconds (about 5 minutes). The data were analyzed using Octet analysis software version 13. The kinetic model used was a 1:1 interaction model, with global fit parameters.

[0721] The results in FIG.s 18A-18D demonstrate that AB25 binds to human (hu), cynomolgus (cyno), and mouse (mu) ephrinB2-ECD with sub-nanomolar affinities. The binding affinity measured for AB425 to rat EphrinB2 was about 3- fold lower compared to mouse, human and cynomolgus EphrinB2 (FIG. 19). Given the high sequence homologies between these species, this apparent lower binding affinity to rat reagent is likely due to the product quality.

[0722] Due to limitations of BLI for measuring high affinity interactions like AB25 to ephrinB2, these molecules were further evaluated by Biacore SPR. The results given in FIG.s 19-20, 21A-21D show that AB25 strongly binds to EphrinB2 across species and testing formats. SPR affinity is in the sub nM range for every species tested. These results compare well with BLI except for rat, which by BLI suggested about a 3-fold lower affinity and by SPR appears to be 2-3-fold higher affinity than the other species tested. BLI and Biacore SPR data demonstrate that AB25 binds human, cyno, rat, and mouse ephrinB2 with similar high affinities in the sub-nanomolar range.

Example 14: anti-Ephrin B2 antibody AB25 – ephrinB2 epitope determination

[0723] Cryo-EM work was conducted at Nanoimaging Services (NIS) core facility. Briefly, the human ephrinB2:AB25 complex was prepared using traditional plunge-freeze technique using either FEI Vibrobot instrument or manual plunger.

[0724] Human ephrinB2:Ab25 complex was prepared by mixing antibody AB25 and sample human ephrinb2 in a 1:1 molar ratio. In summary, a 3µl drop of complex suspension was applied to an EM grid that had been hydrophilized using a PELCO EasiGlow system. After blotting the sample away with filter paper, grids were plunge-frozen in liquid ethane. Grids were stored under liquid nitrogen until transferred to the transmission electron microscope for imaging.

[0725] Electron microscopy was performed using a Thermo Fisher Scientific (Hillsboro, Oregon) Glacios Cryo Transmission Electron Microscope (Cryo-TEM) operated at 200kV and equipped with a TFS CETA-D CMOS camera and a Falcon 4 direct electron detector. Vitreous ice grids were clipped into cartridges, transferred into a cassette and then into the Glacios autoloader, all while maintaining the grids at cryogenic temperature (below -170°C). Automated data-collection is conducted using Leginon software. High magnification images/movies were acquired by selecting targets at a lower magnification.

[0726] Results show that the interaction of AB25 Fab and the huEFNB2 interface can be divided into two sub-interfaces. The first sub-interface mainly encompasses interactions within the solvent exposed G-H loop of huEFNB2 and AB25 Fab's complementary determining regions (CDRs) L1, L3, H1, H2 and H3, which interact through polar and hydrophobic contacts. In this example, residues of the Fab light chain and heavy chain are designated by superscript chain identifiers L and H, respectively. Residues of the heavy chain are relative to SEQ ID NO:12 and residues of the light chain are relative to SEQ ID NO:13. The G-H loop in human EphrinB2 is buried between H1, H2 and L3 loops. As shown in FIG. 23, the hydrophobic residue Tyr^{H33} forms two hydrogen bonds with Gly123 and Leu121 of hu ephrinB2, suggesting hydrophobic interactions. Numbering of hu ephrinB2 residues are relative to SEQ ID NO:79. Majority of the residues involved G-H loop binding sub-interface are CDRH2 residues. As shown in FIG. 24, Asn^{H52}, Ser^{H55} and Asn^{H57} form H-bonds with Glu125. Leu121 forms H-bonds with Trp^{H50} and Thr^{H58}. $AsnH^{57}$ forms additional H-bond with Ser118. In light chain, Ser^{L32} forms a H-bond with side chains of Lys109. Asn^{L33} and Gly^{L34} form H-bond contacts with Asn95 in human ephrinB2. Additionally, Asn^{L33} forms additional H-bond contact with Leu98 in human ephrinB2 (FIG. 25).

[0727] The second sub-interface involve the E-F loop of hu EFNB2 and AB25 Fab. The E-F loop contacts are largely driven by combination of ionic interactions with charged CDRH3 residues and polar interactions with LCDR1 residues. Notably, on the heavy chain contacts (FIG. 26), the

HCDR3 high affinity mutations Lys^{H102} and Arg^{H106} seem critical for the E-F loop interaction. Glu94 of hu EFNB2 establishes two salt bridges, one with the high affinity mutation Lys^{H102}, and with Arg^{H98}. The side chains of Asn95 and Thr96 in huEFNB2 form H-bonds with Arg^{H106} and Thr^{H101} respectively. For the light chain contacts, Trp122 of huEFNB2 seem key residue for light chain contacts, forms a H bond with Leu^{L97} and a π-H bond with Ser^{L99} (FIG. 27). Interestingly, Tyr^{H32} makes H-bond contact with Glu94 of hu ephrinB2, making the H2 loop capable of bridging E-F and G-H loops of human ephrinB2. The binding of AB25 to G-H loop of human ephrinB2 corroborates with the AB25 blocking data on EfnB2 and the EphB receptors.

[0728] As shown in FIG. 28, the AB25 binding sites in EFNB2 are highly conserved across human, cyno, mouse and rat ephrinB2 antigens. This finding supports the BLI and SPR binding data where the binding affinities were conserved at sub-nanomolar range.

