

Anti-IL-34 antibodies have been described in the art, and for example, WO 2016/196679 recites various anti-IL-34 antibodies and potential uses thereof. However, to date, no antibody targeting IL-34 has been approved for therapeutic use.

Thus, there remains an unmet need for alternative and/or improved anti-IL-34 antibodies, pharmaceutical compositions thereof, and methods of using the same for therapeutic and/or in diagnostic applications relating to immune-mediated diseases involving IL-34, and/or diseases treatable with an anti-IL-34 antibody, such as neuroinflammatory disorders, and/or Alzheimer's Disease. Further, there remains an unmet need for alternative and/or improved anti-IL-34 antibodies which have a combination of particularly advantageous properties over prior art anti-IL-34 antibodies, in view of at least one or more properties from the following: 1) desirable association and dissociation rates, 2) potency in neutralization of human IL-34 to achieve an anti-neuroinflammatory response and *in vivo* efficacy, 3) sufficiently potent as a monotherapy for the treatment and/or prevention of immune-mediated and/or inflammatory disorders; 4) a sustained duration of action; 5) sufficiently limited induction of undesirable cytokine release, 6) acceptably low immunogenicity (i.e., sufficiently non-immunogenic in humans); 7) avoidance of untoward immunocompromise; and/or 8) desirable *in vivo* stability, physical and chemical stability including, but not limited to, thermal stability, solubility, low self-association, and pharmacokinetic characteristics which are acceptable for development and/or use in the treatment of inflammatory or neuroinflammatory disorders, for example AD.

Summary of Invention:

In one aspect of the present disclosure, there is provided an antibody that binds human IL-34 wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions (HCDR) HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions (LCDR) LCDR1, LCDR2, and LCDR3, wherein

the HCDR1 comprises SEQ ID NO: 5,

the HCDR2 comprises SEQ ID NO: 6,

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the HCDR3 comprises SEQ ID NO: 7,
the LCDR1 comprises SEQ ID NO: 8,
the LCDR2 comprises SEQ ID NO: 9, and
the LCDR3 comprises SEQ ID NO: 10.

In another aspect of the present disclosure, there is provided an antibody that binds human IL-34 comprising a VH and a VL, wherein the VH comprises HCDR1, HCDR2, and HCDR3, and the VL comprises LCDR1, LCDR2, and LCDR3, wherein

the HCDR1 comprises SEQ ID NO: 15,
the HCDR2 comprises SEQ ID NO: 16,
the HCDR3 comprises SEQ ID NO: 17,
the LCDR1 comprises SEQ ID NO: 8,
the LCDR2 comprises SEQ ID NO: 9, and
the LCDR3 comprises SEQ ID NO: 10.

In a further aspect of the present disclosure, there is provided an antibody that binds murine IL-34 wherein the antibody comprises a VH and a VL, wherein the VH comprises HCDR1, HCDR2, and HCDR3, and the VL comprises LCDR1, LCDR2, and LCDR3, wherein

the HCDR1 comprises SEQ ID NO: 23,
the HCDR2 comprises SEQ ID NO: 24,
the HCDR3 comprises SEQ ID NO: 25,
the LCDR1 comprises SEQ ID NO: 26,
the LCDR2 comprises SEQ ID NO: 27, and
the LCDR3 comprises SEQ ID NO: 28.

In another aspect of the present disclosure, there is provided a nucleic acid comprising a sequence encoding a SEQ ID NO selected from one or more of the group consisting of: 11, 12, 18, 29, and 30.

In a further aspect of the present disclosure, there is provided a vector comprising the nucleic acid disclosed herein.

In another aspect of the present disclosure, there is provided a composition comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 11 or 18, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 12.

In a further aspect of the present disclosure, there is provided a composition comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 29, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 30.

In another aspect of the present disclosure, there is provided a cell comprising the vector disclosed herein.

In a further aspect of the present disclosure, there is provided a cell comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 11 or 18, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 12.

In another aspect of the present disclosure, there is provided a cell comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 29, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 30.

In a further aspect of the present disclosure, there is provided a process of producing an antibody comprising culturing the cell disclosed herein under conditions such that the antibody is expressed and recovering the expressed antibody from the culture medium.

In another aspect of the present disclosure, there is provided an antibody produced by the process disclosed herein.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the antibody disclosed herein, and a pharmaceutically acceptable excipient, diluent or carrier.

