

The IL-33 pathway has been suggested to be involved in various diseases, including ocular diseases (e.g, GA) for which there remains a need to develop improved compositions, and methods for treatment.

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SUMMARY

The present disclosure relates, *inter alia*, to anti-IL-33 antibodies and methods of making and using the same.

In one aspect, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising a heavy chain variable (VH) domain and a light chain variable (VL) domain, the binding domain comprising the following
10 six complementarity-determining regions (CDRs): (a) a CDR-H1 comprising the amino acid sequence of NYWMT (SEQ ID NO: 1); (b) a CDR-H2 comprising the amino acid sequence of SITYTGGGTYYPDSVKG (SEQ ID NO: 2); (c) a CDR-H3 comprising the amino acid sequence of ANYYYNTYGGFPY (SEQ ID NO: 3); (d) a CDR-L1 comprising the amino acid sequence of
15 LASEGFSNDLA (SEQ ID NO: 4); (e) a CDR-L2 comprising the amino acid sequence of AASRLQD (SEQ ID NO: 5); and (f) a CDR-L3 comprising the amino acid sequence of QQGSKYPLT (SEQ ID NO: 6).

In another aspect, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid
20 sequence of SEQ ID NO: 7; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 8; or (c) a VH domain as in (a) and a VL domain as in (b).

In some examples, the VH domain comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVX₁SGX₂X₃X₄X₅X₆PGX₇SX₈X₉X₁₀SCX₁₁ASGFTFN (SEQ ID NO: 9), wherein X₁ is E or Q; X₂ is G
25 or A; X₃ is G or E; X₄ is L or V; X₅ is V or K; X₆ is Q or K; X₇ is G, A, or T; X₈ is L or V; X₉ is R or K; X₁₀ is L or V; and X₁₁ is A, K, or L; (b) an FR-H2 comprising the amino acid sequence of WX₁RQAPGX₂GLEWX₃X₄ (SEQ ID NO: 10), wherein X₁ is I or V; X₂ is K or Q; X₃ is V, M, or I; and X₄ is A or G; (c) an FR-H3 comprising the amino acid sequence of
RX₁TX₂X₃RDX₄X₅X₆X₇X₈X₉YX₁₀X₁₁X₁₂X₁₃SLRX₁₄EDTAX₁₅YYCTR (SEQ ID NO: 11), wherein X₁ is F or V;
30 X₂ is I or M; X₃ is S or T; X₄ is D, N, or T; X₅ is A or S; X₆ is K or T; X₇ is S or N; X₈ is S or T; X₉ is L or V; X₁₀ is L or M; X₁₁ is Q or E; X₁₂ is M or L; X₁₃ is N or S; X₁₄ is A or S; and X₁₅ is V or T; and (d) an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 12).

In some examples, the VH domain comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFN (SEQ ID NO: 17); (b) an FR-H2 comprising the amino
35 acid sequence of WIRQAPGKGLEWVA (SEQ ID NO: 18); (c) an FR-H3 comprising the amino acid sequence of RFTISRDDAKSSLYLQMNSLRAEDTAVYYCTR (SEQ ID NO: 19); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLVTVSS (SEQ ID NO: 12).

In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 7.

In some examples, the VH domain comprises: (a) an FR-H1 comprising the amino acid sequence
40 of EVQLVESGGGLVQPGGSLRLSCAASGFTFN (SEQ ID NO: 17); (b) an FR-H2 comprising the amino

acid sequence of WVRQAPGKGLEWVA (SEQ ID NO: 39); (c) an FR-H3 comprising the amino acid sequence of RFTISRDNKNSLYLQMNSLRAEDTAVYYCTR (SEQ ID NO: 40); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVSS (SEQ ID NO: 12).

In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 41.

5 In some examples, the VH domain comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFN (SEQ ID NO: 17); (b) an FR-H2 comprising the amino acid sequence of WIRQAPGKGLEWIA (SEQ ID NO: 42); (c) an FR-H3 comprising the amino acid sequence of RFTISRDDAKSSLYLQMNSLRAEDTAVYYCTR (SEQ ID NO: 19); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVSS (SEQ ID NO: 12).

10 In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 43.

In some examples, the VH domain comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFN (SEQ ID NO: 17); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGLEWVA (SEQ ID NO: 39); (c) an FR-H3 comprising the amino acid sequence of RFTISRDDAKSSLYLQMNSLRAEDTAVYYCTR (SEQ ID NO: 19); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVSS (SEQ ID NO: 12).

In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 44.

In some examples, the VH domain comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFN (SEQ ID NO: 17); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGLEWVA (SEQ ID NO: 39); (c) an FR-H3 comprising the amino acid sequence of RFTISRDDAKNSLYLQMNSLRAEDTAVYYCTR (SEQ ID NO: 45); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVSS (SEQ ID NO: 12).

In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 46.

In some examples, the VH domain comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFN (SEQ ID NO: 17); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGLEWVA (SEQ ID NO: 39); (c) an FR-H3 comprising the amino acid sequence of RFTISRDNKNSLYLQMNSLRAEDTAVYYCTR (SEQ ID NO: 47); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVSS (SEQ ID NO: 12).

In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 48.

In some examples, the VH domain comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFN (SEQ ID NO: 17); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGLEWIA (SEQ ID NO: 49); (c) an FR-H3 comprising the amino acid sequence of RFTISRDDAKSSLYLQMNSLRAEDTAVYYCTR (SEQ ID NO: 19); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVSS (SEQ ID NO: 12).

In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 50.