[0729] A broader understanding of the epitope for AB25 on EphrinB2 was built through additional molecular studies. AB25 binds an epitope on EphrinB2 that is preserved across multiple species, including human, mouse, rat, and cynomolgus monkey, with similar binding affinities as determined by Octet (BLI) binding. In addition, the binding of AB25 to EphrinB2 blocks the ability of this ligand to interact with its cognate receptors, including EphB2, EphB3, and EphB4. Finally, cryo-EM and crystallography studies further refined our understanding of the binding interactions between AB25 and EphrinB2, elucidating specific amino acid contacts, including both those preserved from the parental B11 antibody and those new residue contacts that give AB25 its enhanced binding properties.

TABLES

[0730] Table 1. Anti-Ephrin B2 antibody sequences

Antibody	SEQ ID NO	Amino Acid Sequence (N to C)	Sequence Name
AB25	1	GYTFTDYY	VH CDR1 (IMGT)
	2	MNPSSGNT	VH CDR2 (IMGT)
	3	ARD**G**T**K**TAT**RV**DY	VH CDR3 (IMGT)
	4	QSLLHSNGYNY	VL CDR1 (IMGT)

Antibody	SEQ ID NO	Amino Acid Sequence (N to C)	Sequence Name
		LGS	VL CDR2 (IMGT)
	5	MQGLLSPVT	VL CDR3 (IMGT)
	6	DYYIH	VH CDR1 (Kabat)
	7	WMNPSSGNTGYAQKFQG	VH CDR2 (Kabat)
	8	D**G**T**K**TAT**RV**DY	VH CDR3 (Kabat)
	9	RSSQSLLHSNGYNYLD	VL CDR1 (Kabat)
	10	LGSNRAS	VL CDR2 (Kabat)
	11	MQGLLSPVT	VL CDR3 (Kabat)
	12	QVQLVQSGAEVKKPGASVRLSCEASGYTFTDYYIHWVRQAPGQGLEWMGWMNPSSGNTGYAQKFQGRVTMTR**QTS**ISTAYMELSSLRSEDTAVYYCARD**G**T**K**TATRVDYWGQGTLVTVSS	VH
	13	EIVLTQSPLSLPVTLGQPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLLSPVTFGQGTRLDIKR	VL
AB51	14	GYTFTDYY	VH CDR1 (IMGT)
	15	MNPSSGNT	VH CDR2 (IMGT)
	16	ARD**M**TG**Y**ATGFDY	VH CDR3 (IMGT)
	17	QSLLHSNGYNY	VL CDR1 (IMGT)
		LGS	VL CDR2 (IMGT)
	18	MQGLLSPVT	VL CDR3 (IMGT)
	19	DYYIH	VH CDR1 (Kabat)
	20	WMNPSSGNTGYAQKFQG	VH CDR2 (Kabat)

Antibody	SEQ ID NO	Amino Acid Sequence (N to C)	Sequence Name
	21	DMTGYATGFDY	VH CDR3 (Kabat)
	22	RSSQSLLHSNGYNYLD	VL CDR1 (Kabat)
	23	LGSNRAS	VL CDR2 (Kabat)
	24	MQGLLSPVT	VL CDR3 (Kabat)
	25	QVQLVQSGAEVKKPGASVRLSCEASGYTFTDYYIHWVRQAPGQGLEWMGWMNPSSGNTGYAQKFQGRVTMTRQTSISTAYMELSSLRSEDTAVYYCARDMTGYATGFDYWGQGTLVTVSS	VH
	26	EIVLTQSPLSLPVTLGQPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLLSPVTFGQGTRLDIKR	VL
AB11	27	GYTFTDYY	VH CDR1 (IMGT)
	28	MNPSSGNT	VH CDR2 (IMGT)
	29	ARDLTGYATGFDY	VH CDR3 (IMGT)
	30	QSLLHSNGYNY	VL CDR1 (IMGT)
		LGS	VL CDR2 (IMGT)
	31	MQGLLSPVT	VL CDR3 (IMGT)
	32	DYYIH	VH CDR1 (Kabat)
	33	WMNPSSGNTGYAQKFQG	VH CDR2 (Kabat)
	34	DLTGYATGFDY	VH CDR3 (Kabat)
	35	RSSQSLLHSNGYNYLD	VL CDR1 (Kabat)
	36	LGSNRAS	VL CDR2 (Kabat)
	37	MQGLLSPVT	VL CDR3 (Kabat)

Antibody	SEQ ID NO	Amino Acid Sequence (N to C)	Sequence Name
	38	QVQLVQSGAEVKKPGASVRLSCEASGYTFTDYYIHWVRQAPGQGLEWMGWMNPSSGNTGYAQKFQGRVTMTR**QTS**ISTAYMELSSLRSEDTAVYYCARD**L**TG**Y**ATGFDYWGQGTLVTVSS	VH
	39	EIVLTQSPLSLPVTLGQPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLLSPVTFGQGTRLDIKR	VL
B11-QTS	40	GYTFTDYY	VH CDR1 (IMGT)
	41	MNPSSGNT	VH CDR2 (IMGT)
	42	ARDITGTATGFDY	VH CDR3 (IMGT)
	43	QSLLHSNGYNY	VL CDR1 (IMGT)
		LGS	VL CDR2 (IMGT)
	44	MQGLLSPVT	VL CDR3 (IMGT)
	45	DYYIH	VH CDR1 (Kabat)
	46	WMNPSSGNTGYAQKFQG	VH CDR2 (Kabat)
	47	DITGTATGFDY	VH CDR3 (Kabat)
	48	RSSQSLLHSNGYNYLD	VL CDR1 (Kabat)
	49	LGSNRAS	VL CDR2 (Kabat)
	50	MQGLLSPVT	VL CDR3 (Kabat)
	51	QVQLVQSGAEVKKPGASVRLSCEASGYTFTDYYIHWVRQAPGQGLEWMGWMNPSSGNTGYAQKFQGRVTMTR**QTS**ISTAYMELSSLRSEDTAVYYCARDITGTATGFDYWGQGTLVTVSS	VH