In another aspect of the present disclosure, there is provided an antibody disclosed herein for use in therapy.

In a further aspect of the present disclosure, there is provided an antibody disclosed herein, or the pharmaceutical composition disclosed herein, for use in the treatment of an immune-mediated disease.

In another aspect of the present disclosure, there is provided a use of the antibody disclosed herein, in the manufacture of a medicament for the treatment of an immune-mediated disease.

In a further aspect of the present disclosure, there is provided a method of determining the human IL-34 level in a bodily fluid comprising:

- (a) contacting the bodily fluid with an anti-human IL-34 diagnostic monoclonal antibody, or antigen-binding fragment thereof, that specifically binds to human IL-34 consisting of the amino acid sequence as in SEQ ID NO: 41, the antibody, or antigen-binding fragment thereof, comprising: light chain complementarity determining regions LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences (SEQ ID NO: 8), (SEQ ID NO: 9), and (SEQ ID NO: 10), respectively, and heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences (SEQ ID NO: 15), (SEQ ID NO: 16), and (SEQ ID NO: 17), respectively;
- (b) optionally, removing any non-specifically bound monoclonal antibody or, antigen-binding fragment thereof, wherein said contacting occurs *ex vivo*; and
- (c) detecting and/or quantifying the amount of monoclonal antibody, or antigen-binding fragment thereof, which is specifically bound to human IL-34.

~~Embodiment~~Examples of the present ~~invention~~disclosure provide novel anti-human IL-34 and anti-murine IL-34 antibodies. According to some ~~embodiment~~examples, the present ~~invention~~disclosure provides antibodies which comprise a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the LCVR comprises complementarity determining regions (CDRs) LCDR1, LCDR2 and LCDR3 and the HCVR comprises CDRs HCDR1, HCDR2 and HCDR3 are selected from the groupings of CDR combinations provided in

Table 1. The sequence identifiers used herein are listed in Table 1, and the sequences are provided in the amino acid and nucleotide sequence listing provided herein.

Table 1: Amino Acid and Nucleotide Sequences

	Antibody 1	Antibody 2	Antibody 3
SEQ ID HC	1	13	19
SEQ ID LC	2	2	20
SEQID HCVR	3	14	21
SEQID LCVR	4	4	22
SEQID HCDR1	5	15	23
SEQID HCDR2	6	16	24
SEQID HCDR3	7	17	25
SEQID LCDR1	8	8	26
SEQID LCDR2	9	9	27
SEQID LCDR3	10	10	28
SEQ ID: DNA HC	11	18	29
SEQ ID DNA LC	12	12	30

Accordingly, embodimentexamples of the present inventiondisclosure also provide antibodies comprising a LCVR and a HCVR selected from:

- a. the LCVR having the amino acid sequence of SEQ ID NO: 4 and the HCVR having the amino acid sequence of SEQ ID NO: 3;
- b. the LCVR having the amino acid sequence of SEQ ID NO: 4 and the HCVR having the amino acid sequence of SEQ ID NO: 14;
- c. the LCVR having the amino acid sequence of SEQ ID NO: 22 and the HCVR having the amino acid sequence of SEQ ID NO: 21.

According to other embodimentexamples, the present inventiondisclosure also provides antibodies comprising a combination of LCVR and HCVR as described above in a-c, with a hinge region and Fc region selected from SEQ ID NO: 51 and SEQ ID NO: 52.

According to other ~~embodiment~~examples, the present ~~invention~~disclosure also provides antibodies comprising a LC and a HC selected from, or having amino acid sequences with at least 95% homology to the amino acid sequences of:

- a. the LC having the amino acid sequence of SEQ ID NO: 2 and the HC having the amino acid sequence of SEQ ID NO: 1;
- b. the LC having the amino acid sequence of SEQ ID NO: 2 and the HC having the amino acid sequence of SEQ ID NO: 13; and
- c. the LC having the amino acid sequence of SEQ ID NO: 20 and the HC having the amino acid sequence of SEQ ID NO: 19.

