IL-6 ANTAGONISTS AND USES THEREOF

RELATED APPLICATIONS

The present application claims priority to U.S. Application Serial No. 61/723,972, filed November 8, 2012 and U.S. Application Serial No. 61/831,699, filed June 6, 2013. The entire content of each of the foregoing applications is hereby incorporated herein by reference.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on December 19, 2013, is named D2046-7044WO_SL.txt and is 46,819 bytes in size.

FIELD OF THE INVENTION

The field of the invention relates to IL-6. More particularly, the field relates to modulators of IL-6 and their uses in treating disease such diseases of the eye.

BACKGROUND

IL-6 is a pleiotropic cytokine with reported roles in inflammation, hematopoiesis, angiogenesis, cell differentiation, and neuronal survival.

SUMMARY

The ~~invention~~disclosure relates to IL-6 antibodies and fragments, and derivatives of such antibodies and fragments that have certain features, including binding specificity to site II of IL-6, and methods of using such antibodies, fragments, and derivatives. Accordingly, the present ~~invention~~disclosure relates to an antibody, fragment, or derivative thereof that can specifically bind to site II of an IL-6. In some embodiments, the antibody, fragment, or derivative can bind to IL-6 with a K_D of 240 pM or less. In some embodiments, the antibody, fragment, or derivative has a T_m of 70°C or greater. In some embodiments, the antibody, fragment, or derivative can bind to IL-6 with a K_D of 240 pM or less and has a T_m of 70°C or greater. The antibody or fragment or derivative thereof can, in some cases, bind to at least one of R24, K27, Y31, D34, S118, or V121 of human IL-6; in some cases the antibody or fragment or derivative thereof can bind to R24, K27, Y31, D34, S118, and V121 of human IL-6. In embodiments, the antibody or fragment or derivative thereof can bind to at least 1, at least 2, at least 3, at least 4, or at least 5 of R24, K27, Y31, D34, S118, and V121 of human IL-6.

In one aspect, there is provided an isolated antibody or antigen binding fragment thereof that can specifically bind to site II of human IL 6, wherein the antibody or fragment thereof comprises:

a. a VL domain sequence that has at least 95, 98 or 99% amino acid sequence identity with a VL domain as set out at amino acids 1-111 of SEQ ID NO: 22; and

b. a VH domain sequence that has at least 95, 98 or 99% amino acid sequence identity with a VH domain as set out at amino acids 1-121 of SEQ ID NO: 23.

In one ~~aspect~~embodiment, provided herein is an antibody or fragment thereof (e.g., an antigen binding fragment thereof) that can specifically bind to site II of a human IL-6.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) can bind to an IL-6 with a K_D of 200 pM or less.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) can bind to an IL-6 with a K_D of 200 pM or less and/or has a T_m of 70°C or greater.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) can bind to an IL-6 with a K_D of 200 pM or less and/or has a T_m of 80°C or greater.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) binds to at least one of R24, K27, Y31, D34, S118, and V121 of a human IL-6. In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) binds to at least two of R24, K27, Y31, D34, S118, and V121 of a human IL-6. In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) binds to at least three of R24, K27, Y31, D34, S118, and V121 of a human IL-6. In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) binds to at least four of R24, K27, Y31, D34, S118, and V121 of a human IL-6. In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) binds to at least five of R24, K27, Y31, D34, S118, and V121 of a human IL-6. In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) binds to R24, K27, Y31, D34, S118, and V121 of human IL-6.

In an ~~aspect~~embodiment provided herein is a an antibody (e.g., an isolated antibody, e.g., an isolated monoclonal antibody) or a fragment thereof (e.g., an antigen binding fragment thereof) that comprises (a) a VH CDR1 as set forth in SEQ ID NO:4, a VH CDR2 as set forth in SEQ ID NO:5, and VH CDR3 as set forth in SEQ ID NO:6; and optionally (b) a VL CDR1 as set forth in SEQ ID NO:7, a VL CDR2 as set forth in SEQ ID NO:8, and a VL CDR3 as set forth in SEQ ID NO:9, wherein the antibody or fragment thereof (e.g., the antigen binding fragment thereof) can specifically bind to a human IL-6. In embodiments, the antibody or fragment thereof comprises heavy chain CDRs VH CDR1, VH CDR2, and VH CDR3 that are identical to the CDR sequences respectively set forth in SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6 or that collectively differ from said CDR sequences by no more than 1, 2, 3, 4, or 5 amino acids. In embodiments, the antibody or fragment thereof comprises light chain CDRs VL CDR1, VL CDR2, and VL CDR3 that are identical to the CDR sequences respectively set forth in SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9 or that collectively differ from said CDR sequences by no more than 1, 2, 3, 4, or 5 amino acids.

