

SUMMARY

[007] The disclosure provides fully human monoclonal antibodies (mAbs) and antigen-binding fragments thereof that bind specifically to Platelet-Derived Growth Factor Subunit B (PDGF-B).

Such antibodies may be useful for treating a subject having pulmonary arterial hypertension (PAH).

[008] The circulating and lung expression of PDGF-B, the potent mitogens for pulmonary smooth muscle cells and fibroblast, are increased in both patients displaying idiopathic PAH and the hypoxia/sugen PAH mouse model. The interactions of PDGF-B with PDGFR $\beta\beta$, PDGFR $\alpha\beta$, and PDGFR $\alpha\alpha$ have been implicated in promoting pathological vascularization and pulmonary vascular remodeling. Accordingly, targeting PDGF-B may provide enhanced efficacy beyond PDGFR β by targeting signaling through PDGFR $\alpha\alpha$, PDGFR $\alpha\beta$ and PDGFR $\beta\beta$ that coordinate to promote abnormal vessel remodeling.

[009] Accordingly, in one aspect, the present disclosure provides an isolated human monoclonal antibody or antigen-binding fragment thereof that binds specifically to human Platelet-Derived Growth Factor Subunit B (PDGF-B), wherein the antibody or antigen-binding fragment exhibits one or more properties selected from the group consisting of: (a) binds to human PDGF-subunit B homodimer (PDGF-BB) at 37°C with a binding dissociation equilibrium constant (K_D) of less than about 1.84pM as measured by surface plasmon resonance; (b) binds to human PDGF-BB at 37°C with a K_D of less than about 1.36pM as measured by surface plasmon resonance; (c) binds to human PDGF-BB at 37°C with a $t_{1/2}$ of greater than or equal to about 1155 minutes as measured by surface plasmon resonance; (d) binds to human PDGF-BB at 25°C with a K_D of less than about 2.79pM as measured by surface plasmon resonance; (e) binds to human PDGF-BB at 25°C with a $t_{1/2}$ of greater than or equal to about 1155 minutes as measured by surface plasmon resonance; (f) inhibits PDGF-B activation against human PDGF-BB with an IC_{50} of less than about 1.9nM as measured in a competition ELISA assay at 25°C; (g) inhibits PDGF-B activation against human PDGF-subunit A and subunit B heterodimer (PDGF-AB) with an IC_{50} of less than about 8.8nM as measured in a competition ELISA assay at 25°C; and (h) blocks interaction between human PDGF-BB and one or more of human PDGFR- $\alpha\alpha$, PDGFR- $\alpha\beta$ and PDGFR- $\beta\beta$.

In another aspect, the present disclosure provides an isolated human antibody or antigen-binding fragment thereof that specifically binds to human PDGF-B, wherein the antibody or antigen-binding fragment comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) sequences selected from the group consisting of SEQ ID NOs: 2 and 22; and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) sequences selected from the group consisting of SEQ ID NOs: 10 and 30. In one example, the present disclosure provides an isolated human monoclonal antibody or antigen-binding fragment thereof that binds specifically to human Platelet-Derived Growth Factor Subunit B (PDGF-B).

[010] In some embodiment examples, the antibody or antigen-binding fragment exhibits one or more properties selected from the group consisting of: (a) binds to human PDGF-subunit B homodimer (PDGF-BB) at 37°C with a binding dissociation equilibrium constant (K_D) of less than about 1.84pM as measured by surface plasmon resonance; (b) binds to human PDGF-BB at 37°C with a K_D of less than about 1.36pM as measured by surface plasmon resonance; (c) binds to human PDGF-BB at 37°C with a $t_{1/2}$ of greater than or equal to about 1155 minutes as measured by surface plasmon resonance; (d) binds to human PDGF-BB at 25°C with a K_D of less than about 2.79pM as measured by surface plasmon resonance; (e) binds to human PDGF-BB at 25°C with a $t_{1/2}$ of greater than or equal to about 1155 minutes as measured by surface plasmon resonance; (f) inhibits PDGF-B activation against human PDGF-BB with an IC_{50} of less than about 1.9nM as measured in a competition ELISA assay at 25°C; (g) inhibits PDGF-B activation against human PDGF-subunit A and subunit B heterodimer (PDGF-AB) with an IC_{50} of less than about 8.8nM as measured in a competition ELISA assay at 25°C; and (h) blocks interaction between human PDGF-BB and one or more of human PDGFR- $\alpha\alpha$, PDGFR- $\alpha\beta$ and PDGFR- $\beta\beta$.

