

IMPROVED IL-6 ANTIBODIES

RELATED APPLICATIONS

5 This application claims priority to U.S. Provisional Application No. 62/077,105, filed November 7, 2014; U.S. Provisional Application No. 62/087,448, filed December 4, 2014; and U.S. Provisional Application No. 62/247,705, filed October 28, 2015. The entire contents of each of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

10 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 as diseases of the eye.

BACKGROUND

15 IL-6 is a pleiotropic cytokine with reported roles in inflammation, hematopoiesis, angiogenesis, cell differentiation, and neuronal survival. The present invention relates to improved IL-6 antibodies and uses thereof.

SUMMARY

20 The invention relates to IL-6 antibodies and fragments (e.g., antigen-binding fragments) or derivatives thereof, as well as nucleic acids encoding the IL-6 antibodies and fragments. The invention also relates to uses of such antibodies, fragments, or derivatives. The antibodies and fragments or derivatives thereof can be used, for example, in the treatment of an IL-6 associated disease. In embodiments, the antibody, fragment, or derivative thereof can bind (e.g., specifically bind) to an IL-6, e.g., to a human IL-6. In embodiments, the antibody, fragment, or
25 derivative thereof can bind (e.g., specifically bind) to site II of an IL-6 (e.g., site II of human IL-6).

In one aspect, there is provided an isolated antibody or antigen binding fragment thereof that binds to human IL-6, comprising (i) a VH CDR1 comprising the sequence of SEQ ID NO:31, a VH CDR2 comprising the sequence of SEQ ID NO:32, a VH CDR3 comprising the sequence of SEQ ID NO:33, a VL CDR1 comprising the sequence of SEQ ID NO:34, a VL CDR2 comprising the sequence of SEQ ID NO:35, and a VL CDR3 comprising the sequence of SEQ ID NO:36.

In one aspect, there is provided an isolated antibody or antigen binding fragment comprising a heavy chain variable region comprising SEQ ID NO:37 and a light chain variable region comprising SEQ ID NO:38.

In one aspect, there is provided an isolated antibody or antigen binding fragment comprising a heavy chain sequence comprising SEQ ID NO:41 or SEQ ID NO: 47 and a light chain sequence comprising SEQ ID NO:42.

In one aspect, there is provided an isolated antigen binding fragment of an antibody comprising a heavy chain sequence comprising SEQ ID NO:39 or SEQ ID NO:54 and a light chain sequence comprising SEQ ID NO:42.

In one aspect, there is provided an isolated antibody or antigen binding fragment comprising a heavy chain sequence comprising SEQ ID NO:47 and a light chain sequence comprising SEQ ID NO:42.

In one aspect, there is provided a host cell comprising the vector as described herein.

In one aspect, there is provided a method of antagonizing IL-6 comprising contacting IL-6 with the antibody or antibody fragment as described herein.

In one aspect, there is provided a method of inhibiting IL-6 cis and trans signaling comprising contacting IL-6 with the antibody or antigen binding fragment as described herein.

In one aspect, there is provided a use of an antibody or antigen binding fragment as described herein in the manufacture of a medicament for treating an IL-6 associated disease characterized by an elevated level of IL-6 in the vitreous.

In one aspect provided herein is a use of an antibody or antigen binding fragment as described herein in the manufacture of a medicament for treating diabetic macular edema (DME), diabetic retinopathy, uveitis, dry eye (e.g., dry eye disease or 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.

In one aspect provided herein is an isolated antibody or antigen binding fragment comprising a heavy chain variable region comprising

- (i) a VH CDR1 comprising the sequence of GYX₁LX₂NYLIE (SEQ ID NO:45),
- (ii) a VH CDR2 comprising the sequence of VX₃TPGX₄GTIN (SEQ ID NO:46), and
- (ii) a VH CDR3,

What is claimed is:

1. An isolated antibody or antigen binding fragment thereof that binds to human IL-6, comprising (i) a VH CDR1 comprising the sequence of SEQ ID NO:31, a VH CDR2 comprising
5 the sequence of SEQ ID NO:32, a VH CDR3 comprising the sequence of SEQ ID NO:33, a VL CDR1 comprising the sequence of SEQ ID NO:34, a VL CDR2 comprising the sequence of SEQ ID NO:35, and a VL CDR3 comprising the sequence of SEQ ID NO:36.