In an ~~aspect~~embodiment provided herein is an IL-6 antibody (e.g., an isolated IL-6 antibody) or a fragment thereof (e.g., an antigen binding fragment thereof) that can dissociate from human IL-6 with a K_D of 240 pM or less (e.g., as determined by surface plasmon resonance). In embodiments, the antibody can neutralize IL-6 activity with an IC50 of 255 pM or less, e.g., as determined in an *in vitro* HEK-Blue™ IL-6 assay.

In an ~~aspect~~embodiment provided herein is an IL-6 antibody ((e.g., an isolated IL-6 antibody) or a fragment (e.g., an antigen binding fragment) thereof, that can competitively inhibit binding to a human IL-6 by an antibody or fragment (e.g., an antigen binding fragment) thereof comprising SEQ ID NO:1 and SEQ ID NO:2 or an antibody or fragment (e.g., an antigen binding fragment) thereof comprising SEQ ID NO:3 and SEQ ID NO:2.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) has a monovalent Kd of 2 nM or greater at pH 5.5.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) is an IgG2 antibody.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) has altered FcRn binding compared to a reference antibody. In embodiments, the FcRn binding is decreased compared to a reference antibody. In embodiments, the Fc domain of the antibody or fragment is altered compared to a reference antibody.

In an ~~aspect~~embodiment provided herein is an IL-6 antibody (an antibody that is capable of binding to an IL-6, e.g., to site II of a human IL-6) or fragment thereof that has a modified Fc domain and exhibits reduced FcRn binding compared to a corresponding antibody having a wild type Fc domain.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) comprises a mutation at one or more of H311, I254, and H436 of SEQ ID NO:23.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) comprises a mutation at two or more of H311, D313, I254, and H436 of SEQ ID NO:23.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) comprises a mutation at three or more of H311, D313, I254, and H436of SEQ ID NO:23.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) comprises a mutation at each of H311, D313, I254, and H436 of SEQ ID NO:23.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) comprises one or more mutations (e.g., 1, 2, 3, or 4 mutations) selected from the group consisting of H311A, H311E, H311N, D313T, I254A, I254R, and H435A.

In embodiments, the antibody or fragment thereof (e.g., an antigen binding fragment thereof) is isolated.

In embodiments, the antibody is a monoclonal antibody or a fragment thereof (e.g., an antigen binding fragment thereof). In embodiments, the antibody is a human monoclonal antibody.

In embodiments, the antibody is an isolated monoclonal antibody or a fragment thereof (e.g., an antigen binding fragment thereof).

In embodiments, the antibody (e.g., the isolated monoclonal antibody) comprises SEQ ID NO:23.

In one aspect, there is provided a composition comprising the antibody or antigen binding fragment as defined herein.

In one aspect, there is provided an isolated antibody or antigen binding fragment as defined herein, or a composition as defined herein, for use in medicine.

In one aspect, there is provided an isolated antibody or antigen binding fragment as defined herein, or a composition as defined herein, for use in the treatment of a subject (e.g., a human) with an ocular disease characterized by an elevated level of IL-6 in the vitreous.

Also provided herein is an antibody or fragment (e.g., an antigen binding fragment) thereof (e.g., an IL-6 antibody or fragment thereof as described herein), or a composition comprising such an antibody or fragment thereof, for use in the treatment of an IL-6 associated disease (e.g., for use in the treatment of a subject, e.g. a human subject, having an IL-6 associated disease). In embodiments, said disease is an ocular disease characterized by an elevated level of IL-6 in the vitreous. In embodiments, said disease is diabetic macular edema (DME), diabetic retinopathy, uveitis, dry eye disease, uveitis, age-related macular degeneration (AMD), proliferative diabetic retinopathy (PDR), retinal vein occlusion (RVO), neuromyelitis optica (NMO), corneal transplant, corneal abrasion, or physical injury to the eye. In embodiments, said disease is DME. In embodiments, said disease is dry eye disease. In embodiments, said disease is dry eye syndrome. In embodiments, said disease is uveitis. In embodiments, said disease is AMD. In embodiments, said disease is PDR. In embodiments, said disease is PDR. In embodiments, said disease is corneal transplant, corneal abrasion, or physical injury to the eye. In embodiments, the antibody or fragment (e.g., the antigen binding fragment) thereof is suitable for delivery to the vitreous of the eye. In embodiments, the antibody or fragment (e.g., the antigen binding fragment) thereof is delivered to the vitreous of the eye.