Antibody	SEQ ID NO	Amino Acid Sequence (N to C)	Sequence Name
	52	EIVLTQSPLSLPVTLGQPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLLSPVTFGQGTRLDIKR	VL
B11-DTS	53	GYTFTDYY	VH CDR1 (IMGT)
	54	MNPSSGNT	VH CDR2 (IMGT)
	55	ARDITGTATGFDY	VH CDR3 (IMGT)
	56	QSLLHSNGYNY	VL CDR1 (IMGT)
		LGS	VL CDR2 (IMGT)
	57	MQGLLSPVT	VL CDR3 (IMGT)
	58	DYYIH	VH CDR1 (Kabat)
	59	WMNPSSGNTGYAQKFQG	VH CDR2 (Kabat)
	60	DITGTATGFDY	VH CDR3 (Kabat)
	61	RSSQSLLHSNGYNYLD	VL CDR1 (Kabat)
	62	LGSNRAS	VL CDR2 (Kabat)
	63	MQGLLSPVT	VL CDR3 (Kabat)
	64	QVQLVQSGAEVKKPGASVRLSCEASGYTFTDYYIHWVRQAPGQGLEWMGWMNPSSGNTGYAQKFQGRVTMTR**DTS**ISTAYMELSSLRSEDTAVYYCARDITGTATGFDYWGQGTLVTVSS	VH
	65	EIVLTQSPLSLPVTLGQPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLLSPVTFGQGTRLDIKR	VL
B11-NTS	66	GYTFTDYY	VH CDR1 (IMGT)
	67	MNPSSGNT	VH CDR2 (IMGT)

Antibody	SEQ ID NO	Amino Acid Sequence (N to C)	Sequence Name
	68	ARDITGTATGFDY	VH CDR3 (IMGT)
	69	QSLLHSNGYNY	VL CDR1 (IMGT)
		LGS	VL CDR2 (IMGT)
	70	MQGLLSPVT	VL CDR3 (IMGT)
	71	DYYIH	VH CDR1 (Kabat)
	72	WMNPSSGNTGYAQKFQG	VH CDR2 (Kabat)
	73	DITGTATGFDY	VH CDR3 (Kabat)
	74	RSSQSLLHSNGYNYLD	VL CDR1 (Kabat)
	75	LGSNRAS	VL CDR2 (Kabat)
	76	MQGLLSPVT	VL CDR3 (Kabat)
	77	QVQLVQSGAEVKKPGASVRLSCEASGYTFTDYYIHWVRQAPGQGLEWMGWMNPSSGNTGYAQKFQGRVTMTR**NTS**ISTAYMELSSLRSEDTAVYYCARDITGTATGFDYWGQGTLVTVSS	VH
	78	EIVLTQSPLSLPVTLGQPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLLSPVTFGQGTRLDIKR	VL
AB18	86	GYTFTDYY	VH CDR1 (IMGT)
	87	MNPSSGNT	VH CDR2 (IMGT)
	88	ARD**S**TGTAT**KL**DY	VH CDR3 (IMGT)
	89	QSLLHSNGYNY	VL CDR1 (IMGT)
		LGS	VL CDR2 (IMGT)
	90	MQGLLSPVT	VL CDR3 (IMGT)

Antibody	SEQ ID NO	Amino Acid Sequence (N to C)	Sequence Name
	91	DYYIH	VH CDR1 (Kabat)
	92	WMNPSSGNTGYAQKFQG	VH CDR2 (Kabat)
	93	D**S**TGTAT**KL**DY	VH CDR3 (Kabat)
	94	RSSQSLLHSNGYNYLD	VL CDR1 (Kabat)
	95	LGSNRAS	VL CDR2 (Kabat)
	96	MQGLLSPVT	VL CDR3 (Kabat)
	98	QVQLVQSGAEVKKPGASVRLSCEASGYTFTDYYIHWVRQAPGQGLEWMGWMNPSSGNTGYAQKFQGRVTMTR**QTS**ISTAYMELSSLRSEDTAVYYCARD**S**TGTATKLDYWGQGTLVTVSS	VH
	99	EIVLTQSPLSLPVTLGQPASISCRSSQSLLHSNGYNYLDWYLQKPGQSPQLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQGLLSPVTFGQGTRLDIKR	VL