[011] In some embodiment examples, the antibody or antigen-binding fragment comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) sequences selected from the group consisting of SEQ ID NOs: 2 and 22; and three light chain CDRs (LCDR1, LCDR2 and LCDR3)

contained within any one of the light chain variable region (LCVR) sequences selected from the group consisting of SEQ ID NOs: 10 and 30.

[012] In some [embodimentexamples](#), the isolated human antibody or antigen-binding fragment thereof comprises an HCVR comprising an amino acid sequence having at least 90% identity to the sequence of SEQ ID NO:2 or SEQ ID NO:22.

[013] In some [embodimentexamples](#), the antibody or antigen-binding fragment comprises a LCVR comprising an amino acid sequence having at least 90% identity to the sequence of SEQ ID NO:10 or SEQ ID NO:30.

[014] In some [embodimentexamples](#), the antibody or antigen-binding fragment comprises: (a) a HCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2 and 22; and (b) a LCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 10 and 30.

[015] In some [embodimentexamples](#), the antibody or antigen-binding fragment comprises: (a) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4 and 24; (b) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 6 and 26; (c) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 28; (d) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 12 and 32; (e) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14 and 34; and/or (f) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16 and 36.

[016] In some [embodimentexamples](#), the antibody or antigen-binding fragment comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10 and 22/30.

[017] In some [embodimentexamples](#), the antibody or antigen-binding fragment comprises (i) a light chain immunoglobulin comprising the amino acid sequence set forth in SEQ ID NO: 20, and a heavy chain immunoglobulin comprising the amino acid sequence set forth in SEQ ID NO: 18; and/or (ii) a light chain immunoglobulin comprising the amino acid sequence set forth in SEQ ID NO: 40, and a heavy chain immunoglobulin comprising the amino acid sequence set forth in SEQ ID NO: 38.

[018] In some [embodimentexamples](#), the antigen-binding fragment is a Fab fragment, a F(ab')₂ fragment, a Fd fragment, a Fv fragment, a single-chain Fv (scFv) molecule, or a dAb fragment.

[019] [In another aspect, the present disclosure provides an isolated antibody or antigen-binding fragment thereof that binds the same epitope on human PDGF-B as the antibody, or antigen binding fragment as disclosed herein.](#) In another [aspectexample](#), the disclosure provides an isolated antibody or antigen-binding fragment thereof that binds the same epitope on human PDGF-B as the antibody, or antigen

binding fragment comprising three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) sequences selected from the group consisting of SEQ ID NOs: 2 and 22; and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) sequences selected from the group consisting of SEQ ID NOs: 10 and 30.

[020] [In another aspect, the present disclosure provides an isolated antibody or antigen-binding fragment thereof that competes for binding to human PDGF-B as the antibody, or antigen binding fragment as disclosed herein.](#) In another ~~aspect~~[example](#), the disclosure provides an isolated antibody or antigen-binding fragment thereof that competes for binding to human PDGF-B as the antibody, or antigen binding fragment comprising three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) sequences selected from the group consisting of SEQ ID NOs: 2 and 22; and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) sequences selected from the group consisting of SEQ ID NOs: 10 and 30.

[021] In another ~~aspect~~[example](#), the ~~invention~~[disclosure](#) provides nucleic acid molecules encoding anti-PDGF antibodies or fragments thereof. Recombinant expression vectors carrying the nucleic acids of the ~~invention~~[disclosure](#), and host cells into which such vectors have been introduced, are also encompassed by the ~~invention~~[disclosure](#), as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

[022] In another aspect, the disclosure provides a method for making an antibody or antigen-binding fragment disclosed herein, the method comprising: (i) introducing one or more polynucleotides encoding a light immunoglobulin chain of said antibody or fragment and a heavy immunoglobulin chain of said antibody or fragment into a host cell; (ii) culturing the host cell in a growth medium under condition favorable to expression of the polynucleotide(s); and (iii) optionally, isolating the antibody or fragment from the host cell and/or medium in which the host cell is grown.

[023] In another aspect, the disclosure provides [an antibody or antigen-binding fragment produced by the method as disclosed herein. In one example, the present disclosure provides](#) an antibody or antigen-binding fragment produced by the method comprising: (i) introducing one or more polynucleotides encoding a light immunoglobulin chain of said antibody or fragment and a heavy immunoglobulin chain of said antibody or fragment into a host cell; (ii) culturing the host cell in a growth medium under condition favorable to expression of the polynucleotide(s); and (iii) optionally, isolating the antibody or fragment from the host cell and/or medium in which the host cell is grown.