Also provided herein is a method of treating an IL-6 associated disease, the method comprising administering to a subject an IL-6 antibody or fragment thereof (e.g., an antigen binding fragment thereof), e.g., an IL-6 antibody or fragment thereof as described herein. In embodiments, the IL-6 antibody or fragment thereof (e.g., an antigen binding fragment thereof), is administered in a therapeutically effective amount. In embodiments, the IL-6 associated disease is an ocular disease characterized by an elevated level of IL-6 in the vitreous. In embodiments, the IL-6 associated disease is diabetic macular edema (DME), diabetic retinopathy, uveitis, dry eye syndrome, dry eye disease, uveitis, age-related macular degeneration (AMD), proliferative diabetic retinopathy (PDR), retinal vein occlusion (RVO), neuromyelitis optica (NMO), corneal transplant, corneal abrasion, or physical injury to the eye. In embodiments, the antibody or fragment thereof (e.g., the antigen binding fragment thereof), is suitable for delivery to the vitreous of the eye. In embodiments, the antibody or fragment thereof (e.g., the antigen binding fragment thereof), is delivered to the vitreous of the subject's eye. In embodiments, the IL-6 associated disease is diabetic macular edema and the antibody or fragment thereof is delivered to the vitreous of the subject's eye.

In one aspect, there is provided a vector comprising a sequence encoding the antibody or antibody fragment as defined herein.

In another ~~aspect~~embodiment provided herein is a vector comprising a sequence encoding an IL-6 antibody or fragment thereof (e.g., an antigen binding fragment thereof) described herein. In embodiments, the vector comprises a sequence encoding SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, or SEQ ID NO:9.

In one aspect, there is provided a cell that expresses a sequence encoding the antibody or antibody fragment as defined herein.

In another ~~aspect~~embodiment provided herein is a cell that can express the sequence of an IL-6 antibody or fragment thereof (e.g., an antigen binding fragment thereof) described herein. In embodiments, the cell can express one or more of SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, or SEQ ID NO:9.

In yet another ~~aspect~~embodiment, the ~~invention~~disclosure relates to a method of reducing systemic effects of inhibiting an IL-6 in a subject, the method comprising administering to the subject an antibody or fragment thereof that can inhibit an activity of IL-6 and has reduced Fc activity compared to a corresponding antibody or fragment thereof having a wild type Fc domain. In some cases, the method of reducing systemic effects of inhibiting an IL-6 in a subject including administering to the subject an IL-6 antagonist that has FcRn binding greater than 1 μM, e.g., at low pH such as pH 5.5.

"Treat", "treating" and "treatment" refer to a method of ameliorating a signs or symptoms or a disease.

As used herein, the term "disease" includes diseases and disorders.

The entire disclosure of each patent document and scientific article referred to herein, and those patent documents and scientific articles cited thereby, is expressly incorporated by reference herein for all purposes.

Additional features and advantages of the ~~invention~~disclosure are more particularly described below.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph illustrating results of an experiment in which an anti-IL-6 antibody was administered IVT in rat CNV model. Anti-VEGF antibody was administered as a positive control and the negative control was vehicle alone. $p = 0.0054$ on Day 15 and $p = 0.0005$ on Day 22 for anti-IL-6 vs. vehicle control.

Fig. 2 is a graph illustrating results of a binding experiment testing the ability of the murine 64 antibody to inhibit binding of IL-6/IL-6R to gp130.

Fig 3A is a graph illustrating an experiment in which 020 was tested for the ability to block IL-6 signaling in the absence of an excess of soluble IL-6Rα. Experiments were performed in HEK-Blue-IL-6 cells with 0.2 ng/mL IL-6 and 2μg/mL IL6Rα.