[0731] Table 2. Ephrin B2 sequences

Sequence Name	SEQ ID NO	Amino Acid Sequence (N to C)
Human Ephrin B2 (NCBI - NP_004084.1)	79	MAVRRDSVWKYCWGVLMVLCRTAISKSIVLEPIYWNSSNSKFLPGQGLVLYPQIGDKLDIICPKVDSKTVGQYEYYKVYMVDKDQADRCTIKKENTPLLNCAKPDQDIKFTIKFQEFSPNLWGLEFQKNKDYYIISTSNGSLEGLDNQEGGVCQTRAMKILMKVGQDASSAGSTRNKDPTRRPELEAGTNGRSSTTSPFVKPNPGSSTDGNSAGHSGNNILGSEVALFAGIASGCIIFIVIIITLVVLLLKYRRRHRKHSPQHTTTLSLSTLATPKRSGNNNGSEPSDIIIPLRTADSVFCPHYEKVSGDYGHPVYIVQEMPPQSPANIYYKV
6His-HuEphrinB2-(26-229)-Avi (PR005)	80	HHHHHHKSIVLEPIYWNSSNSKFLPGQGLVLYPQIGDKLDIICPKVDSKTVGQYEYYKVYMVDKDQADRCTIKKENTPLLNCAKPDQDIKFTIKFQEFSPNLWGLEFQKNKDYYIISTSNGSLEGLDNQEGGVCQTRAMKILMKVGQDASSAGSTRNKDPTRRPELEAGTNGRSSTTSPFVKPNPGSSTDGNSAGHSGNNILGSEVALFAGGSGLNDIFEAQKIEWHE

Sequence Name	SEQ ID NO	Amino Acid Sequence (N to C)
6His-HuEphrinB2-(26-229)-hIgG1-Fc (PR001)	81	HHHHHHKSIVLEPIYWNSSNSKFLPGQGLVLYPQIGDKLDIICPKVDS KTVGQYEYYKVYMVDKDQADRCTIKKENTPLLNCAKPDQDIKFTIK FQEFSPNLWGLEFQKNKDYYIISTSNGSLEGLDNQEGGVCQTRAMKI LMKVGQDASSAGSTRNKDPTRRPELEAGTNGRSSTTSPFVKPNPGSST DGNSAGHSGNNILGSEVALFAGGSEPKSSDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSPGK
6His-HuEphrinB2-ECD-Del182-194-hIgG1-Fc (PR054)	82	HHHHHHKSIVLEPIYWNSSNSKFLPGQGLVLYPQIGDKLDIICPKVDS KTVGQYEYYKVYMVDKDQADRCTIKKENTPLLNCAKPDQDIKFTIK FQEFSPNLWGLEFQKNKDYYIISTSNGSLEGLDNQEGGVCQTRAMKI LMKVGQDASSAGSTRNKDPTRTTSPFVKPNPGSSTDGNSAGHSGNNI LGSEVALFAGGSEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGK
6His-HuEphrinB2-ECD-Del197-218-hIgG1-Fc (PR055)	83	HHHHHHKSIVLEPIYWNSSNSKFLPGQGLVLYPQIGDKLDIICPKVDS KTVGQYEYYKVYMVDKDQADRCTIKKENTPLLNCAKPDQDIKFTIK FQEFSPNLWGLEFQKNKDYYIISTSNGSLEGLDNQEGGVCQTRAMKI LMKVGQDASSAGSTRNKDPTRRPELEAGTNGRSSTTNILGSEVALFA GGSEPKSSDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K
Ephrin B2 ECD 197-218	84	SPFVKPNPGSSTDGNSAGHSGN
Ephrin B2 Full ECD 26-229	85	KSIVLEPIYWNSSNSKFLPGQGLVLYPQIGDKLDIICPKVDSKTVGQYE YYKVYMVDKDQADRCTIKKENTPLLNCAKPDQDIKFTIKFQEFSPNL WGLEFQKNKDYYIISTSNGSLEGLDNQEGGVCQTRAMKILMKVGQD ASSAGSTRNKDPTRRPELEAGTNGRSSTTSPFVKPNPGSSTDGNSAGH SGNNILGSEVALFA
Signal Peptide	97	MAVRRDSVWKYCWGVLMVLCRTAIS
Consensus Ephrin B2 portion including ECD	100	KXQADRCTIKKENTPLLNCAXPDQDXKFTIKFQEFSPNLWGLEFQKN KDYYIISTSNGSL

Sequence Name	SEQ ID NO	Amino Acid Sequence (N to C)
Cynomolgus Ephrin B2 portion	101	KDQADRCTIKKENTPLLNCAKPDQDIKFTIKFQEFSPNLWGLEFQKNK DYYIISTSNGSL
Human Ephrin B2 portion	102	KDQADRCTIKKENTPLLNCAKPDQDIKFTIKFQEFSPNLWGLEFQKNK DYYIISTSNGSL
Mouse Ephrin B2 portion	103	KDQADRCTIKKENTPLLNCARPDQDVKFTIKFQEFSPNLWGLEFQKN KDYYIISTSNGSL
Rat Ephrin B2 portion	104	KEQADRCTIKKENTPLLNCARPDQDVKFTIKFQEFSPNLWGLEFQKN KDYYIISTSNGSL
Cynomolgus Ephrin B2 (residues 26-229)	105	KSIVLEPIYWNSSNSKFLPGQGLVLYPQIGDKLDIICPKVDSKTVGQYE YYKVYMVDKDQADRCTIKKENTPLLNCAKPDQDIKFTIKFQEFSPNL WGLEFQKNKDYYIISTSNGSLEGLDNQEGGVCQTRAMKILMKVGQA AGSAGSTRNKDPTRRPELEPGTNGRSSTTSPFVKPNPGSSTDGNSAGH SGNNILGSEVALFAGGSGLNDIFEAQKIEWHE
Mouse Ephrin B2 (residues 26-229)	106	SIVLEPIYWNSSNSKFLPGQGLVLYPQIGDKLDIICPKVDSKTVGQYEY YKVYMVDKDQADRCTIKKENTPLLNCARPDQDVKFTIKFQEFSPNL WGLEFQKNKDYYIISTSNGSLEGLDNQEGGVCQTRAMKILMKVGQD ASSAGSARNHGPTRRPELEAGTNGRSSTTSPFVKPNPGSSTDGNSAGH SGNNLLGSEVALFAGGSGLNDIFEAQKIEWHE
Rat Ephrin B2 (residues 26-229)	107	SIVLEPIYWNSSNSKFLPGQGLVLYPQIGDKLDIICPKVDSKTVGQYEY YKVYMVDKEQADRCTIKKENTPLLNCARPDQDVKFTIKFQEFSPNLW GLEFQKNKDYYIISTSNGSLEGLDNQEGGVCQTRAMKILMKVGQDAS SAGSTRNNDPTRRPELEAGTNGRSSTTSPFVKPNPGSSTDGNSAGHSG NNLLGSEVALFAG