35 In some examples, the VH domain comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFN (SEQ ID NO: 17); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGKGLEWIA (SEQ ID NO: 49); (c) an FR-H3 comprising the amino acid sequence of RFTISRDDSKSTLYLQMNSLRAEDTAVYYCTR (SEQ ID NO: 51); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVSS (SEQ ID NO: 12).

40 In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 52.

In some examples, the VL domain comprises: (a) an FR-L1 comprising the amino acid sequence of X₁IX₂X₃TQSPX₄X₅LSX₆SX₇GX₈X₉X₁₀X₁₁X₁₂X₁₃C (SEQ ID NO: 13), wherein X₁ is D or E; X₂ is Q or V; X₃ is M or L; X₄ is S or A; X₅ is S or T; X₆ is A or L; X₇ is V, P, or L; X₈ is D or E; X₉ is R or T; X₁₀ is V or A; X₁₁ is T or S; X₁₂ is I or L; and X₁₃ is T, S, or E; (b) an FR-L2 comprising the amino acid sequence of
5 WX₁QQKX₂GX₃X₄PX₅X₆LIY (SEQ ID NO: 14), wherein X₁ is Y or F; X₂ is P or S; X₃ is K or Q; X₄ is S or A; X₅ is K, R, or Q; and X₆ is L or S; (c) an FR-L3 comprising the amino acid sequence of
GX₁PX₂RFSGSGSGTX₃FX₄LX₅ISX₆X₇X₈PEDX₉AX₁₀YX₁₁C (SEQ ID NO: 15), wherein X₁ is V or I; X₂ is S or A; X₃ is D or R; X₄ is T or S; X₅ is T or K; X₆ is S or G; X₇ is L or M; X₈ is Q or E; X₉ is F, V, or E; X₁₀ is T, V, or D; and X₁₁ is F or Y; and (d) an FR-L4 comprising the amino acid sequence of FGX₁GTX₂EIK
10 (SEQ ID NO: 16), wherein X₁ is G or S and X₂ is V or L.

In some examples, the VL domain comprises: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 21); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKSPKLLIY (SEQ ID NO: 22); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISLQPEDFATYFC (SEQ ID NO: 23); and (d) an FR-L4 comprising the amino
15 acid sequence of FGGGTKVEIK (SEQ ID NO: 24).

In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 8.

In one aspect, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 7 and (b) a VL domain comprising the amino acid
20 sequence of SEQ ID NO: 8. In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 7 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8.

In another aspect, provided herein is an isolated antibody that specifically binds IL-33, or an
25 antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 25 and (b) a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 26. In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a heavy chain (HC) comprising an amino acid
30 sequence of SEQ ID NO: 25 and (b) a light chain (LC) comprising an amino acid sequence of SEQ ID NO: 26.

In some examples, the VL domain comprises: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 21); (b) an FR-L2 comprising the amino acid sequence of WFQQKPGKAPKSLIY (SEQ ID NO: 53); (c) an FR-L3 comprising the amino acid sequence of
35 GVPSRFSGSGSGTDFTLTISLQPEDFATYYC (SEQ ID NO: 54); and (d) an FR-L4 comprising the amino acid sequence of FGGGTKVEIK (SEQ ID NO: 24).

In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 55.

In some examples, the VL domain comprises: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 21); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKSLIY (SEQ ID NO: 56); (c) an FR-L3 comprising the amino acid sequence of
40 GVPSRFSGSGSGTDFTLTISLQPEDFATYFC (SEQ ID NO: 23); and (d) an FR-L4 comprising the amino acid sequence of FGGGTKVEIK (SEQ ID NO: 24).

In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 57.

In some examples, the VL domain comprises: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 21); (b) an FR-L2 comprising the amino acid sequence of WFQQKPGKAPKSLIY (SEQ ID NO: 53); (c) an FR-L3 comprising the amino acid sequence of
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GVPSRFSGSGSGTDFTLTISLQPEDFATYFC (SEQ ID NO: 23); and (d) an FR-L4 comprising the amino acid sequence of FGGGTKVEIK (SEQ ID NO: 24).

In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 58.

5 In some examples, the VL domain comprises: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 21); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKAPKSLIY (SEQ ID NO: 56); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISLQPEDFATYYC (SEQ ID NO: 54); and (d) an FR-L4 comprising the amino acid sequence of FGGGTKVEIK (SEQ ID NO: 24).

In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 59.

10 In some examples, the VL domain comprises: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 21); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGKSPKLLIY (SEQ ID NO: 22); (c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISLQPEDVATYYC (SEQ ID NO: 60); and (d) an FR-L4 comprising the amino acid sequence of FGGGTKVEIK (SEQ ID NO: 24).

15 In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 61.

In one aspect, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises:

(i) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 41 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 55;

(ii) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 43 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 55;

(iii) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 41 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8;

(iv) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 43 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8;

(v) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 44 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8;

(vi) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 46 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8;

(vii) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 48 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8;

(viii) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 43 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 57;

(ix) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 44 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 57;

(x) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 46 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 57;

(xi) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 48 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 57;

(xii) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 50 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 57;

(xiii) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 43 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 58;

(xiv) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 44 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 58;

(xv) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 46 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 58;

(xvi) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 48 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 58;

(xvii) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 50 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 58;

(xviii) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 43 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 59;

(xix) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 44 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 59;

(xx) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 46 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 59;

(xxi) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 48 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 59;

(xxii) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 50 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 59; or

(xxiii) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 52 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 61. In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 41 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 55.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 43 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 55.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 41 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 43 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 44 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 46 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 48 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 8.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 43 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 57.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 44 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 57.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 46 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 57.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 48 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 57.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 50 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 57.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 43 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 58.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 44 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 58.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 46 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 58.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 50 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 58.