As used herein “Antibody 1” refers to an antibody having the HCDR1 amino acid sequence of SEQ ID NO: 5, the HCDR2 amino acid sequence of SEQ ID NO: 6, the HCDR3 amino acid sequence of SEQ ID NO: 7, the LCDR1 amino acid sequence of SEQ ID NO: 8, the LCDR2 amino acid sequence of SEQ ID NO: 9, the LCDR3 amino acid sequence of SEQ ID NO: 10, the HCVR amino acid sequence of SEQ ID NO: 3, the LCVR amino acid sequence of SEQ ID NO: 4, the HC amino acid sequence of SEQ ID NO: 1, the LC amino acid sequence of SEQ ID NO: 2, the HC DNA sequence of SEQ ID NO: 11, and the LC DNA sequence of SEQ ID NO: 12. The framework and CDR sequences in each of the antibodies for which sequences are set forth herein are annotated using annotation rules in agreement with the method of North, *et al.*, *J. Mol. Biol.* 2011: 406: 228-256 unless otherwise specified.

As used herein “Antibody 2” refers to an antibody having the HCDR1 amino acid sequence of SEQ ID NO: 15, the HCDR2 amino acid sequence of SEQ ID NO: 16, the HCDR3 amino acid sequence of SEQ ID NO: 17, the LCDR1 amino acid sequence of SEQ ID NO: 8, the LCDR2 amino acid sequence of SEQ ID NO: 9, the LCDR3 amino acid sequence of SEQ ID NO: 10, the HCVR amino acid sequence of SEQ ID NO: 14, the LCVR amino acid sequence of SEQ ID NO: 4, the HC amino acid sequence of SEQ ID NO: 13, the LC amino acid sequence of SEQ ID NO: 2, the HC DNA sequence of SEQ ID NO: 18, and the LC DNA sequence of SEQ ID NO: 12. The framework and CDR sequences in each of the antibodies for which sequences are set forth herein are

annotated using annotation rules in agreement with the method of North, *et al.* *J. Mol. Biol.* 2011: 406: 228-256 unless otherwise specified.

As used herein “Antibody 3” refers to an antibody having the HCDR1 amino acid sequence of SEQ ID NO: 23, the HCDR2 amino acid sequence of SEQ ID NO: 24, the HCDR3 amino acid sequence of SEQ ID NO: 25, the LCDR1 amino acid sequence of SEQ ID NO: 26, the LCDR2 amino acid sequence of SEQ ID NO: 27, the LCDR3 amino acid sequence of SEQ ID NO: 28, the HCVR amino acid sequence of SEQ ID NO: 21, the LCVR amino acid sequence of SEQ ID NO: 22, the HC amino acid sequence of SEQ ID NO: 19, the LC amino acid sequence of SEQ ID NO: 20, the HC DNA sequence of SEQ ID NO: 29, and the LC DNA sequence of SEQ ID NO: 30. The framework and CDR sequences in each of the antibodies for which sequences are set forth herein are annotated using annotation rules in agreement with the method of North, *et al.* *J. Mol. Biol.* 2011: 406: 228-256 unless otherwise specified.

The carboxy-terminal portion of each HC defines a constant region primarily responsible for effector functions, and in some embodimentexamples of the present inventiondisclosure the antibodies have one or more modifications in the constant region of each HC that reduce effector functions. Preferably, embodimentexamples of the present inventiondisclosure are IgG4 antibodies, and thus contain an IgG4 Fc region, or an Fc region derived from human IgG4, e.g., a modified IgG4 Fc region.

According to some embodimentexamples, modifications in the constant region of both HCs which reduce effector functions, and amino acid substitutions are introduced into the IgG4 hinge and Fc regions. Thus, some embodimentexamples have modifications in the constant region of both HCs which include the amino acid alanine at both residues 230 and 231 (exemplified in HC of Antibody 1, HC of Antibody 2, and SEQ ID NO: 52, respectively), and further modifications in the constant region of both HCs promoting stability, including the amino acid proline at residue 224 (exemplified in HC of Antibody 1, HC of Antibody 2, and for example in SEQ ID NO: 51), and the deletion of the amino acid lysine at residue 443 (exemplified HC of SEQ ID NO.1).