WHAT IS CLAIMED IS:

1. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:66, a CDR H2 as set forth in SEQ ID NO:67, and a CDR H3, wherein said CDR H3 is a variant of SEQ ID NO:68;

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:69, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:70; and

wherein said variant of SEQ ID NO:68 comprises the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4, position 6, position 10, and position 11 relative to SEQ ID NO:68.

2. The antibody of claim 1, wherein the variant of SEQ ID NO:68 includes one substitution.

3. The antibody of claim 1, wherein the variant of SEQ ID NO:68 includes two substitutions.

4. The antibody of claim 1, wherein the variant of SEQ ID NO:68 includes three substitutions.

5. The antibody of claim 1, wherein the variant of SEQ ID NO:68 includes four substitutions.

6. The antibody of claim 1, wherein the variant of SEQ ID NO:68 comprises a I4S, I4A, I4G, I4P, I4R, I4K, I4C, or I4M substitution at the position corresponding to position 4 of SEQ ID NO:68.

7. The antibody of claim 1, wherein the variant of SEQ ID NO:68 comprises a G6N, G6K, or G6R substitution at the position corresponding to position 6 of SEQ ID NO:68.

8. The antibody of claim 1, wherein the variant of SEQ ID NO:68 comprises a G10K or G10R substitution at the position corresponding to position 10 of SEQ ID NO:68.

9. The antibody of claim 1, wherein the variant of SEQ ID NO:68 comprises an F11L, F11V, or F11I substitution at the position corresponding to position 11 of SEQ ID NO:68.

10. The antibody of claim 1, wherein the variant of SEQ ID NO:68 comprises a I4G substitution at the position corresponding to position 4 of SEQ ID NO:68, a G6K substitution at the position corresponding to position 6 of SEQ ID NO:68, an G10R substitution at the position corresponding to position 10 of SEQ ID NO:68, and a F11V substitution at the position corresponding to position 11 of SEQ ID NO:68.

11. The antibody of claim 1, wherein the variant of SEQ ID NO:68 is SEQ ID NO:3.

12. The antibody of claim 1, wherein the variant of SEQ ID NO:68 comprises a I4S substitution at the position corresponding to position 4 of SEQ ID NO:68, an G10K substitution at the position corresponding to position 10 of SEQ ID NO:68, and a F11L substitution at the position corresponding to position 11 of SEQ ID NO:68.

13. The antibody of claim 1, wherein the variant of SEQ ID NO:68 is SEQ ID NO:88.

14. The antibody of claim 1, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:12.

15. The antibody of claim 14, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:12.

16. The antibody of claim 15, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:12.

17. The antibody of claim 16, wherein said heavy chain variable domain comprises SEQ ID NO:12.

18. The antibody of claim 1, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:13.

19. The antibody of claim 18, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:13.

20. The antibody of claim 19, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:13.

21. The antibody of claim 20, wherein said light chain variable domain comprises SEQ ID NO:13.

22. The antibody of claim 1, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:98.

23. The antibody of claim 22, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:98.

24. The antibody of claim 23, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:98.

25. The antibody of claim 24, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:98.

26. The antibody of claim 25, wherein said heavy chain variable domain comprises SEQ ID NO:98.

27. The antibody of claim 1, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:99.

28. The antibody of claim 27, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:99.

29. The antibody of claim 28, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:99.

30. The antibody of claim 29, wherein said light chain variable domain comprises SEQ ID NO:99.

31. The antibody of claim 1, wherein said antibody is an IgG.

32. The antibody of claim 1, wherein said antibody is a humanized antibody or a chimeric antibody.

33. The antibody of claim 1, wherein said antibody comprises a Fab fragment.

34. The antibody of claim 1, wherein said antibody is a single-chain variable fragment (scFv).

35. The antibody of claim 1, wherein said antibody is capable of binding an Ephrin B2 protein.

36. The antibody of claim 35, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

37. The antibody of claim 36, wherein said extracellular domain comprises the sequence of SEQ ID NO:100.

38. The antibody of claim 36, wherein said extracellular domain comprises the sequence of SEQ ID NO:85.

39. The antibody of claim 36, wherein the extracellular domain comprises a glutamic acid at a position corresponding to position 69, an asparagine corresponding to position 70, and a threonine corresponding to position 71 of SEQ ID NO:85.