5 In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 43 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 59.

10 In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 44 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 59.

15 In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 46 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 59.

20 In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 48 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 59.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 50 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 59.

25 In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 52 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 61.

In one aspect, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises:

(i) a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 35; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a VH domain as in (a) and a VL domain as in (b);

(ii) a binding domain comprising (a) a heavy chain (HC) comprising an amino acid sequence of SEQ ID NO: 37 and (b) a light chain (LC) comprising an amino acid sequence of SEQ ID NO: 38; or

30 (iii) a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 65; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 69; or (c) a VH domain as in (a) and a VL domain as in (b). In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence
35 having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 35; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a VH domain as in (a) and a VL domain as in (b).

In some examples, the VH domain comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGTSLKLSCLASGFTFN (SEQ ID NO: 27); (b) an FR-H2 comprising the amino acid sequence of WIRQAPGKGLEWIA (SEQ ID NO: 28); (c) an FR-H3 comprising the amino acid sequence of RFTISRDDAKSTLYLQMNSLRSEDATYYCTR (SEQ ID NO: 29); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVSS (SEQ ID NO: 12).

In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 35.

In some examples, the VL domain comprises: (a) an FR-L1 comprising the amino acid sequence of DIQMTQSPASLSASLGETVSIEC (SEQ ID NO: 31); (b) an FR-L2 comprising the amino acid sequence of WYQQKSGKSPQLLIY (SEQ ID NO: 32); (a) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTRFSLKISGMQPEDEADYFC (SEQ ID NO: 33); and (d) an FR-L4 comprising the amino acid sequence of FGSGTKLEIK (SEQ ID NO: 34).

In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 36.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 35 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 36.

In another example, provided herein is an isolated antibody that specifically binds IL-33, wherein the antibody comprises a binding domain comprising (a) a heavy chain (HC) comprising an amino acid sequence of SEQ ID NO: 37 and (b) a light chain (LC) comprising an amino acid sequence of SEQ ID NO: 38.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 65; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 69; or (c) a VH domain as in (a) and a VL domain as in (b).

In some examples, the VH domain comprises: (a) an FR-H1 comprising the amino acid sequence of EVQLVQSGAEVKKPGASVKVSKASGFTFN (SEQ ID NO: 62); (b) an FR-H2 comprising the amino acid sequence of WVRQAPGQGLEWMG (SEQ ID NO: 63); (c) an FR-H3 comprising the amino acid sequence of RVTMTRDTSTSTVYMELSSLRSEDTAVYYCTR (SEQ ID NO: 64); and (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVSS (SEQ ID NO: 12).

In some examples, the VH domain comprises the amino acid sequence of SEQ ID NO: 65.

In some examples, the VL domain comprises: (a) an FR-L1 comprising the amino acid sequence of EIVLTQSPATLSLSPGERATLSC (SEQ ID NO: 66); (b) an FR-L2 comprising the amino acid sequence of WYQQKPGQAPRLLIY (SEQ ID NO: 67); (c) an FR-L3 comprising the amino acid sequence of GIPARFSGSGSGTDFTLTISSLEPEDFAVYYC (SEQ ID NO: 68); and (d) an FR-L4 comprising the amino acid sequence of FGSGTKVEIK (SEQ ID NO: 24).

In some examples, the VL domain comprises the amino acid sequence of SEQ ID NO: 69.

In another example, provided herein is an isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 65 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 69.

In some examples, the antibody specifically binds human or cyno IL-33.

In some examples, the antibody specifically binds both human and cyno IL-33.

In some examples, the antibody specifically binds both human and cyno IL-33 with a K_D of about 1 nM or lower.

In some examples, the antibody specifically binds human IL-33 with a K_D between about 100 fM and about 1 nM.

In some examples, the antibody specifically binds human IL-33 with a K_D between about 750 fM and about 300 pM.

5 In some examples, the antibody specifically binds human IL-33 with a K_D between about 1 pM and about 200 pM.

In some examples, the antibody specifically binds human IL-33 with a K_D of about 118 pM.

In some examples, the antibody specifically binds human IL-33 with a K_D of about 15 pM.

In some examples, the antibody specifically binds cyno IL-33 with a K_D between about 100 fM
10 and about 1 nM.

In some examples, the antibody specifically binds cyno IL-33 with a K_D between about 1 pM and about 500 pM.

In some examples, the antibody specifically binds cyno IL-33 with a K_D between about 20 pM and about 50 pM.

15 In some examples, the antibody specifically binds cyno IL-33 with a K_D of about 35 pM.

In some examples, the antibody specifically binds both human and cyno IL-33 with a K_D of between about 1 pM and about 500 pM.

In some examples, the antibody specifically binds both human and cyno IL-33 with a K_D of between about 10 pM and about 40 pM.

20 In some examples, the antibody is capable of inhibiting the binding of IL-33 to an IL-33 receptor.

In some examples, the inhibiting is measured using a cell-based blocking assay.

In some examples, the antibody inhibits binding of human IL-33 to an IL-33 receptor with an IC_{50} of between about 800 fM and about 100 pM.

In some examples, the IC_{50} is between about 1 pM and about 50 pM.

25 In some examples, the IC_{50} is about 31 pM.

In some examples, the antibody has a viscosity of less than about 5 centipoise (cP) at a concentration of about 180 mg/mL.

In some examples, the antibody has a viscosity of between about 3 cP and about 5 cP at a concentration of about 180 mg/mL.

30 In some examples, the antibody has a viscosity of about 4.6 cP at a concentration of about 180 mg/mL.

In some examples, the antibody has a turbidity (optical density (OD)) of about 0.5 or lower at a concentration of about 150 mg/ml or higher in phosphate-buffered saline (PBS) pH 7.4.