The antibodies of the present inventiondisclosure are believed to have a combination of particularly advantageous properties over prior art anti-IL-34 antibodies, including but

not limited to, one or more of the following properties: 1) desirable association and dissociation rates, 2) potency in neutralization of human IL-34 to achieve an anti-neuroinflammatory response and *in vivo* efficacy, 3) sufficiently potent as a monotherapy for the treatment and/or prevention of immune-mediated and/or inflammatory disorders; 4) a sustained duration of action; 5) sufficiently limited induction of undesirable cytokine release, 6) acceptably low immunogenicity (i.e., sufficiently non-immunogenic in humans); 7) avoidance of untoward immunocompromise; and/or 8) desirable *in vivo* stability, physical and chemical stability including, but not limited to, thermal stability, solubility, low self-association, and pharmacokinetic characteristics which are acceptable for development and/or use in the treatment of inflammatory or neuroinflammatory disorders, for example AD.

Embodiment Examples of the present invention disclosure provide a significant advance over the prior art by providing compositions and methods useful in the prevention, downregulation, or amelioration of inflammatory and/or neuroinflammatory related disorders, through IL-34 neutralization, using a pharmacologically advantageous anti-human IL-34 antibody as provided in the embodiment examples described herein. Anti-human IL-34 antibodies of the present invention disclosure are capable of improving immune and/or inflammatory pathology, or restoring immune homeostasis, preferably, through inhibition of the innate arm of the immune response, and/or abrogation of microgliosis or other monocyte/macrophage lineage cellular activation and or proliferation, thereby directly modifying underlying disease pathology. The use of such antibodies clinically may lead to durable long-term improvement of the disease(s) being treated.

Further, there is a need for diagnostic anti-human IL-34 antibodies that are specific for human IL-34, and possess improved binding affinity, and demonstrate enhanced sensitivity in human IL-34 determinations, and improved enzyme-linked immunosorbent assay (ELISA) assay conditions that result in minimal interference and broad dilutional linearity. According to some aspects of the present invention disclosure, anti-human IL-34 antibodies, including human IL-34 neutralizing antibodies, are provided which bind human IL-34 given by SEQ ID NO: 41. Interleukin 34 (IL-34; also known as uncharacterized protein C16orf77) is secreted as a homodimer consisting of 39 kDa

monomers. It belongs to no known cytokine family. Human IL-34 is synthesized as a 242 amino acid (AA) precursor that contains a 20 AA signal sequence, and results in a 222 AA mature chain. As used herein IL-34 refers to the mature chain. The mature chain contains one potential site of N-linked glycosylation. Human IL-34 is 71% identical to mouse IL-34 on the amino acid level. IL-34 is expressed in various tissues, including the heart, brain, liver, kidney, spleen, thymus, testes, ovary, small intestine, prostate, and colon, and is most abundant in the spleen. “h IL-34” or “human IL-34” when used herein in reference to an IL-34 polypeptide, unless otherwise stated, refers to wild-type human IL-34, and preferably has the amino acid sequence set forth in SEQ ID NO: 41, which is mature IL-34 having the leader sequence removed. (See, for example, Lin et.al., Science (2008) Vol. 320, Issue 5877, pp. 807-811).

An exemplary human IL-34 (including the 20 AA signal peptide sequence which is removed to yield the mature polypeptide) is:

MPRGFTWLRYLGI FLGVALGNEPLEMWPLTQNEECTVTGFLRDKLQYRS
RLQYMKHYFPI NYKISVPYEGVFRIANVTRLQRAQVSERELRYLWVLVSLSATES
VQDVLLEGHP SWKYLQEVETLLLNVQQGLTDVEVSPKVESVLSLLNAPGPNLKL
VRPKALLDNCFRVMELLYCSCCKQSSVLNWQDCEVPSPQSCSPEPSLQYAATQL
YPPPPWSPSSPPHSTG SVRPVRAQGEGLLP

(SEQ ID NO: 41, see NCBI Ref. Seq. No. NP_689669.2, March 1, 2018).

According to some aspects of the present ~~invention~~disclosure, anti-murine IL-34 antibodies, including murine IL-34 neutralizing antibodies, are provided which bind human IL-34 given by SEQ ID NO. 42. An exemplary murine IL-34 (including the 20 AA signal peptide sequence which is removed to yield the mature polypeptide) is:

MPWGLAWLYCLGILLDVALGNENLEIWTLTQDKECDLTGYLRGKLQYK
NRLQYMKHYFPIN YRIAPYEGVLRVANITRLQKAHV SERELRYLWVLVSLNAT
ESVMDVLLEGHP SWKYLQEVQTLLENVQRSLMDVEIGPHVEAVLSLLSTPGLSL
KLVRPKALLDNCFRVMELLYCSCCKQSPILKWQDCEL PRLHPHSPGSLMQCTAT
NVYPLSRQTPTSLPGSPSSSHGSLP

(SEQ ID NO: 42, see NCBI Ref. Seq. No. NP_001128572.1, March 1, 2018).