[024] In some ~~embodiment~~[examples](#), the antibody, or antigen binding fragment comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) sequences selected from the group consisting of SEQ ID NOs: 2 and 22; and three light chain CDRs (LCDR1, LCDR2 and LCDR3)

contained within any one of the light chain variable region (LCVR) sequences selected from the group consisting of SEQ ID NOs: 10 and 30.

[025] In another aspect, the disclosure provides an injection device or vessel comprising an antibody or antigen-binding fragment disclosed herein.

[026] In another aspect, the disclosure provides a pharmaceutical composition comprising an isolated human antibody or antigen-binding fragment thereof that binds to human PDGF-B as described above or disclosed herein, and a pharmaceutically acceptable carrier or diluent; and, optionally, one or more additional therapeutic agents.

[027] In some [embodimentexamples](#), the one or more additional therapeutic agents comprise an iron supplement.

[028] In another aspect, the disclosure provides [the use of the antibody, or antigen-binding fragment thereof as disclosed herein; or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for preventing or treating pulmonary arterial hypertension \(PAH\) in a subject in need thereof. In another aspect, the present disclosure provides an antibody, or antigen-binding fragment thereof as disclosed herein, for use in therapy. In another aspect, the present disclosure provides a composition comprising one or more antibodies or antigen-binding fragments thereof as disclosed herein, for use in therapy. In one example, the present disclosure provides](#) a method for preventing or treating pulmonary arterial hypertension (PAH) in a patient in need thereof, comprising administering an effective amount of an antibody or an antigen-binding fragment thereof that binds to human PDGF-B as disclosed herein; or a pharmaceutical composition comprising an isolated human antibody or antigen-binding fragment thereof that binds to human PDGF-B as disclosed herein to the patient.

[029] In some [embodimentexamples](#), the antibody or antigen-binding fragment thereof is administered subcutaneously, intravenously, intradermally, orally, or intramuscularly.

[030] In some [embodimentexamples](#), the PAH produces a condition selected from the group consisting of thickening of the pulmonary artery in the subject; decreasing stroke volume in the subject; decreasing right ventricle cardiac output in the subject; and decreasing survival time of the subject; and administration of the antibody, or antigen-binding fragment, treats the condition or reduces the severity of one or more symptoms of the condition.

[031] In another [aspectexample](#), the disclosure provides an antibody, or antigen-binding fragment thereof that binds to human PDGF-B as disclosed herein, for use in treating a patient with PAH.

[032] In another [aspectexample](#), the disclosure provides a composition comprising one or more antibodies or antigen-binding fragments that bind to human PDGF-B as disclosed herein, for use in treating PAH.

[033] In another [aspectexample](#), the disclosure provides use of the isolated antibody, or antigen-binding fragment thereof that binds to human PDGF-B as disclosed herein, in the manufacture of a medicament for treating a patient with PAH.

[034] In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein is capable of neutralizing PDGF-BB, PDGF-AB and/or PDGF-AB/BB and preventing PDGF driven calcium flux in a cell. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein is capable of neutralizing PDGF-BB and preventing PDGF

driven calcium flux in a cell. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein is capable of neutralizing PDGF-AB and preventing PDGF driven calcium flux in a cell. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein is capable of neutralizing PDGF-AB/BB and preventing PDGF driven calcium flux in a cell.

[035] In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein is capable of neutralizing PDGF-BB, PDGF-AB and/or PDGF-AB/BB and preventing PDGF driven cellular proliferation. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein is capable of neutralizing PDGF-BB and preventing PDGF driven cellular proliferation. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein is capable of neutralizing PDGF-AB and preventing PDGF driven cellular proliferation. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein is capable of neutralizing PDGF-AB/BB and preventing PDGF driven cellular proliferation.

[036] In some [embodimentexamples](#), the cell is a human cell. In some [embodimentexamples](#), the cell is selected from the group consisting of pulmonary artery smooth muscle cell and primary human lung fibroblast.

[037] In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein bind to the outside edge of β -sheet region of PDGF-BB. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein bind to the interstrand loops of PDGF-BB. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein bind to the outside edge of β -sheet region and the interstrand loops of PDGF-BB. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein bind to one or more residues of PDGF-BB selected from the group consisting of W40, R73, K80, K81, P82, F84, K86, and R56. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein binds to a W40 residue of PDGF-BB. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein binds to a R73 residue of PDGF-BB. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein binds to a K80 residue of PDGF-BB. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein binds to a K81 residue of PDGF-BB. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein binds to a P82 residue of PDGF-BB. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein binds to a F84 residue of PDGF-BB. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof,

described herein binds to a K86 residue of PDGF-BB. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein binds to a R56 residue of PDGF-BB.

