

IMPROVED IL-6 ANTIBODIES

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 62/077,105, filed
5 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

The invention relates to IL-6 antibodies and fragments (e.g., antigen-binding fragments)
20 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
comprising

(a) a heavy chain variable region sequence that is at least 90 % identical to SEQ ID
30 NO:37, wherein the heavy chain variable region comprises

- (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,

wherein one or more of the following is true: X₁ is not A, X₂ is not S, X₃ is not I and X₄ is not S,
5 and

- (b) a light chain variable region comprising (i) a sequence comprising SEQ ID NO:38 or
- (ii) a sequence that is at least 90% identical to SEQ ID NO:38.

In one aspect, there is provided an isolated antibody or antigen binding fragment thereof comprising (i) a VH CDR1 comprising the sequence of SEQ ID NO:31, a VH CDR2 comprising
10 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
15 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
20 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.

25 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.

30 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, the

method comprising administering to a subject a therapeutically effective amount of an IL-6 antibody or antigen binding fragment as described herein.

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

- 5 (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 comprising
 - (a) a heavy chain variable region sequence that is at least 90 % identical to SEQ ID NO:37, wherein the heavy chain variable region comprises
 - (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
 - (iii) a VH CDR3,wherein one or more of the following is true: X₁ is not A, X₂ is not S, X₃ is not I and X₄ is not S, and
 - (b) a light chain variable region comprising (i) a sequence comprising SEQ ID NO:38 or (ii) a sequence that is at least 90% identical to SEQ ID NO:38.
2. An isolated antibody or antigen binding fragment thereof 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.
3. The antibody or antigen binding fragment of claim 1 or claim 2, wherein the antibody or antigen binding fragment comprises a heavy chain variable region sequence comprising SEQ ID NO:37.
4. The antibody or antigen binding fragment of claim 2, wherein the antibody or antigen binding fragment comprises a heavy chain sequence comprising SEQ ID NO:39 or SEQ ID NO:54.
5. The antibody or antigen binding fragment of claim 2, wherein the antibody or antigen binding fragment comprises a heavy chain sequence comprising SEQ ID NO:41.

6. The antibody or antigen binding fragment of claim 2, wherein the antibody or antigen binding fragment comprises a heavy chain sequence comprising SEQ ID NO:47.

7. The antibody or antigen binding fragment of any one of claims 2-6, wherein the antibody or antigen binding fragment further comprises a light chain variable region sequence comprising SEQ ID NO:38.

8. The antibody or antigen binding fragment of any one of claims 2-6, wherein the antibody or antigen binding fragment further comprises a light chain sequence comprising SEQ ID NO:42.

9. 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.

10. 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.

11. 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.

12. The antibody or antigen binding fragment of claims 5 or 10, 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.

13. 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.

14. 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.

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

16. A nucleic acid comprising a sequence encoding an antibody or antigen binding fragment according to any one of claims 1 to 14.

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

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

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

20. 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.

21. Use of an antibody or antigen binding fragment of any of claims 1-14 in the manufacture of a medicament for treating an IL-6 associated disease, the method comprising administering to a subject a therapeutically effective amount of an IL-6 antibody or antigen binding fragment of any one of claims 1 to 14.

22. The use as in claim 21, wherein the IL-6 associated disease is an ocular disease characterized by an elevated level of IL-6 in the vitreous.

23. The use as in claim 21 or 22, wherein the IL-6 associated disease is 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.

24. The use as in claim 23, wherein the antibody or antigen binding fragment is delivered to the vitreous of the subject's eye.

25. The use as in any one of claims 21-24, 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.