As used herein, “human anti-IL34 antibody” or “anti-human IL-34 antibody” refers to an antibody that binds to human IL-34, and when administered *in vitro* or *in vivo*, results in an IL-34 activity-neutralizing and/or blocking response, such as at least one significantly lessened desired activity, for example a desired reduction in IL-34 signaling as evidenced by a change in an IL-34 responsive molecular or cellular endpoint. For instance, microglia number, density, or phenotype in the CNS, is an example of an IL-34 responsive molecular or cellular effect. As used herein, the terms “signaling” and “signal transduction” and “IL-34-mediated”, as they relate to IL-34, refer to cellular and/or intercellular responses which result from the activity of IL-34.

The term “antibody,” as used herein, refers to an immunoglobulin molecule that binds an antigen. ~~Embodiment~~Examples of an antibody include a monoclonal antibody, polyclonal antibody, human antibody, humanized antibody, chimeric antibody or conjugated antibody. The antibodies can be of any class (e.g., IgG, IgE, IgM, IgD, IgA) and any subclass (e.g., IgG1, IgG2, IgG3, IgG4). An exemplary antibody is an immunoglobulin G (IgG) type antibody comprised of four polypeptide chains: two heavy chains (HC) and two light chains (LC) that are cross-linked via inter-chain disulfide bonds. LCs are classified as kappa or lambda, which are each characterized by a specific constant region. ~~Embodiment~~Examples of the present ~~invention~~disclosure may comprise an IgG1 or IgG4 antibody, and further comprise kappa light chains or lambda light chains. Preferably antibodies of the present ~~invention~~disclosure comprise light chain constant regions which are kappa constant regions.

HCs are classified as gamma, mu, alpha, delta, or epsilon, and define the isotype of an antibody as IgG, IgM, IgA, IgD, or IgE, respectively. The amino-terminal portion of each of the four polypeptide chains includes a variable region of about 100-125 or more amino acids primarily responsible for antigen recognition. The carboxyl-terminal portion of each of the four polypeptide chains contains a constant region primarily responsible for effector functions. Each heavy chain is comprised of a heavy chain variable region (VH) and a heavy chain constant region. The constant region of the heavy chains contains CH1, CH2, and CH3 domains. CH1 comes after the HCVR; the CH1 and HCVR form the heavy chain portion of an antigen-binding (Fab) fragment, which is the part of an antibody that binds antigen(s). CH2 comes after the hinge region and before CH3. CH3

comes after CH2 and is at the carboxy-terminal end of the heavy chain. The constant region of the light chains contains one domain, CL. CL comes after the LCVR; the CL and LCVR form the light chain portion of a Fab.

The antibodies of the present ~~invention~~disclosure include IgG HCs which can be further divided into subclasses, e.g., IgG1, IgG2, IgG3, IgG4, and ~~embodiment~~examples of the present ~~invention~~disclosure may include one or more modifications in the constant region of each HC, for example that enhance or reduce effector function. The term “Fc region” as used herein refers to a region of an antibody, which comprises the CH2 and CH3 domains of the antibody heavy chain. Optionally, the Fc region may include a portion of the hinge region or the entire hinge region of the antibody heavy chain. IgG1 is known to induce antibody-dependent cell cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), and Fc mutations described herein may reduce aggregation, reduce or enhance ADCC or CDC activities, (or other functions), and/or modify the pharmacokinetics of the antibodies. ~~Embodiment~~Examples of anti-human IL-34 antibodies described herein have reduced binding to the FcγR and C1q receptors, thereby reducing or eliminating the cytotoxicity which may be induced by antibodies with wild type IgG Fc regions. Thus, according to some ~~embodiment~~examples, mutations are introduced in the Fc region at positions as described herein. Patient safety can be improved with sufficiently reduced or eliminated effector functions of such anti-human IL-34 antibodies comprising a modified Fc region, and in combination with other properties described herein, provide therapeutic agents with an improved profile of useful activities while avoiding undesirable activities.