In some examples, the antibody has a turbidity (OD) of between about 0.25 and about 0.5 at a
35 concentration of about 150 mg/ml to about 250 mg/ml.

In some examples, the antibody has a turbidity (OD) of about 0.38 at a concentration of about 200 mg/ml.

In some examples, the antibody is monoclonal, human, humanized, or chimeric.

In some examples, the antibody is an antibody fragment that binds IL-33.

40 In some examples, the antibody fragment is an Fab, Fab'-SH, Fv, scFv, or (Fab')₂ fragment.

In some examples, the antibody fragment is an Fab.
 In some examples, the antibody is a full-length antibody.
 In some examples, the antibody is an IgG antibody.
 In some examples, the IgG antibody is an IgG1 antibody.
 In some examples, the IgG antibody is an IgG4 antibody.
 In some examples, the antibody is a monospecific antibody.
 In some examples, the antibody is a multispecific antibody.
 In some examples, the antibody is a bispecific antibody.
 In some examples, the bispecific antibody comprises a second binding domain that binds to a
 second biological molecule, wherein the second biological molecule is interleukin-13 (IL-13), interleukin-4
 (IL-4), interleukin-5 (IL-5), interleukin-17 (IL-17), Factor D, HtrA1, VEGF, or a VEGF receptor.
 In one aspect, provided herein is an isolated nucleic acid or a set of isolated nucleic acids
 encoding the antibody as disclosed herein. In another example, provided herein is an isolated nucleic
 acid encoding any one of the antibodies disclosed herein or a set of isolated nucleic acids together
 encoding the antibody.
 In another aspect, provided herein is a vector or a set of vectors comprising the isolated nucleic
 acid or set of isolated nucleic acids as disclosed herein. In another example, provided herein is a vector
 or a set of vectors comprising any of the isolated nucleic acids or set of isolated nucleic acids disclosed
 herein.
 In another aspect, provided herein is a host cell comprising the vector or the set of vectors as
 disclosed herein. In another example, provided herein is a host cell comprising any one of the vectors or
 the set of vectors disclosed herein.
 In some examples, the host cell is a mammalian cell.
 In some examples, the mammalian cell is a Chinese hamster ovary (CHO) cell.
 In some examples, the host cell is a prokaryotic cell.
 In some examples, the prokaryotic cell is *E. coli*.
 In one aspect, provided herein is a method of producing an antibody that specifically binds to IL-
 33, the method comprising culturing the host cell as disclosed herein in a culture medium. In another
 example, provided herein is a method of producing an antibody that specifically binds to IL-33, the
 method comprising culturing any one of the host cells disclosed herein in a culture medium.
 In some examples, the method further comprises recovering the antibody from the host cell or the
 culture medium.
 In one aspect, provided herein is a pharmaceutical composition comprising the antibody as
 disclosed herein, further comprising a pharmaceutically acceptable carrier, excipient, or diluent.
 In another example, provided herein is a composition comprising any one of the antibodies
 disclosed herein.
 In some examples, the composition further comprises a pharmaceutically acceptable carrier,
 excipient, or diluent.
 In some examples, the composition is a pharmaceutical composition.
 In some examples, the pharmaceutical composition further comprises an ST2 binding antagonist,
 a Factor D binding antagonist, an HtrA1 binding antagonist, a VEGF antagonist, a tryptase-beta binding
 antagonist, a chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) binding
 antagonist, an interleukin-13 (IL-13) binding antagonist, an interleukin-17 (IL-17) binding antagonist, a
 JAK1 antagonist, and/or an interleukin-5 (IL-5) binding antagonist.
 In some examples, the pharmaceutical composition comprises a Factor D binding antagonist.
 In some examples, the Factor D binding antagonist is an anti-Factor D antibody or an antigen-
 binding fragment thereof.
 In some examples, the pharmaceutical composition comprises an HtrA1 binding antagonist.

In some examples, the HtrA1 binding antagonist is an anti-HtrA1 antibody or an antigen-binding fragment thereof.

In some examples, the pharmaceutical composition comprises a VEGF antagonist.

In some examples, the VEGF antagonist is an anti-VEGF antibody or an antigen-binding
5 fragment thereof.

In some examples, the antibody concentration is about 1 mg/mL to about 400 mg/mL.

In some examples, the antibody concentration is about 150 mg/mL to about 250 mg/mL.

In some examples, the antibody concentration is about 175 mg/mL to about 225 mg/mL.

In some examples, the antibody concentration is about 200 mg/mL.

10 In another example, provided herein is any one of the antibodies disclosed herein or any one of the compositions disclosed herein for use as a medicament.

In another example, provided herein is any one of the antibodies disclosed herein or any one of the compositions disclosed herein for use in treating an IL-33-mediated disorder.

15 In some examples, the IL-33-mediated disorder is an ocular disorder, an inflammatory condition, an immune disorder, a fibrotic disorder, an eosinophilic disorder, an infection, pain, a central nervous system disorder, or a solid tumor.

In some examples, the ocular disorder is age-related macular degeneration (AMD), retinopathy of the eye, polypoidal choroidal vasculopathy (PCV), diabetic macular edema, dry eye disease, Behcet's disease, retina detachment, glaucoma, uveitis, retinitis pigmentosa, Leber Congenital Amaurosis,
20 Stargardt's disease, traumatic eye injury, or conjunctivitis.

In some examples, the AMD is geographic atrophy (GA), wet AMD, or dry AMD.

In some examples, the AMD is GA.

In some examples, the AMD is intermediate AMD or advanced AMD.

25 In some examples, the retinopathy of the eye is diabetic retinopathy (DR) or retinopathy of prematurity (ROP).

In some examples, the retinopathy of the eye is high-altitude DR.