2. The antibody or antigen binding fragment of claim 1, wherein the antibody or antigen
10 binding fragment comprises a heavy chain variable region sequence comprising SEQ ID NO:37.

3. The antibody or antigen binding fragment of claim 12, wherein the antibody or antigen binding fragment comprises a heavy chain sequence comprising SEQ ID NO:39 or SEQ ID NO:54.

4. The antibody or antigen binding fragment of claim 1, wherein the antibody or antigen binding fragment comprises a heavy chain sequence comprising SEQ ID NO:41.

5. The antibody or antigen binding fragment of claim 1, wherein the antibody or antigen
20 binding fragment comprises a heavy chain sequence comprising SEQ ID NO:47.

6. The antibody or antigen binding fragment of any one of claims 1-5, wherein the antibody or antigen binding fragment further comprises a light chain variable region sequence comprising SEQ ID NO:38.

7. The antibody or antigen binding fragment of any one of claims 1-5, wherein the antibody or antigen binding fragment further comprises a light chain sequence comprising SEQ ID NO:42.

8. An isolated antibody or antigen binding fragment comprising a heavy chain variable region comprising SEQ ID NO:37 and a light chain variable region comprising SEQ ID NO:38.

9. An isolated antibody or antigen binding fragment comprising a heavy chain sequence comprising SEQ ID NO:41 or SEQ ID NO: 47 and a light chain sequence comprising SEQ ID NO:42.

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10. An isolated antigen binding fragment of an antibody comprising a heavy chain sequence comprising SEQ ID NO:39 or SEQ ID NO:54 and a light chain sequence comprising SEQ ID NO:42.

10 11. The antibody or antigen binding fragment of claims 4 or 9, wherein the antibody or antigen binding fragment comprises a mutation at one or more positions corresponding to H311, D313, I254, or H436 in SEQ ID NO:41.

15 12. The antibody or antigen binding fragment of any one of the preceding claims, wherein the antibody or antigen binding fragment is an IgG2-A isoform or an IgG2-A/B isoform, but not an IgG2-B isoform.

13. An isolated antibody or antigen binding fragment comprising a heavy chain sequence comprising SEQ ID NO:47 and a light chain sequence comprising SEQ ID NO:42.

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14. A composition comprising the antibody or antigen binding fragment of any one of claims 1 to 13 and, a pharmaceutically acceptable carrier.

25 15. A nucleic acid comprising a sequence encoding an antibody or antigen binding fragment according to any one of claims 1 to 13.

16. A vector comprising the nucleic acid of claim 15.

17. A host cell comprising the vector of claim 16.

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18. A method of antagonizing IL-6 comprising contacting IL-6 with the antibody or antibody fragment of any one of claims 1-13.

5 19. A method of inhibiting IL-6 cis and trans signaling comprising contacting IL-6 with the antibody or antigen binding fragment of any one of claims 1-13.

20. Use of an antibody or antigen binding fragment of any of claims 1-13 in the manufacture of a medicament for treating an IL-6 associated disease characterized by an elevated level of IL-6 in the vitreous.

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21. Use of an antibody or antigen binding fragment of any of claims 1-13 in the manufacture of a medicament for treating diabetic macular edema (DME), diabetic retinopathy, uveitis, dry eye (e.g., dry eye disease or dry eye syndrome), age-related macular degeneration (AMD), proliferative diabetic retinopathy (PDR), retinal vein occlusion (RVO), neuromyelitis
15 optica (NMO), corneal transplant, corneal abrasion, or physical injury to the eye.

22. The use of claim 21, for the treatment of diabetic macular edema, wherein the antibody or fragment thereof is to be delivered to the vitreous of a subject's eye.

20 23. The isolated antibody or antigen binding fragment of claim 11, wherein the mutation at position I254 are selected from I254A and I254R.

24. The isolated antibody or antigen binding fragment of claim 11, wherein the mutation at position H311 are selected from H311A, H331E and H311N.

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25. The isolated antibody or antigen binding fragment of claim 11, wherein the mutation at position D313 is D313T.

26. The isolated antibody or antigen binding fragment of claim 11, wherein the
30 mutation at position H436 is H436A.