When expressed in certain biological systems, antibodies are glycosylated in the Fc region. Typically, glycosylation occurs in the Fc region of the antibody at a highly conserved N-glycosylation site. N-glycans typically attach to asparagine. Antibodies may be glycosylated at other positions as well. Antibodies of the present ~~invention~~disclosure are monoclonal antibodies. Monoclonal antibodies are antibodies derived from a single copy or clone including, for example, any eukaryotic, prokaryotic or phage clone, and not defined by the method by which it is produced. Monoclonal antibodies can be produced, for example, by hybridoma technologies, recombinant technologies, phage display technologies, synthetic technologies, e.g., CDR-grafting, or combinations of such or other

technologies known in the art. The present ~~invention~~disclosure contemplates the antibodies of the present ~~invention~~disclosure are human or humanized antibodies. In the context of monoclonal antibodies, the terms “human” and “humanized” are well-known to those of ordinary skill in the art (Weiner LJ, J. Immunother. 2006; 29: 1-9; Mallbris L, et al., J. Clin. Aesthet. Dermatol. 2016; 9: 13-15). Exemplary ~~embodiment~~examples of antibodies of the present ~~invention~~disclosure also include antibody fragments or antigen-binding fragments, which comprise at least a portion of an antibody retaining the ability to specifically interact with an antigen such as Fab, Fab', F(ab')₂, Fv fragments, scFv antibody fragments, disulfide-linked Fvs (sdFv), a Fd fragment and linear antibodies.

The amino terminal portion of each LC and HC includes a variable region of about 100-120 amino acids primarily responsible for antigen recognition via the CDRs contained therein. The VH and VL regions can be further subdivided into regions of hyper-variability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). The CDRs are exposed on the surface of the protein and are important regions of the antibody for antigen binding specificity. Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxyl-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Herein, the three CDRs of the heavy chain are referred to as “HCDR1, HCDR2, and HCDR3” and the three CDRs of the light chain are referred to as “LCDR1, LCDR2 and LCDR3”. The CDRs contain most of the residues that form specific interactions with the antigen. The functional ability of an antibody to bind a specific antigen is largely influenced by the six CDRs. Assignment of amino acid residues to the CDRs may be done according to the well-known schemes, including those described in Kabat (Kabat et al., “Sequences of Proteins of Immunological Interest,” National Institutes of Health, Bethesda, Md. (1991)), Chothia (Chothia et al., “Canonical structures for the hypervariable regions of immunoglobulins”, Journal of Molecular Biology, 196, 901-917 (1987); Al-Lazikani et al., “Standard conformations for the canonical structures of immunoglobulins”, Journal of Molecular Biology, 273, 927-948 (1997)), North (North et al., “A New Clustering of Antibody CDR Loop Conformations”, Journal of Molecular

Biology, 406, 228-256 (2011)), or IMGT (the international ImMunoGeneTics database available on at www.imgt.org; see Lefranc et al., Nucleic Acids Res. 1999; 27:209-212).

For the purposes of the present ~~invention~~disclosure, and except where specified otherwise, the North CDR definitions are used for the anti-IL-34 antibodies described herein, and assignment of amino acids to CDR domains within the LCVR and HCVR regions. Below is table of CDR sequences for Antibody 1 based on North definitions. The skilled artisan can also apply alternative definitions of Kabat, Chothia, and/or IMGT, to specify CDR's according to those conventions for Antibodies of the present ~~invention~~disclosure including Antibodies 1-3 in Table 1.

Exemplary CDRs of Antibody 1 (or Antibodies of the present disclosure)						
Ab	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
North	AASGFTFSSY ATS (SEQ ID NO: 5)	AISHSGRSTY YADSVKG (SEQ ID NO: 6)	ARGRSSLDT (SEQ ID NO: 7)	RASQSISS AYLA (SEQ ID NO: 8)	YASSIRPT (SEQ ID NO: 9)	SQYGDSL (SEQ ID NO: 10)

Antibody ~~embodiment~~examples of the present ~~invention~~disclosure possess a combination of several pharmacologically useful and important activities, and in one respect are capable of binding with high affinity to human IL-34 and high specificity for human IL-34, as well as other useful properties. The terms “bind” and “binds” as used herein are intended to mean, unless indicated otherwise, the ability of a protein or molecule to form attractive interactions with another protein or molecule, which results in proximity of the two proteins or molecules as determined by common methods known in the art. The phrase “specifically binds”, as used herein in reference to the affinity of an anti-IL-34 antibody for human IL-34, is intended to mean, unless indicated otherwise, a K_D of preferably less than about 1×10^{-11} M, even more preferably, between about 1×10^{-11} M and about 1×10^{-12} M, as determined by common methods known in the art, including by use of a SPR biosensor, and/or MSD, essentially as described herein. The phrase “specifically binds” also indicates the relative affinity of an anti-IL-34 antibody for human IL-34, as

compared to other antigens, wherein the affinity for human IL-34 results in a specific recognition of human IL-34.