In some examples, the conjunctivitis is infectious conjunctivitis or non-infectious conjunctivitis.

In some examples, the conjunctivitis is allergic conjunctivitis.

30 In some examples, the inflammatory condition is asthma, sepsis, septic shock, atopic dermatitis, allergic rhinitis, rheumatoid arthritis, or chronic obstructive pulmonary disease (COPD).

In some examples, the immune disorder is asthma, rheumatoid arthritis, allergy, anaphylaxis, anaphylactic shock, allergic rhinitis, psoriasis, inflammatory bowel disease (IBD), Crohn's disease, diabetes, or liver disease.

In some examples, the fibrotic disease is idiopathic pulmonary fibrosis (IPF).

35 In some examples, the eosinophilic disorder is an eosinophil-associated gastrointestinal disorder (EGID).

In some examples, the EGID is eosinophilic esophagitis.

In some examples, the infection is a helminth infection, a protozoan infection, or a viral infection.

40 In some examples, the protozoan infection is a *Leishmania major* infection.

In some examples, the viral infection is a respiratory syncytial virus (RSV) infection or an influenza infection.

In some examples, the pain is inflammatory pain.

In some examples, the central nervous system disorder is Alzheimer's disease.

5 In some examples, the solid tumor is a breast tumor, a colon tumor, a prostate tumor, a lung tumor, a kidney tumor, a liver tumor, a pancreas tumor, a stomach tumor, an intestinal tumor, a brain tumor, a bone tumor, and a skin tumor.

10 In some examples, the antibody or composition is used in combination with an ST2 binding antagonist, a Factor D binding antagonist, an HtrA1 binding antagonist, a VEGF antagonist, a tryptase-beta binding antagonist, a CRTH2 binding antagonist, an IL-13 binding antagonist, an IL-17 binding antagonist, a JAK1 antagonist, and/or an IL-5 binding antagonist.

In some examples, the antibody or composition is used in combination with a Factor D binding antagonist.

15 In some examples, the Factor D binding antagonist is an anti-Factor D antibody or an antigen-binding fragment thereof.

In some examples, the antibody or composition is used in combination with an HtrA1 binding antagonist.

In some examples, the HtrA1 binding antagonist is an anti-HtrA1 antibody or an antigen-binding fragment thereof.

20 In some examples, the antibody or composition is used in combination with a VEGF antagonist.

In some examples, the VEGF antagonist is an anti-VEGF antibody or an antigen-binding fragment thereof.

25 In another example, provided herein is the use of any one of the antibodies disclosed herein or any one of the compositions disclosed herein in the manufacture of a medicament for treating an IL-33-mediated disorder.

In some examples, the IL-33-mediated disorder is an ocular disorder, an inflammatory condition, an immune disorder, a fibrotic disorder, an eosinophilic disorder, an infection, pain, a central nervous system disorder, or a solid tumor.

30 In some examples, the ocular disorder is AMD, retinopathy of the eye, PCV, diabetic macular edema, dry eye disease, Behcet's disease, retina detachment, glaucoma, uveitis, retinitis pigmentosa, Leber Congenital Amaurosis, Stargardt's disease, traumatic eye injury, or conjunctivitis.

In some examples, the AMD is GA, wet AMD, or dry AMD.

In some examples, the AMD is GA.

In some examples, the AMD is intermediate AMD or advanced AMD.

35 In some examples, the retinopathy of the eye is DR or ROP.

In some examples, the retinopathy of the eye is high-altitude DR.

In some examples, the conjunctivitis is infectious conjunctivitis or non-infectious conjunctivitis.

In some examples, the conjunctivitis is allergic conjunctivitis.

40 In some examples, the inflammatory condition is asthma, sepsis, septic shock, atopic dermatitis, allergic rhinitis, rheumatoid arthritis, or COPD.

In some examples, the immune disorder is asthma, rheumatoid arthritis, allergy, anaphylaxis, anaphylactic shock, allergic rhinitis, psoriasis, IBD, Crohn's disease, diabetes, or liver disease.

In some examples, the fibrotic disease is IPF.

In some examples, the eosinophilic disorder is an EGID.

5 In some examples, the EGID is eosinophilic esophagitis.

In some examples, the infection is a helminth infection, a protozoan infection, or a viral infection.

In some examples, the protozoan infection is a *Leishmania major* infection.

In some examples, the viral infection is an RSV infection or an influenza infection.

In some examples, the pain is inflammatory pain.

10 In some examples, the central nervous system disorder is Alzheimer's disease.

In some examples, the solid tumor is a breast tumor, a colon tumor, a prostate tumor, a lung tumor, a kidney tumor, a liver tumor, a pancreas tumor, a stomach tumor, an intestinal tumor, a brain tumor, a bone tumor, and a skin tumor.

15 In some examples, the medicament is formulated for use in combination with an ST2 binding antagonist, a Factor D binding antagonist, an HtrA1 binding antagonist, a VEGF antagonist, a tryptase-beta binding antagonist, a CRTH2 binding antagonist, an IL-13 binding antagonist, an IL-17 binding antagonist, a JAK1 antagonist, and/or an IL-5 binding antagonist.

In some examples, the medicament is formulated for use in combination with a Factor D binding antagonist.

20 In some examples, the Factor D binding antagonist is an anti-Factor D antibody or an antigen-binding fragment thereof.

In some examples, the medicament is formulated for use in combination with an HtrA1 binding antagonist.

25 In some examples, the HtrA1 binding antagonist is an anti-HtrA1 antibody or an antigen-binding fragment thereof.

In some examples, the medicament is formulated for use in combination with a VEGF antagonist.