Fig 3B is a graph illustrating an experiment in which 020 was tested for the ability to block IL-6 signaling in the absence presence of an excess of soluble IL-6Rα. Experiments were performed in HEK-Blue-IL-6 cells with 0.2 ng/mL IL-6 and 2μg/mL IL6Rα.

DETAILED DESCRIPTION

IL-6 has been implicated as playing a role in a number of diseases such as rheumatoid arthritis, and has been reported to be significantly up-regulated in a number of diseases, including ocular diseases. IL-6 can act via both cis- and trans-mechanisms. In the cis mechanism, it is believed that free IL-6 binds to membrane bound IL-6 receptor (IL-6R is also referred to as IL-6Rα and CD126), and the IL-6/IL-6R complex then interacts with gp130 (also referred to as CD130, oncostatin M receptor, IL-6Rbeta, and IL-6 signal transducer), to activate

What is claimed is:

1. An isolated antibody or antigen binding fragment thereof that can specifically bind to site II of a human IL-6.

2. An isolated monoclonal antibody or antigen binding fragment thereof comprising

a. a VH CDR1 as set forth in SEQ ID NO:4, a VH CDR2 as set forth in SEQ ID NO:5, and VH CDR3 as set forth in SEQ ID NO:6; and

b. comprising a VL CDR1 as set forth in SEQ ID NO:7, the VL CDR2 as set forth in SEQ ID NO:8, and the VL CDR3 as set forth in SEQ ID NO:9,

wherein the antibody or antigen binding fragment thereof can specifically bind to a human IL-6 (e.g., can specifically bind to site II of a human IL-6).

3. The isolated antibody or antigen binding fragment of claim 1 or claim 2, wherein the antibody or antigen binding fragment can bind to an IL-6 with a K_D of 240 pM or less, and has a T_m of 70°C or greater.

4. The antibody or antigen binding fragment of claim 1 or claim 2, wherein the antibody or antigen binding fragment can bind to an IL-6 with a K_D of 240 pM or less and has a T_m of 80°C or greater.

5. The antibody or antigen binding fragment of claim 1, claim 2, claim 3, or claim 4, wherein the antibody or antigen binding fragment thereof binds to at least one of R24, K27, Y31, D34, S118, or V121 of a human IL-6.

6. The antibody or antigen binding fragment of claim 1, claim 2, claim 3, or claim 4, wherein the antibody or antigen binding fragment thereof binds to R24, k27, Y31, D34, S118, and V121 of human IL-6.

7. An isolated IL-6 antibody, or antigen binding fragment thereof, that

a. can dissociate from human IL-6 with a K_D of 240 pM or less as determined by surface plasmon resonance, and

b. can neutralize IL-6 activity in an *in vitro* HEK-Blue™ IL-6 assay with an IC50 of 255 pM or less.

8. An isolated IL-6 antibody or antigen binding fragment thereof, that can competitively inhibit binding to a human IL-6 by an antibody or antigen binding fragment thereof comprising SEQ ID NO:1 and SEQ ID NO:2 or an antibody or antigen binding fragment comprising SEQ ID NO:3 and SEQ ID NO:2.

9. An isolated antibody or fragment thereof that can specifically bind to site II of human IL-6, wherein the antibody or fragment thereof comprises: (a) a light chain variable domain comprising an amino sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 12, and a heavy chain variable domain comprising an amino sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 11.

10. An isolated IL-6 antibody or antigen binding fragment thereof of any one of claims 1-9, wherein the antibody or antigen binding fragment thereof has a monovalent Kd of 2 nM or greater at pH 5.5.

11. The antibody or antigen binding fragment of any one of claims 1-10, wherein the antibody is an IgG2 antibody.

12. The antibody or antigen binding fragment of any one of claims 1-11, wherein the antibody or antigen binding fragment has altered FcRn binding compared to a reference antibody or fragment thereof.

13. The antibody or antigen binding fragment of claim 12, wherein the FcRn binding is decreased compared to a reference antibody.

14. The antibody or antigen binding fragment thereof of claim 12 or 13, wherein the Fc domain of the antibody or antigen binding fragment is altered compared to a reference antibody.

15. The antibody or antigen binding fragment of claim 1, wherein the antibody or antigen binding fragment thereof comprises a mutation at one or more of H311, D313, I254, or H436 of SEQ ID NO:23.

