

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

IL-6 is a pleiotropic cytokine with reported roles in inflammation, hematopoiesis,
15 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, provided herein is an isolated anti-IL-6 antibody or antigen binding
fragment thereof comprising: a) a heavy chain variable (VH) domain comprising a VH CDR1
comprising the amino acid sequence of SEQ ID NO:31, a VH CDR2 comprising the amino acid
30 sequence of SEQ ID NO:32, and a VH CDR3 comprising the amino acid sequence of SEQ ID
NO:33, and b) a light chain variable (VL) domain comprising a VL CDR1 comprising the amino

acid sequence of SEQ ID NO:34, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:35, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:36.

In one aspect, provided herein is a pharmaceutical composition comprising the isolated antibody or antigen binding fragment thereof of any one of claims 1-36 and a pharmaceutically acceptable carrier.

In one aspect, provided herein is the use of the pharmaceutical composition of any one of claims 27-29 in the manufacture of a medicament for the treatment of an IL-6 disease characterized by an elevated level of IL-6.

In one aspect, provided herein is the use of the pharmaceutical composition of any one of claims 27-29 in the manufacture of a medicament for the treatment of an ocular disease characterized by an elevated level of IL-6.

In one aspect, provided herein is the use of any one of claims 27-29 in the manufacture of a medicament for the treatment of diabetic macular edema (DME), diabetic retinopathy, dry eye, allergic conjunctivitis, uveitis, age-related macular degeneration (AMD), proliferative diabetic retinopathy (PDR), Rhegmatogenous retinal detachment (RRD), retinal vein occlusion (RVO), neuromyelitis optica (NMO), corneal transplant, corneal abrasion, or physical injury to the eye, characterized by an elevated level of IL-6.

In one aspect, provided herein is an isolated nucleic acid comprising a sequence encoding the isolated antibody or antigen binding fragment thereof according to any one of claims 1 to 26.

In one aspect, provided herein is an isolated vector comprising the nucleic acid of claim 35.

In one aspect, provided herein is an isolated host cell comprising the vector of claim 36.

In one aspect, provided herein is the pharmaceutical composition of any one of claims 27-29 for use in therapy.

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 anti-IL-6 antibody or antigen binding fragment thereof comprising:
 - a) a heavy chain variable (VH) domain comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:32, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:33, and
 - b) a light chain variable (VL) domain comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:34, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:35, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:36.
2. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the VH domain comprises an amino acid sequence, excluding the CDRs, that is at least 90% identical to the amino acid sequence represented by SEQ ID NO:37.
3. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the VH domain comprises the amino acid sequence represented by SEQ ID NO:37.
4. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the VL domain comprises an amino acid sequence that is at least 90% identical, excluding the CDRs, to the amino acid sequence represented by SEQ ID NO:38.
5. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the VL domain comprises the amino acid sequence represented by amino acids 1-111 of SEQ ID NO:38.
6. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the VL domain comprises the amino acid sequence represented by SEQ ID NO:38.
7. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the VH domain comprises the amino acid sequence represented by SEQ ID NO:37 and the VL domain comprises the amino acid sequence represented by SEQ ID NO:38.
8. The isolated antibody or antigen binding fragment thereof of claim 1, wherein the VH domain comprises the amino acid sequence represented by SEQ ID NO:37 and the VL domain comprises the amino acid sequence represented by amino acids 1-111 of SEQ ID NO:38.

9. The isolated antibody or antigen binding fragment thereof of claim 1, comprising a light chain comprising an amino acid sequence that is at least 90% identical, excluding the CDRs, to the amino acid sequence represented by SEQ ID NO: 42 that comprises the VL domain.
10. The isolated antibody or antigen binding fragment thereof of claim 1, comprising a light chain comprising the amino acid sequence represented by SEQ ID NO: 42 that comprises the VL domain.
11. The isolated antibody or antigen binding fragment thereof of claim 1, comprising a heavy chain comprising an amino acid sequence that is at least 90% identical, excluding the CDRs, to the amino acid sequence represented by SEQ ID NO:41 that comprise the VH domain.
12. The isolated antibody or antigen binding fragment thereof of claim 1, comprising a heavy chain comprising the amino acid sequence represented by SEQ ID NO:41 that comprises the VH domain.
13. The isolated antibody or antigen binding fragment thereof of claim 1, comprising a heavy chain comprising the amino acid sequence represented by SEQ ID NO:41 that comprises the VH domain and a light chain comprising the amino acid sequence represented by SEQ ID NO:42 that comprises the VL.
14. The isolated antibody or antigen binding fragment thereof of claim 1, comprising the amino acid sequence represented by SEQ ID NO:39 that comprises the VH domain.
15. The isolated antibody or antigen binding fragment thereof of claim 1, comprising the amino acid sequence represented by amino acids 1-225 of SEQ ID NO:39 that comprises the VH domain.
16. The isolated antibody or antigen binding fragment thereof of claim 1, comprising an amino acid sequence that is at least 90% identical to the amino acid sequence represented by SEQ ID NO:54 that comprises the VH domain.
17. The isolated antibody or antigen binding fragment thereof of claim 1, comprising an amino acid sequence represented by SEQ ID NO:54 that comprises the VH domain.