In some examples, the VEGF antagonist is an anti-VEGF antibody or an antigen-binding fragment thereof.

30 In one aspect, provided herein is use of the antibody as disclosed herein in the manufacture of a medicament for treating an IL-33-mediated disorder in a subject in need thereof. In another example, provided herein is a method of treating an IL-33-mediated disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of any one of the antibodies disclosed herein or any one of the compositions disclosed herein.

35 In some examples, the IL-33-mediated disorder is an ocular disorder, an inflammatory condition, an immune disorder, a fibrotic disorder, an eosinophilic disorder, an infection, pain, a central nervous system disorder, or a solid tumor.

In some examples, the ocular disorder is AMD, retinopathy of the eye, PCV, diabetic macular edema, dry eye disease, Behcet's disease, retina detachment, glaucoma, uveitis, retinitis pigmentosa, Leber Congenital Amaurosis, Stargardt's disease, traumatic eye injury, or conjunctivitis.

40 In some examples, the AMD is GA, wet AMD, or dry AMD.

In some examples, the AMD is GA.

In some examples, the AMD is intermediate AMD or advanced AMD.

In some examples, the retinopathy of the eye is DR or ROP.

In some examples, the retinopathy of the eye is high-altitude DR.

In some examples, the conjunctivitis is infectious conjunctivitis or non-infectious conjunctivitis.

In some examples, the conjunctivitis is allergic conjunctivitis.

5 In some examples, the inflammatory condition is asthma, sepsis, septic shock, atopic dermatitis, allergic rhinitis, rheumatoid arthritis, or COPD.

In some examples, the immune disorder is asthma, rheumatoid arthritis, allergy, anaphylaxis, anaphylactic shock, allergic rhinitis, psoriasis, IBD, Crohn's disease, diabetes, and liver disease.

In some examples, the fibrotic disease is IPF.

10 In some examples, the eosinophilic disorder is an EGID.

In some examples, the EGID is eosinophilic esophagitis.

In some examples, the infection is a helminth infection, a protozoan infection, or a viral infection.

In some examples, the protozoan infection is a Leishmania major infection.

In some examples, the viral infection is an RSV infection or an influenza infection.

15 In some examples, the pain is inflammatory pain.

In some examples, the solid tumor is a breast tumor, a colon tumor, a prostate tumor, a lung tumor, a kidney tumor, a liver tumor, a pancreas tumor, a stomach tumor, an intestinal tumor, a brain tumor, a bone tumor, and a skin tumor.

In some examples, the method further comprises administering to the subject an ST2 binding antagonist, a Factor D binding antagonist, an HtrA1 binding antagonist, a VEGF antagonist, a tryptase-beta binding antagonist, a CRTH2 binding antagonist, an IL-13 binding antagonist, an IL-17 binding antagonist, a JAK1 antagonist, and/or an IL-5 binding antagonist.

20 In some examples, the method further comprises administering to the subject a Factor D binding antagonist.

25 In some examples, the Factor D binding antagonist is anti-Factor D antibody or an antigen-binding fragment thereof.

In some examples, the method further comprises administering to the subject an HtrA1 binding antagonist.

In some examples, the HtrA1 binding antagonist is an anti-HtrA1 antibody or an antigen-binding fragment thereof.

30 In some examples, the method further comprises administering to the subject a VEGF antagonist.

In some examples, the VEGF antagonist is an anti-VEGF antibody or an antigen-binding fragment thereof.

In another example, provided herein is a method of treating GA in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of any one of the antibodies disclosed herein or any one of the compositions disclosed herein.

35 In some examples, the antibody is an Fab fragment.

In some examples, the antibody or the composition is administered intravitreally, ocularly, intraocularly, juxtasclerally, subtenonally, superchoroidally, topically, intravenously, intramuscularly, intradermally, percutaneously, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly,

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intraprostatically, intrapleurally, intratracheally, intrathecally, intranasally, intravaginally, intrarectally, topically, intratumorally, intraperitoneally, peritoneally, intraventricularly, subcutaneously, subconjunctivally, intravesicularly, mucosally, intrapericardially, intraumbilically, intraorbitally, orally, transdermally, by inhalation, by injection, by eye drop, by implantation, by infusion, by continuous
5 infusion, by localized perfusion bathing target cells directly, by catheter, by lavage, in cremes, or in lipid compositions.

In some examples, the antibody or the composition is administered intravitreally, ocularly, intraocularly, juxtasclerally, subtenonally, superchoroidally, or topically.

In some examples, the antibody or the composition is administered intravitreally by injection.

10 In some examples, the antibody or the composition is administered topically by eye drop or ointment.

In some examples, the antibody or the composition is administered by a port delivery device.
In some examples, the subject is a human.

15 **Brief Description of the Drawings**

FIGS. 1A and 1B are sequence alignments of the heavy chain variable region (VH) and light chain variable region (VL) sequences of the 1E1 hybridoma and 1E1v8 anti-IL-33 antibody clones. Complementarity-determining region (CDR) sequences according to Kabat definition are underlined.

20 **FIGS. 2A and 2B** are sequence alignments of the VH and VL sequences of the indicated anti-IL-33 antibody clones. CDR sequences according to Kabat definition are underlined.

FIG. 3A is a network plot showing relationships between clones or bins of anti-IL-33 antibody clones based on blocking activity.

FIG. 3B is a heatmap showing relationships between clones or bins of anti-IL-33 antibody clones based on blocking activity.

25 **FIGS. 3C-3E** are a series of graphs showing results of epitope binning using surface plasmon resonance (SPR). The graphs show normalized response as a function of time.