40. The antibody of claim 35, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

41. The antibody of claim 35, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of less than about 1 nM.

42. The antibody of claim 40, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

43. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:66, a CDR H2 as set forth in SEQ ID NO:67 and a CDR H3, wherein said CDR H3 is a variant of SEQ ID NO:68;

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:69, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:70; and

wherein said variant of SEQ ID NO:68 comprises the sequence of SEQ ID NO:68 including at least one substitution thereto at positions corresponding to position 4 and position 7 relative to SEQ ID NO:68.

44. The antibody of claim 43, wherein the variant of SEQ ID NO:68 includes one substitution.

45. The antibody of claim 43, wherein the variant of SEQ ID NO:68 includes two substitutions.

46. The antibody of claim 43, wherein the variant of SEQ ID NO:68 comprises a I4L, I4K, I4Y, I4V, I4M, I4T, I4F, I4A, I4Q, I4S, I4G, I4R, I4W, I4H, or I4N substitution at the position corresponding to position 4 of SEQ ID NO:68.

47. The antibody of claim 43, wherein the variant of SEQ ID NO:68 comprises a T7Y, T7F, or T7S at the position corresponding to position 7 of SEQ ID NO:68.

48. The antibody of claim 43, wherein the variant of SEQ ID NO:68 comprises an I4M substitution at the position corresponding to position 4 of SEQ ID NO:68 and a T7Y substitution at the position corresponding to position 7 of SEQ ID NO:68.

49. The antibody of claim 43, wherein the variant of SEQ ID NO:68 is SEQ ID NO:16.

50. The antibody of claim 43, wherein the variant of SEQ ID NO:68 comprises an I4L substitution at the position corresponding to position 4 of SEQ ID NO:68 and a T7Y substitution at the position corresponding to position 7 of SEQ ID NO:68.

51. The antibody of claim 43, wherein the variant of SEQ ID NO:68 is SEQ ID NO:29.

52. The antibody of claim 43, wherein the heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:25.

53. The antibody of claim 52, wherein the heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:25.

54. The antibody of claim 53, wherein the heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:25.

55. The antibody of claim 54, wherein the heavy chain variable domain comprises SEQ ID NO:25.

56. The antibody of claim 43, wherein the light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:26.

57. The antibody of claim 56, wherein the light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:26.

58. The antibody of claim 57, wherein the light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:26.

59. The antibody of claim 58, wherein the light chain variable domain comprises SEQ ID NO:26.

60. The antibody of claim 43, wherein the heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:38.

61. The antibody of claim 60, wherein the heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:38.

62. The antibody of claim 61, wherein the heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:38.

63. The antibody of claim 62, wherein the heavy chain variable domain comprises SEQ ID NO:38.

64. The antibody of claim 43, wherein the light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:39.

65. The antibody of claim 64, wherein the light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:39.

66. The antibody of claim 65, wherein the light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:39.

67. The antibody of claim 66, wherein the light chain variable domain comprises SEQ ID NO:39.

68. The antibody of claim 43, wherein said antibody is an IgG.

69. The antibody of claim 43, wherein said antibody is a humanized antibody or a chimeric antibody.

70. The antibody of claim 43, wherein said antibody comprises a Fab fragment.

71. The antibody of claim 43, wherein said antibody is a single-chain variable fragment (scFv).

72. The antibody of claim 43, wherein said antibody is capable of binding an Ephrin B2 protein.

73. The antibody of claim 43, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

74. The antibody of claim 73, wherein the extracellular domain of said Ephrin B2 protein comprises residues corresponding to positions 197-218 of SEQ ID NO:79.

75. The antibody of claim 72, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

76. The antibody of claim 72, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 1.496 nM.

77. The antibody of claim 72, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 1.259 nM.

78. The antibody of claim 75, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

79. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 set forth in SEQ ID NO:3;

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:5.

80. The antibody of claim 79, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:12.

81. The antibody of claim 80, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:12.

82. The antibody of claim 81, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:12.

83. The antibody of claim 82, wherein said heavy chain variable domain comprises SEQ ID NO:12.

84. The antibody of claim 79, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:13.

85. The antibody of claim 84, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:13.

86. The antibody of claim 85, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:13.

87. The antibody of claim 86, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:13.

88. The antibody of claim 87, wherein said light chain variable domain comprises SEQ ID NO:13.

89. The antibody of claim 79, wherein said antibody is an IgG.

90. The antibody of claim 79, wherein said antibody comprises a Fab fragment.

91. The antibody of claim 79, wherein said antibody is a single-chain variable fragment (scFv).

92. The antibody of claim 79, wherein said antibody is capable of binding an Ephrin B2 protein.

93. The antibody of claim 92, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

94. The antibody of claim 93, wherein said extracellular domain comprises the sequence of SEQ ID NO:100.

95. The antibody of claim 93, wherein said extracellular domain comprises the sequence of SEQ ID NO:85.

96. The antibody of claim 93, wherein the extracellular domain comprises a glutamic acid at a position corresponding to position 69, an asparagine corresponding to position 70, and a threonine corresponding to position 71 of SEQ ID NO:85.

97. The antibody of claim 92, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

98. The antibody of claim 92, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of less than about 1 nM.

99. The antibody of claim 97, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

100. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:14, a CDR H2 as set forth in SEQ ID NO:15 and a CDR H3 set forth in SEQ ID NO:16;

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:17, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:18.