[038] In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein is internalized into a cell in a ligand dependent manner through a PDGF receptor. In some [embodimentexamples](#), the cell is a human cell. In some [embodimentexamples](#), the cell is selected from the group consisting of pulmonary artery smooth muscle cell and primary human lung fibroblast.

[039] In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein is capable of reducing right ventricular systolic pressure in a subject in need thereof. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein is capable of reducing right ventricular hypertrophy in a subject in need thereof. In some [embodimentexamples](#), the antibody, or antigen binding fragment thereof, described herein is capable of reducing right ventricular systolic pressure and right ventricular hypertrophy in a subject in need thereof.

[040] Other [embodimentexamples](#) will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[041] **Figure 1** is a graph depicting the screening results of the monoclonal anti-PDGF antibodies from the VI-3 mice.

[042] **Figure 2** is a schematic depicting the study performed for determining the binding Kinetics of 17 anti-PDGF-B antibodies at 25 °C and 37 °C.

[043] **Figure 3A** is a schematic depicting the cross-competition study between purified anti-PDGF-BB monoclonal antibodies.

[044] **Figure 3B** is a matrix showing the results of an antibody cross-competition assay in which a first anti-PDGF-B antibody (mAb-1) was applied to a human PDGF-BB-coated sensor tip, followed by treatment with a second anti-PDGF-B antibody (mAb-2). Binding responses for each antibody combination tested are depicted.

[045] **Figures 4A-4B** are graphs depicting that 5 strong anti-PDGF-B antibodies were identified which blocked >70%; 3 anti-PDGF-B antibodies blocked both PDGF-BB and PDGF-AB with IC₅₀ value ranges for PDGF-BB of 0.23-1.8nM; 2 anti-PDGF-B antibodies blocked only PDGF-BB with IC₅₀ value ranges of 0.55-0.64nM ; 6 moderate anti-PDGF-B antibodies blocked >45%; 2 anti-PDGF-B antibodies blocked both PDGF-BB and PDGF-AB with IC₅₀ value ranges for PDGF-BB of 2.8-13nM; 4 anti-PDGF-B antibodies blocked only PDGF-BB with IC₅₀ value ranges of 0.64-2.8nM ; and 6 anti-PDGF-B antibodies were non-blockers. **Figure 4C** is a table

Claims

What is claimed is:

1. An isolated human monoclonal antibody or antigen-binding fragment thereof that binds specifically to human Platelet-Derived Growth Factor Subunit B (PDGF-B), wherein the antibody or antigen-binding fragment exhibits one or more properties selected from the group consisting of:

(a) binds to human PDGF-subunit B homodimer (PDGF-BB) at 37°C with a binding dissociation equilibrium constant (K_D) of less than about 1.84pM as measured by surface plasmon resonance;

(b) binds to human PDGF-BB at 37°C with a K_D of less than about 1.36pM as measured by surface plasmon resonance;

(c) binds to human PDGF-BB at 37°C with a $t_{1/2}$ of greater than or equal to about 1155 minutes as measured by surface plasmon resonance;

(d) binds to human PDGF-BB at 25°C with a K_D of less than about 2.79pM as measured by surface plasmon resonance;

(e) binds to human PDGF-BB at 25°C with a $t_{1/2}$ of greater than or equal to about 1155 minutes as measured by surface plasmon resonance;

(f) inhibits PDGF-B activation against human PDGF-BB with an IC_{50} of less than about 1.9nM as measured in a competition ELISA assay at 25°C;

(g) inhibits PDGF-B activation against human PDGF-subunit A and subunit B heterodimer (PDGF-AB) with an IC_{50} of less than about 8.8nM as measured in a competition ELISA assay at 25°C; and

(h) blocks interaction between human PDGF-BB and one or more of human PDGFR- $\alpha\alpha$, PDGFR- $\alpha\beta$ and PDGFR- $\beta\beta$.

2. An isolated human antibody or antigen-binding fragment thereof that specifically binds to human PDGF-B, wherein the antibody or antigen-binding fragment comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained

within any one of the heavy chain variable region (HCVR) sequences selected from the group consisting of SEQ ID NOs: 2 and 22; and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) sequences selected from the group consisting of SEQ ID NOs: 10 and 30.

3. The isolated human antibody or antigen-binding fragment thereof of any one of claims 1-2, wherein the antibody or antigen-binding fragment comprises an HCVR comprising an amino acid sequence having at least 90% identity to the sequence of SEQ ID NO:2 or SEQ ID NO:22.

4. The isolated human antibody or antigen-binding fragment thereof of any one of claims 1-3, wherein the antibody or antigen-binding fragment comprises a LCVR comprising an amino acid sequence having at least 90% identity to the sequence of SEQ ID NO:10 or SEQ ID NO:30.