Antibody ~~embodiment~~examples of the present ~~invention~~disclosure may be expressed and produced by a variety of techniques known in the art from constructs comprising sequences of the present ~~embodiment~~examples. The terms “nucleic acid” or “polynucleotide”, as used interchangeably herein, refer to polymers of nucleotides, including single-stranded and / or double-stranded nucleotide-containing molecules, such as DNA, cDNA and RNA molecules, incorporating native, modified, and/or analogs of, nucleotides. Polynucleotides of the present disclosure may also include substrates incorporated therein, for example, by DNA or RNA polymerase or a synthetic reaction. A DNA molecule of the present ~~invention~~disclosure is a DNA molecule that comprises a non-naturally occurring polynucleotide sequence encoding a polypeptide having the amino acid sequence of at least one of the polypeptides in an antibody of the present ~~invention~~disclosure (e.g., heavy chain, light chain, variable heavy chain, and variable light chain).

An isolated DNA encoding a HCVR or LCVR region can be converted to a full-length heavy chain gene by operably linking the respective HCVR or LCVR-encoding DNA to another DNA molecule encoding heavy or light chain constant regions, to form a heavy or light chain respectively. The sequences of human, as well as other mammalian, heavy chain constant region genes are known in the art. DNA fragments encompassing these regions can be obtained, *e.g.*, by standard PCR amplification.

The polynucleotides of the present ~~invention~~disclosure can be expressed in a host cell after the sequences have been operably linked to an expression control sequence. The expression vectors are typically replicable in the host organisms either as episomes, or as an integral part of the host chromosomal DNA. Commonly, expression vectors will contain selection markers, *e.g.*, tetracycline, neomycin, and dihydrofolate reductase, to permit detection of those cells transformed with the desired DNA sequences. The vectors containing the polynucleotide sequences of interest (*e.g.*, the polynucleotides encoding the polypeptides of the antibody and expression control sequences) can be transferred into the host cell by well-known methods, which vary depending on the type of cellular host.

The antibodies of the present ~~invention~~disclosure can readily be produced in mammalian cells, non-limiting examples of which includes CHO, NS0, HEK293 or COS cells. The host cells are cultured using techniques well known in the art. Mammalian expression of antibodies typically results in glycosylation. Glycosylation of antibodies is typically either N-linked or O-linked. N-linked glycosylation refers to the attachment of a carbohydrate moiety to the side chain of an asparagine residue. O-linked glycosylation refers to the attachment of a sugar, for example N-acetylgalactosamine, galactose, or xylose to a hydroxyamino acid. Typically, glycosylation occurs in the Fc region of the antibody at a highly conserved N-glycosylation site (e.g., position 297 in IgG1, according to IMGT or EU Index numbering). Glycosylation sites can be modified to alter glycosylation (e.g., blocking or reducing glycosylation or altering the amino acid sequence to produce additional or diverse glycosylation).

Mammalian expression of antibodies from IgG subclasses can result in clipping of C-terminal amino acids from one or both heavy chains; for example, one or two C-terminal amino acids can be removed for IgG1 antibodies. For IgG1 antibodies, if a C-terminal lysine is present, then it may be truncated or clipped off from the heavy chain during expression. Additionally, a penultimate glycine may also be truncated or clipped off from the heavy chain as well.

Mammalian expression of antibodies can also result in the modification of N-terminal amino acids. For example, where the N-terminal most amino acid of a heavy chain or light chain is a glutamine, it may be modified into pyro-glutamic acid.