101. The antibody of claim 100, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:25.

102. The antibody of claim 101, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:25.

103. The antibody of claim 102, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:25.

104. The antibody of claim 103, wherein said heavy chain variable domain comprises SEQ ID NO:25.

105. The antibody of claim 100, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:26.

106. The antibody claim 105, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:26.

107. The antibody claim 106, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:26.

108. The antibody claim 107, wherein said light chain variable domain comprises SEQ ID NO:26.

109. The antibody of claim 100, wherein said antibody is an IgG.

110. The antibody of claim 100, wherein said antibody is a humanized antibody or a chimeric antibody.

111. The antibody of claim 100, wherein said antibody comprises a Fab fragment.

112. The antibody of claim 100, wherein said antibody is a single-chain variable fragment (scFv).

113. The antibody of claim 100, wherein said antibody is capable of binding an Ephrin B2 protein.

114. The antibody of claim 113, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

115. The antibody of claim 114, wherein the extracellular domain of said Ephrin B2 protein comprises residues corresponding to positions 197-218 of SEQ ID NO:79.

116. The antibody of claim 113, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

117. The antibody of claim 116, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 1.496 nM.

118. The antibody of claim 116, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

119. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:27, a CDR H2 as set forth in SEQ ID NO:28 and a CDR H3 set forth in SEQ ID NO:29;

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:30, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:31.

120. The antibody of claim 119, wherein the heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:38.

121. The antibody of claim 120, wherein the heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:38.

122. The antibody of claim 121, wherein the heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:38.

123. The antibody of claim 119, wherein the heavy chain variable domain comprises SEQ ID NO:38.

124. The antibody of claim 119, wherein the light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:39.

125. The antibody of claim 124, wherein the light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:39.

126. The antibody of claim 125, wherein the light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:39.

127. The antibody of claim 126, wherein the light chain variable domain comprises SEQ ID NO:39.

128. The antibody of claim 123, wherein said antibody is an IgG.

129. The antibody of claim 123, wherein said antibody is a humanized antibody or a chimeric antibody.

130. The antibody of claim 123, wherein said antibody comprises a Fab fragment.

131. The antibody of claim 123, wherein said antibody is a single-chain variable fragment (scFv).

132. The antibody of claim 123, wherein said antibody is capable of binding an Ephrin B2 protein.

133. The antibody of claim 132, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

134. The antibody of claim 133, wherein the extracellular domain of said Ephrin B2 protein comprises residues corresponding to positions 197-218 of SEQ ID NO:79.

135. The antibody of claim 132, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

136. The antibody of claim 132, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 1.259 nM.

137. The antibody of claim 135, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

138. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises:

a CDR H1 as set forth in SEQ ID NO:86, a CDR H2 as set forth in SEQ ID NO:87 and a CDR H3 set forth in SEQ ID NO:88;

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:89, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:90.

139. The antibody of claim 138, wherein said heavy chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:98.

140. The antibody of claim 139, wherein said heavy chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:98.

141. The antibody of claim 140, wherein said heavy chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:98.

142. The antibody of claim 141, wherein said heavy chain variable domain comprises SEQ ID NO:98.

143. The antibody of claim 138, wherein said light chain variable domain comprises a sequence having at least 90% identity to SEQ ID NO:99.

144. The antibody of claim 143, wherein said light chain variable domain comprises a sequence having at least 95% identity to SEQ ID NO:99.

145. The antibody of claim 144, wherein said light chain variable domain comprises a sequence having at least 98% identity to SEQ ID NO:99.

146. The antibody of claim 145, wherein said light chain variable domain comprises SEQ ID NO:99.

147. The antibody of claim 138, wherein said antibody is an IgG.

148. The antibody of claim 138, wherein said antibody comprises a Fab fragment.

149. The antibody of claim 138, wherein said antibody is a single-chain variable fragment (scFv).

150. The antibody of claim 138, wherein said antibody is capable of binding an Ephrin B2 protein.

151. The antibody of claim 150, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

152. The antibody of claim 150, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 0.01 nM to about 10 nM.

153. The antibody of claim 152, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

154. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain,

wherein said heavy chain variable domain comprises SEQ ID NO:51; and
wherein said light chain variable domain comprises SEQ ID NO:52.

155. An anti-Ephrin B2 antibody comprising a heavy chain variable domain and a light chain variable domain,
wherein said heavy chain variable domain comprises SEQ ID NO:64; and
wherein said light chain variable domain comprises SEQ ID NO:65.

156. The antibody of claim 154, wherein said antibody is an IgG.

157. The antibody of claim 154, wherein said antibody is a humanized antibody or a chimeric antibody.

158. The antibody of claim 154, wherein said antibody comprises a Fab fragment.

159. The antibody of claim 154, wherein said antibody is a single-chain variable fragment (scFv).

160. The antibody of claim 154, wherein said antibody is capable of binding an Ephrin B2 protein.

161. The antibody of claim 160, wherein said antibody is capable of binding the extracellular domain of the Ephrin B2 protein.

162. The antibody of claim 161, wherein the extracellular domain of said Ephrin B2 protein comprises residues corresponding to positions 197-218 of SEQ ID NO:79.

163. The antibody of claim 160, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) from about 10 nM to about 200 nM.

164. The antibody of claim 160, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 81.5 nM.

165. The antibody of claim 160, wherein said antibody is capable of binding said Ephrin B2 protein with an equilibrium dissociation constant (K_D) of about 141 nM.