16. The antibody or antigen binding fragment thereof of claim 15, wherein the antibody comprises one or more mutations selected from the group consisting of H311A, H311E, H311N and D313T, I254A, I254R, and H436A.

17. An isolated monoclonal antibody comprising SEQ ID NO:25.

18. An isolated IL-6 antibody or fragment thereof that specifically binds to site II of human IL-6, and exhibits reduced FcRn binding compared to a corresponding antibody having a wild type Fc domain.

19. The antibody or antigen binding fragment of any one of the preceding claims, for use in the treatment of a subject (e.g., a human) with an IL-6 associated disease.

20. The antibody or antigen binding fragment of claim 19, wherein said disease is an ocular disease characterized by an elevated level of IL-6 in the vitreous.

21. The antibody or antigen binding fragment of claim 19 or 20, for use in the treatment of a subject (e.g., a human) with diabetic macular edema (DME), diabetic retinopathy, uveitis, dry eye syndrome, uveitis, age-related macular degeneration (AMD), proliferative diabetic retinopathy (PDR), retinal vein occlusion (RVO), neuromyelitis optica (NMO), corneal transplant, corneal abrasion, or physical injury to the eye.

22. The antibody or antigen binding fragment of claim 21, for use in the treatment of a subject (e.g., a human) with DME.

23. A composition comprising the antibody or antigen binding fragment of any one of claims 1-18.

24. A composition comprising the antibody of claim 1 or claim 2, wherein said antibody is a human monoclonal antibody.

25. The composition of claim 23 or 24 for use in the treatment of an IL-6 associated disease.

26. The composition of claim 25 for use in the treatment of an ocular disease characterized by an elevated level of IL-6 in the vitreous.

27. The composition of claim 23 or 24 for use in the treatment of diabetic macular edema (DME), diabetic retinopathy, uveitis, dry eye syndrome, age-related macular degeneration (AMD), proliferative diabetic retinopathy (PDR), retinal vein occlusion (RVO), neuromyelitis optica (NMO), corneal transplant, corneal abrasion, or physical injury to the eye.

28. A method of treating an IL-6 associated disease, the method comprising administering to a subject a therapeutically effective amount of an IL-6 antibody or fragment thereof of any one of claims 1-18.

29. The method of claim 28, wherein the IL-6 associated disease is an ocular disease characterized by an elevated level of IL-6 in the vitreous.

30. The method of claim 28 or 29, wherein the IL-6 associated disease is diabetic macular edema (DME), diabetic retinopathy, dry eye syndrome, age-related macular degeneration (AMD), proliferative diabetic retinopathy (PDR), retinal vein occlusion (RVO), neuromyelitis optica (NMO), corneal transplant, corneal abrasion, or physical injury to the eye.

31. The method of claim 29, wherein the antibody or antigen binding fragment is delivered to the vitreous of the subject's eye.

32. The method of claim 29, wherein the IL-6 associated disease is diabetic macular edema and the antibody or fragment thereof is delivered to the vitreous of the subject's eye.

33. A vector comprising a sequence encoding SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, or SEQ ID NO:9.

34. A cell that can express one or more of SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, or SEQ ID NO:9.

35. A method of reducing systemic effects of inhibiting an IL-6 in a subject, the method comprising administering to the subject an antibody or fragment thereof that can inhibit an activity of IL-6 and has reduced FcRn binding activity compared to a corresponding antibody or fragment thereof having a wild type Fc domain.

36. The method of claim 35, wherein the K_D is greater than 1 μM at a pH of 5 to 6.

What is claimed is:

1. An isolated antibody or antigen binding fragment thereof that can specifically bind to site II of human IL-6, wherein the antibody or fragment thereof comprises:

a. a VL domain sequence that has at least 95, 98 or 99% amino acid sequence identity with a VL domain as set out at amino acids 1-111 of SEQ ID NO: 22; and

b. a VH domain sequence that has at least 95, 98 or 99% amino acid sequence identity with a VH domain as set out at amino acids 1-121 of SEQ ID NO: 23.

2. The isolated antibody or antigen binding fragment of claim 1, wherein the antibody or antigen binding fragment can bind to an IL-6 with a K_D of 240 pM or less, and has a T_m of 70°C or greater,

optionally wherein the antibody or antigen binding fragment can bind to an IL-6 with a K_D of 240 pM or less and has a T_m of 80°C or greater.