Detailed Description of Embodiments of the Invention

I. Definitions

30 The term “about” as used herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter *per se*.

An “acceptor human framework” for the purposes herein is a framework comprising the amino acid sequence of a light chain variable domain (VL) framework or a heavy chain variable domain (VH) framework derived from a human immunoglobulin framework or a human consensus framework, as
35 defined below. An acceptor human framework “derived from” a human immunoglobulin framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain amino acid sequence changes. In some embodiments, the number of amino acid changes are 10 or less, 9 or less, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less. In some embodiments,
40

WHAT IS CLAIMED IS:

1. An isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising a heavy chain variable (VH) domain and a light chain variable (VL) domain, the binding domain comprising the following six complementarity-determining regions (CDRs):

- (a) a CDR-H1 comprising the amino acid sequence of NYWMT (SEQ ID NO: 1);
- (b) a CDR-H2 comprising the amino acid sequence of SITYTGGGTYYPDSVKG (SEQ ID NO: 2);
- (c) a CDR-H3 comprising the amino acid sequence of ANYYYNTYGGFPY (SEQ ID NO: 3);
- (d) a CDR-L1 comprising the amino acid sequence of LASEGFSNDLA (SEQ ID NO: 4);
- (e) a CDR-L2 comprising the amino acid sequence of AASRLQD (SEQ ID NO: 5); and
- (f) a CDR-L3 comprising the amino acid sequence of QQGSKYPLT (SEQ ID NO: 6).

2. An isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 7; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 8; or (c) a VH domain as in (a) and a VL domain as in (b).

3. The antibody of claim 1 or 2, wherein the VH domain comprises:

- (a) an FR-H1 comprising the amino acid sequence of EVQLVX₁SGX₂X₃X₄X₅X₆PGX₇SX₈X₉X₁₀SCX₁₁ASGFTFN (SEQ ID NO: 9), wherein X₁ is E or Q; X₂ is G or A; X₃ is G or E; X₄ is L or V; X₅ is V or K; X₆ is Q or K; X₇ is G, A, or T; X₈ is L or V; X₉ is R or K; X₁₀ is L or V; and X₁₁ is A, K, or L;
- (b) an FR-H2 comprising the amino acid sequence of WX₁RQAPGX₂GLEWX₃X₄ (SEQ ID NO: 10), wherein X₁ is I or V; X₂ is K or Q; X₃ is V, M, or I; and X₄ is A or G;
- (c) an FR-H3 comprising the amino acid sequence of RX₁TX₂X₃RDX₄X₅X₆X₇X₈X₉YX₁₀X₁₁X₁₂X₁₃SLRX₁₄EDTAX₁₅YYCTR (SEQ ID NO: 11), wherein X₁ is F or V; X₂ is I or M; X₃ is S or T; X₄ is D, N, or T; X₅ is A or S; X₆ is K or T; X₇ is S or N; X₈ is S or T; X₉ is L or V; X₁₀ is L or M; X₁₁ is Q or E; X₁₂ is M or L; X₁₃ is N or S; X₁₄ is A or S; and X₁₅ is V or T; and
- (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVSS (SEQ ID NO: 12).

4. The antibody of any one of claims 1-3, wherein the VH domain comprises:

- (a) an FR-H1 comprising the amino acid sequence of EVQLVESGGGLVQPGGSLRLSCAASGFTFN (SEQ ID NO: 17);
- (b) an FR-H2 comprising the amino acid sequence of WIRQAPGKGLEWVA (SEQ ID NO: 18);
- (c) an FR-H3 comprising the amino acid sequence of RFTISRDDAKSSLYLQMNSLRAEDTAVYYCTR (SEQ ID NO: 19); and
- (d) an FR-H4 comprising the amino acid sequence of WGQGTLTVSS (SEQ ID NO: 12).

5. The antibody of any one of claims 1-3, wherein the VH domain comprises the amino acid sequence of SEQ ID NO: 7.

6. The antibody of any one of claims 1-5, wherein the VL domain comprises:

(a) an FR-L1 comprising the amino acid sequence of

X₁IX₂X₃TQSPX₄X₅LSX₆SX₇GX₈X₉X₁₀X₁₁X₁₂X₁₃C (SEQ ID NO: 13), wherein X₁ is D or E; X₂ is Q or V; X₃ is M or L; X₄ is S or A; X₅ is S or T; X₆ is A or L; X₇ is V, P, or L; X₈ is D or E; X₉ is R or T; X₁₀ is V or A; X₁₁ is T or S; X₁₂ is I or L; and X₁₃ is T, S, or E;

(b) an FR-L2 comprising the amino acid sequence of WX₁QKX₂GX₃X₄PX₅X₆LIY (SEQ ID NO: 14), wherein X₁ is Y or F; X₂ is P or S; X₃ is K or Q; X₄ is S or A; X₅ is K, R, or Q; and X₆ is L or S;

(c) an FR-L3 comprising the amino acid sequence of

GX₁PX₂RFSGSGSGTX₃FX₄LX₅ISX₆X₇X₈PEDX₉AX₁₀YX₁₁C (SEQ ID NO: 15), wherein X₁ is V or I; X₂ is S or A; X₃ is D or R; X₄ is T or S; X₅ is T or K; X₆ is S or G; X₇ is L or M; X₈ is Q or E; X₉ is F, V, or E; X₁₀ is T, V, or D; and X₁₁ is F or Y; and

(d) an FR-L4 comprising the amino acid sequence of FGX₁GTX₂EIK (SEQ ID NO: 16), wherein X₁ is G or S and X₂ is V or L.