5. The isolated human antibody or antigen-binding fragment thereof of any one of claims 1-4, wherein the antibody or antigen-binding fragment comprises: (a) a HCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2 and 22; and (b) a LCVR comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 10 and 30.

6. The isolated human antibody or antigen-binding fragment thereof of any one of claims 1-5, wherein the antibody or antigen-binding fragment comprises:

(a) a HCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4 and 24;

(b) a HCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 6 and 26;

(c) a HCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 8 and 28;

(d) a LCDR1 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 12 and 32;

(e) a LCDR2 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 14 and 34; and/or

(f) a LCDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 16 and 36.

7. The isolated human antibody or antigen-binding fragment of any one of claims 1-6, wherein the antibody or antigen-binding fragment comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10 and 22/30.

8. The isolated human antibody or antigen-binding fragment of any one of claims 1-7, wherein the antibody or antigen-binding fragment comprises

(i) a light chain immunoglobulin comprising the amino acid sequence set forth in SEQ ID NO: 20, and

a heavy chain immunoglobulin comprising the amino acid sequence set forth in SEQ ID NO: 18; and/or

(ii) a light chain immunoglobulin comprising the amino acid sequence set forth in SEQ ID NO: 40, and

a heavy chain immunoglobulin comprising the amino acid sequence set forth in SEQ ID NO: 38.

9. The antigen-binding fragment of any one of claims 1-8, wherein the antigen-binding fragment is a Fab fragment, a F(ab')₂ fragment, a Fd fragment, a Fv fragment, a single-chain Fv (scFv) molecule, or a dAb fragment.

10. An isolated antibody or antigen-binding fragment thereof that binds the same epitope on human PDGF-B as the antibody, or antigen binding fragment, of any one of claims 1-9.

11. An isolated antibody or antigen-binding fragment thereof that competes for binding to human PDGF-B as the antibody, or antigen binding fragment, of any one of claims 1-9.

12. A method for making an antibody or antigen-binding fragment of any one of claims 1-11 comprising:

(i) introducing one or more polynucleotides encoding a light immunoglobulin chain of said antibody or fragment and a heavy immunoglobulin chain of said antibody or fragment into a host cell;

(ii) culturing the host cell in a growth medium under condition favorable to expression of the polynucleotide(s); and

(iii) optionally, isolating the antibody or fragment from the host cell and/or medium in which the host cell is grown.

13. An antibody or antigen-binding fragment ~~which~~ produced by the method of claim 12.

14. An injection device or vessel comprising an antibody or antigen-binding fragment of any one of claims 1-11 and 13.

15. A pharmaceutical composition comprising an isolated human antibody or antigen-binding fragment thereof that binds to human PDGF-B according to any one of claims 1-11 and 13, and a pharmaceutically acceptable carrier or diluent; and, optionally, one or more additional therapeutic agents.

16. The pharmaceutical composition of claim 15, wherein the one or more additional therapeutic agents comprise an iron supplement.

17. Use of the antibody, or antigen-binding fragment thereof, of any one of claims 1-11 and 13; or the pharmaceutical composition of any one of claims 15-16, in the manufacture of a medicament ~~A method~~ for preventing or treating pulmonary arterial hypertension (PAH) in a ~~patient subject~~ in need thereof, ~~comprising administering an effective amount of an antibody or an antigen-binding fragment thereof according to any one of claims 1-11 and 13; or a pharmaceutical composition according to any one of claims 15-16 to the patient.~~

18. The ~~method~~ use of claim 17, wherein the antibody, or antigen-binding fragment thereof, is ~~for administered~~ subcutaneously, intravenously, intradermally, orally, or intramuscularly administration.

19. The ~~method~~use of any one of claims 17-18, wherein the PAH produces a condition selected from the group consisting of thickening of the pulmonary artery in the subject; decreasing stroke volume in the subject; decreasing right ventricle cardiac output in the subject; and decreasing survival time of the subject;

~~and administration of the antibody, or antigen-binding fragment, treats the condition or reduces the severity of one or more symptoms of the condition.~~

20. An antibody, or antigen-binding fragment thereof, of any one of claims 1-11 and 13 for use in ~~treating a patient with PAH~~therapy.

21. A composition comprising one or more antibodies or antigen-binding fragments thereof of any one of claims 1-11 and 13, for use in ~~therapy~~treating PAH.

~~22. Use of the isolated antibody, or antigen-binding fragment thereof, of any one of claims 1-11 and 13 in the manufacture of a medicament for treating a patient with PAH.~~