3. The isolated antibody or antigen binding fragment of claim 1 or claim 2, wherein the antibody or antigen binding fragment thereof binds to at least one of R24, K27, Y31, D34, S118, and V121 of a human IL-6,

optionally wherein the antibody or antigen binding fragment thereof binds to R24, K27, Y31, D34, S118, and V121 of human IL-6.

4. The isolated antibody or antigen binding fragment of any one of claims 1 to 3, that

a. can dissociate from human IL-6 with a K_D of 240 pM or less (e.g. as determined by surface plasmon resonance), and

b. can neutralize IL-6 activity with an IC50 of 255 pM or less (e.g. as determined in an *in vitro* HEK-Blue™ IL-6 assay).

5. The isolated antibody or antigen binding fragment of any one of claims 1 to 4 that can competitively inhibit binding to a human IL-6 by an antibody or antigen binding fragment

thereof comprising SEQ ID NO: 1 and SEQ ID NO: 2 or an antibody or antigen binding fragment comprising SEQ ID NO: 3 and SEQ ID NO: 2.

6. The isolated antibody or antigen binding fragment of any one of claims 1 to 5, wherein the antibody is an IgG2 antibody.

7. The isolated antibody or antigen binding fragment thereof of any one of claims 1 to 6, wherein the antibody comprises one or more mutations selected from the group consisting of H311A, H311E, H311N, D313T, I254A, I254R, and H436A of SEQ ID NO: 23.

8. The isolated antibody or antigen binding fragment of claim 7, that exhibits reduced FcRn binding compared to a corresponding antibody having a wild type Fc domain.

9. The isolated antibody or antigen binding fragment of any one of claims 1 to 8, wherein the antibody or fragment thereof comprises:

a. CDR sequences that collectively differ by no more than 1, 2, 3, 4 or 5 amino acids from a VH CDR1 as set forth in SEQ ID NO: 4, a VH CDR2 as set forth in SEQ ID NO: 5, and VH CDR3 as set forth in SEQ ID NO: 6; and

b. CDR sequences that collectively differ by no more than 1, 2, 3, 4 or 5 amino acids from a VL CDR1 as set forth in SEQ ID NO: 7, the VL CDR2 as set forth in SEQ ID NO: 8, and the VL CDR3 as set forth in SEQ ID NO: 9.

10. The isolated antibody or antigen binding fragment of any one of claims 1 to 9, wherein the antibody or fragment thereof comprises:

a. a VH CDR1 as set forth in SEQ ID NO:4, a VH CDR2 as set forth in SEQ ID NO:5, and VH CDR3 as set forth in SEQ ID NO:6; and

b. a VL CDR1 as set forth in SEQ ID NO:7, the VL CDR2 as set forth in SEQ ID NO:8, and the VL CDR3 as set forth in SEQ ID NO:9.

11. A composition comprising the antibody or antigen binding fragment of any one of claims 1 to 10.

12. An isolated antibody or antigen binding fragment as claimed in any one of claims 1 to 10, or a composition as claimed in claim 11, for use in medicine.

13. An isolated antibody or antigen binding fragment as claimed in any one of claims 1 to 10, or a composition as claimed in claim 11, for use in the treatment of a subject (e.g., a human) with an ocular disease characterized by an elevated level of IL-6 in the vitreous.

14. The isolated antibody, antigen binding fragment, or composition for use according to claim 13, wherein the ocular disease is diabetic macular edema (DME), diabetic retinopathy, uveitis, dry eye syndrome, age-related macular degeneration (AMD), proliferative diabetic retinopathy (PDR), retinal vein occlusion (RVO), neuromyelitis optica (NMO), corneal transplant, corneal abrasion, or physical injury to the eye.

15. The isolated antibody, antigen binding fragment, or composition for use according to claim 13 or claim 14, wherein the antibody, antigen binding fragment or composition is delivered to the vitreous of the subject's eye.

16. The isolated antibody, antigen binding fragment, or composition for use according to claim 15, wherein the ocular disease is diabetic macular edema (DME).

17. A vector comprising a sequence encoding the antibody or antibody fragment of any one of claims 1 to 10.

18. A cell that expresses a sequence encoding the antibody or antibody fragment of any one of claims 1 to 10.