7. The antibody of any one of claims 1-5, wherein the VL domain comprises:

(a) an FR-L1 comprising the amino acid sequence of DIQMTQSPSSLSASVGDRVITTC (SEQ ID NO: 21);

(b) an FR-L2 comprising the amino acid sequence of WYQQKPGKSPKLLIY (SEQ ID NO: 22);

(c) an FR-L3 comprising the amino acid sequence of GVPSRFSGSGSGTDFTLTISLQPEDFATYFC (SEQ ID NO: 23); and

(d) an FR-L4 comprising the amino acid sequence of FGGGTKVEIK (SEQ ID NO: 24).

8. The antibody of any one of claims 1-5, wherein the VL domain comprises the amino acid sequence of SEQ ID NO: 8.

9. An isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a VH domain comprising the amino acid sequence of SEQ ID NO: 7 and (b) a VL domain comprising the amino acid sequence of SEQ ID NO: 8.

10. An isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises a binding domain comprising (a) a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 25 and (b) a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 26.

11. An isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises:

[illegible]

(xxi) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 48 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 59;

(xxii) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 50 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 59; or

(xxiii) a binding domain comprising (a) a VH domain comprising an amino acid sequence of SEQ ID NO: 52 and (b) a VL domain comprising an amino acid sequence of SEQ ID NO: 61.

12. An isolated antibody that specifically binds IL-33, or an antigen-binding fragment thereof, wherein the antibody comprises:

(i) a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 35; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 36; or (c) a VH domain as in (a) and a VL domain as in (b);

(ii) a binding domain comprising (a) a heavy chain (HC) comprising an amino acid sequence of SEQ ID NO: 37 and (b) a light chain (LC) comprising an amino acid sequence of SEQ ID NO: 38; or

(iii) a binding domain comprising (a) a VH domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 65; (b) a VL domain comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 69; or (c) a VH domain as in (a) and a VL domain as in (b).

13. The antibody of any one of claims 1-12, wherein the antibody specifically binds both human and cynomolgus monkey (cyno) interleukin-33 (IL-33) with a K_D of about 1 nM or lower and/or inhibits the binding of human IL-33 to an IL-33 receptor with a 50% inhibitory concentration (IC₅₀) of between about 800 fM and about 100 pM.

14. The antibody of any one of claims 1-13, wherein the antibody has a viscosity of less than about 5 centipoise (cP) at a concentration of about 180 mg/mL and/or a turbidity (optical density (OD)) of about 0.5 or lower at a concentration of about 150 mg/mL or higher in phosphate-buffered saline (PBS) pH 7.4.

15. The antibody of any one of claims 1-14, wherein the antibody is monoclonal, human, humanized, or chimeric.

16. The antibody of any one of claims 1-15, wherein the antibody is an antibody fragment that binds IL-33.

17. The antibody of claim 16, wherein the antibody fragment is an Fab, Fab'-SH, Fv, scFv, or (Fab')₂ fragment.

18. The antibody of any one of claims 1-17, wherein the antibody is a monospecific antibody.

19. The antibody of any one of claims 1-17, wherein the antibody is a multispecific antibody.

20. The antibody of claim 19, wherein the antibody is a bispecific antibody.
21. An isolated nucleic acid or a set of isolated nucleic acids encoding the antibody of any one of claims 1-20.
22. A vector or a set of vectors comprising the isolated nucleic acid or set of isolated nucleic acids of claim 21.
23. A host cell comprising the vector or the set of vectors of claim 22.
24. A method of producing an antibody that specifically binds to IL-33, the method comprising culturing the host cell of claim 23 in a culture medium.
25. A pharmaceutical composition comprising the antibody of any one of claims 1-20, further comprising a pharmaceutically acceptable carrier, excipient, or diluent.
26. Use of the antibody of any one of claims 1-20 in the manufacture of a medicament for treating an IL-33-mediated disorder in a subject in need thereof.
27. The use of claim 26, wherein the IL-33-mediated disorder is an ocular disorder, an inflammatory condition, an immune disorder, a fibrotic disorder, an eosinophilic disorder, an infection, pain, a central nervous system disorder, or a solid tumor.
28. The use of claim 27, wherein the ocular disorder is AMD, retinopathy of the eye, PCV, diabetic macular edema, dry eye disease, Behcet's disease, retina detachment, glaucoma, uveitis, retinitis pigmentosa, Leber Congenital Amaurosis, Stargardt's disease, traumatic eye injury, or conjunctivitis.
29. The use of claim 28, wherein the AMD is GA, wet AMD, or dry AMD.
30. The use of any one of claims 26-29, wherein the medicament is for administration with an ST2 binding antagonist, a Factor D binding antagonist, an HtrA1 binding antagonist, a VEGF antagonist, a tryptase-beta binding antagonist, a CRTH2 binding antagonist, an IL-13 binding antagonist, an IL-17 binding antagonist, a JAK1 antagonist, and/or an IL-5 binding antagonist.
31. The use of any one of claims 26-30, wherein the antibody is to be administered intravitreally, ocularly, intraocularly, juxtasclerally, subtenonally, superchoroidally, topically, intravenously, intramuscularly, intradermally, percutaneously, intraarterially, intraperitoneally, intralesionally, intracranially, intraarticularly, intraprostatically, intrapleurally, intratracheally, intrathecally, intranasally, intravaginally, intrarectally, topically, intratumorally, intraperitoneally, peritoneally, intraventricularly,

subcutaneously, subconjunctivally, intravesicularly, mucosally, intrapericardially, intraumbilically, intraorbitally, orally, transdermally, by inhalation, by injection, by eye drop, by implantation, by infusion, by continuous infusion, by localized perfusion bathing target cells directly, by catheter, by lavage, in cremes, or in lipid compositions.