166. The antibody of claim 165, wherein the K_D is determined by Octet® Bio-Layer Interferometry (BLI), Biacore™, or Surface-Enhanced Raman Scattering (SERS).

167. An anti-Ephrin B2 antibody, wherein said anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody comprising a heavy chain variable domain comprising:

a CDR H1 as set forth in SEQ ID NO:1, a CDR H2 as set forth in SEQ ID NO:2 and a CDR H3 set forth in SEQ ID NO:3; and

a light chain variable domain comprising:

a CDR L1 as set forth in SEQ ID NO:4, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:5.

168. An anti-Ephrin B2 antibody, wherein said anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody comprising a heavy chain variable domain comprising:

a CDR H1 as set forth in SEQ ID NO:14, a CDR H2 as set forth in SEQ ID NO:15 and a CDR H3 set forth in SEQ ID NO:16; and

a light chain variable domain comprising:

a CDR L1 as set forth in SEQ ID NO:17, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:18.

169. An anti-Ephrin B2 antibody, wherein said anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody comprising a heavy chain variable domain comprising:

a CDR H1 as set forth in SEQ ID NO:27, a CDR H2 as set forth in SEQ ID NO:28 and a CDR H3 set forth in SEQ ID NO:29; and

a light chain variable domain comprising:

a CDR L1 as set forth in SEQ ID NO:30, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:31.

170. An anti-Ephrin B2 antibody, wherein said anti-Ephrin B2 antibody binds the same epitope as an anti-Ephrin B2 antibody comprising a heavy chain variable domain comprising:

a CDR H1 as set forth in SEQ ID NO:86, a CDR H2 as set forth in SEQ ID NO:87 and a CDR H3 set forth in SEQ ID NO:88;

wherein said light chain variable domain comprises:

a CDR L1 as set forth in SEQ ID NO:89, a CDR L2 comprising LGS, and a CDR L3 as set forth in SEQ ID NO:90.

171. The antibody of claim 1, wherein said antibody is attached to a therapeutic agent.

172. The antibody of claim 1, wherein said antibody is attached to a diagnostic agent.

173. A method of treating fibrosis in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of an antibody of claim 1.

174. The method of claim 173, wherein said fibrosis is liver fibrosis, lung fibrosis, skin fibrosis, cardiac fibrosis, kidney fibrosis, gut fibrosis, or cystic fibrosis.

175. The method of claim 173, wherein said fibrosis is skin fibrosis.

176. The method of claim 175, wherein said subject has systemic sclerosis, keloids, hypertrophic scars, or a combination thereof.

177. The method of claim 176, wherein said subject has systemic sclerosis.

178. The method of claim 173, wherein said fibrosis is lung fibrosis.

179. The method of claim 178, wherein the subject has interstitial lung disease.

180. The method of claim 179, wherein the interstitial lung disease is non-specific interstitial pneumonia, rheumatoid arthritis interstitial lung disease, hypersensitivity

pneumonitis, berylliosis, respiratory bronchiolitis interstitial lung disease, desquamative interstitial pneumonitis, sarcoidosis, acute interstitial pneumonitis, cryptogenic-organizing pneumonitis, lymphocytic interstitial pneumonitis, or pleuroparenchymal fibroelastosis

181. The method of claim 178, wherein the lung fibrosis is idiopathic pulmonary fibrosis, systemic sclerosis associated pulmonary fibrosis, progressive pulmonary fibrosis, pulmonary fibrosis associated with Sjogrens Syndrome., pneumoconiosis, asbestosis, silicosis, radiation-induced pulmonary fibrosis, drug-induced pulmonary fibrosis, COVID-19-related pulmonary fibrosis, pulmonary fibrosis following acute respiratory distress syndrome, pulmonary fibrosis associated with lymphangioleiomyomatosis, familial pulmonary fibrosis, pulmonary fibrosis associated with Hermansky Pudlak syndrome, or pulmonary fibrosis associated with dyskeratosis congenita.

182. The method of claim 181, wherein the lung fibrosis is idiopathic pulmonary fibrosis, systemic sclerosis associated pulmonary fibrosis, or progressive pulmonary fibrosis.

183. The method of claim 182, wherein the lung fibrosis is idiopathic pulmonary fibrosis.

184. The method of claim 182, wherein the lung fibrosis is systemic sclerosis associated pulmonary fibrosis.

185. The method of claim 173, wherein said fibrosis is cardiac fibrosis.

186. The method of claim 185, wherein said subject has chronic heart failure or has previously had a myocardial infarction.

187. The method of claim 173, wherein said fibrosis is liver fibrosis.

188. The method of claim 187, wherein said subject has nonalcoholic fatty liver disease, metabolic dysfunction-associated steatohepatitis, cirrhosis, primary biliary cholangitis, or primary sclerosing cholangitis.

189. The method of claim 173, wherein said fibrosis is kidney fibrosis.

190. The method of claim 189, wherein said subject has chronic kidney disease or diabetic nephropathy.

191. The method of claim 173, wherein said fibrosis is gut fibrosis.

192. The method of claim 191, wherein said subject has Crohn's disease or fibrostenotic inflammatory bowel disease.

193. The method of claim 173, wherein said fibrosis is cystic fibrosis.

194. A method of inhibiting migration of an Ephrin-B2 expressing cell, the method comprising contacting said cell with the anti-Ephrin B2 antibody of claim 1.