18. The isolated antibody or antigen binding fragment thereof of claim 1, comprising a heavy chain comprising the amino acid sequence represented by SEQ ID NO:47 that comprises the VH domain.
- 5 19. The isolated antibody or antigen binding fragment thereof of claim 1, comprising a heavy chain comprising the amino acid sequence represented by SEQ ID NO:47 that comprises the VH domain and a light chain comprising the amino acid sequence represented by SEQ ID NO:42 that comprises the VL.
20. The isolated antibody or antigen binding fragment thereof of any one of claims 1-19, wherein the antibody is an IgG2 antibody.
- 10 21. The isolated antibody or antigen binding fragment thereof of claim 20, wherein the antibody or antigen binding fragment is an IgG2-A isoform or an IgG2-A/B isoform.
22. The isolated antibody or antigen binding fragment thereof of claim 1, comprising a heavy chain comprising the amino acid sequence represented by SEQ ID NO:41 comprising 0, 1, 2, 3, or 4 mutations at positions I254, H311, D313, or H436.
- 15 23. The isolated antibody or antigen binding fragment thereof of claim 22, wherein the mutation at position I254 is I254A or I254R.
24. The isolated antibody or antigen binding fragment thereof of any one of claims 22 or 23, wherein the mutation at position H311 is H311A, H311E or H311N.
- 20 25. The isolated antibody or antigen binding fragment thereof of any one of claims 22-24, wherein the mutation at position D313 is D313T.
26. The isolated antibody or antigen binding fragment thereof of any one of claims 22-25, wherein the mutation at position H436 is H436A.
27. A pharmaceutical composition comprising the isolated antibody or antigen binding fragment thereof of any one of claims 1-36 and a pharmaceutically acceptable carrier.
- 25 28. The pharmaceutical composition of claim 27, wherein the composition comprises at least 60, 70, 80, 90, 95, or 99% of IgG2-A or IgG2-A/B isoforms of the antibody, or a combination thereof.

29. The pharmaceutical composition of claim 27 or 28, wherein the composition comprises less than 10%, 5%, 2%, 1%, or 0.5% of IgG2-B isoforms of the antibody.
30. Use of the pharmaceutical composition of any one of claims 27-29 in the manufacture of a medicament for the treatment of an IL-6 disease characterized by an elevated level of IL-6.
- 5 31. Use of the pharmaceutical composition of any one of claims 27-29 in the manufacture of a medicament for the treatment of an ocular disease characterized by an elevated level of IL-6.
32. The use of claim 31, wherein the IL-6 associated disease is an ocular disease characterized by an elevated level of IL-6 in the vitreous.
33. Use of any one of claims 27-29 in the manufacture of a medicament for the treatment of
10 diabetic macular edema (DME), diabetic retinopathy, dry eye, allergic conjunctivitis, uveitis, age-related macular degeneration (AMD), proliferative diabetic retinopathy (PDR), Rhegmatogenous retinal detachment (RRD), retinal vein occlusion (RVO), neuromyelitis optica (NMO), corneal transplant, corneal abrasion, or physical injury to the eye, characterized by an elevated level of IL-6.
- 15 34. The use of claim 31 or 32, wherein the ocular disease is dry eye disease or dry eye syndrome, characterized by an elevated level of IL-6.
35. An isolated nucleic acid comprising a sequence encoding the isolated antibody or antigen binding fragment thereof according to any one of claims 1 to 26.
36. An isolated vector comprising the nucleic acid of claim 35.
- 20 37. An isolated host cell comprising the vector of claim 36.
38. The pharmaceutical composition of any one of claims 27-29 for use in therapy.