An antibody of the present ~~invention~~disclosure, or a pharmaceutical composition comprising the same, may be administered by parenteral routes, non-limiting examples of which are subcutaneous administration and intravenous administration. An antibody of the present ~~invention~~disclosure may be administered to a patient with pharmaceutically acceptable carriers, diluents, or excipients in single or multiple doses. Pharmaceutical compositions of the present ~~invention~~disclosure can be prepared by methods well known in the art (e.g., Remington: The Science and Practice of Pharmacy, 22nd ed. (2012), A. Loyd et al., Pharmaceutical Press) and comprise an antibody, as disclosed herein, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

Uses of antibody ~~embodiment~~examples of the present ~~invention~~disclosure:

According to some ~~embodiment~~examples, the anti-IL-34 antibodies of the present ~~invention~~disclosure are useful in the treatment of immune-mediated diseases. As used herein, the term “immune-mediated disease” or “inflammatory disease or disorder” are used interchangeably and refer to undesirable conditions that arise from an inappropriate, or excessive immune responses in which IL-34 inhibition results in more homeostatic and less pathological responses. The term “immune-mediated disease” or “inflammatory disorder” is meant to include such conditions, whether they be mediated by microglia or macrophage cellular immune responses, or those of similar tissue-resident cell types, such as histiocytes, Kupffer cells, alveolar macrophages, intestinal macrophages, macrophage-like synoviocytes, or Langerhans cells. Exemplary diseases contemplated to be treated by the antibodies of the ~~invention~~disclosure described herein include Alzheimer’s Disease; a Tauopathy disease; Sjogren’s syndrome (SS); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD), atopic dermatitis, kidney disease, sepsis, and/or non-alcoholic fatty liver disease (NAFLD).

In some more specific ~~embodiment~~examples, the immune-mediated disease is Alzheimer’s Disease (AD). According to other ~~embodiment~~examples of the present ~~invention~~disclosure, the anti-IL-34 antibodies are useful in diagnostic applications for immune-mediated diseases. In some ~~embodiment~~examples, the immune-mediated diseases are at least one of AD; Sjogren’s syndrome (SS); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD), atopic dermatitis, kidney disease, sepsis, and/or non-alcoholic fatty liver disease (NAFLD).

The present ~~invention~~disclosure further provides pharmaceutical compositions comprising an anti-IL-34 antibody of the present ~~invention~~disclosure and one or more pharmaceutically acceptable carriers, diluents or excipients. Further, the present ~~invention~~disclosure provides a method of treating an immune-mediated disease, such as AD; Sjogren’s syndrome (SS); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD), atopic dermatitis, kidney disease, sepsis, and/or non-alcoholic fatty liver disease (NAFLD), comprising administering to a patient in need thereof a pharmaceutical composition of the present ~~invention~~disclosure.

In addition, the present [inventiondisclosure](#) provides a method of treating immune-mediated diseases. More particularly, the present [inventiondisclosure](#) provides a method of treating immune-mediated diseases, including AD; Sjogren's syndrome (SS); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD), atopic dermatitis, kidney disease, sepsis, and/or non-alcoholic fatty liver disease (NAFLD), comprising administering to a patient in need thereof an effective amount of an anti-IL-34 antibody of the present [inventiondisclosure](#).

The present [inventiondisclosure](#) also provides an anti-IL-34 antibody of the present [inventiondisclosure](#) for use in therapy. More particularly, the present [inventiondisclosure](#) provides an anti-IL-34 antibody of the present [inventiondisclosure](#) for use in treatment of immune-mediated diseases including AD; Sjogren's syndrome (SS); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD), atopic dermatitis, kidney disease, sepsis, and/or non-alcoholic fatty liver disease (NAFLD).

In certain [embodimentexamples](#), the present [inventiondisclosure](#) provides the use of an anti-IL-34 antibody of the present [inventiondisclosure](#) in the manufacture of a medicament for the treatment of one or more immune-mediated diseases including AD; Sjogren's syndrome (SS); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD), atopic dermatitis, kidney disease, sepsis, and/or non-alcoholic fatty liver disease (NAFLD).

Antibodies of the present [inventiondisclosure](#) are useful in the identification of immune-mediated disorders wherein IL-34 may contribute to the etiopathogenesis of the disorder. In further [embodimentexamples](#), the present [inventiondisclosure](#) provides a method of treating an immune-mediated disease in a patient. Such methods comprise the steps of contacting a patient sample with an anti-IL-34 antibody and detecting binding between human IL-34 in the patient sample and the antibody; and diagnosing the patient as having; at risk for; in need of treatment for; and/or at risk of symptoms relating to an immune-mediated disease when the presence of IL-34 in the patient sample is detected as above a reference value observed in non-diseased individuals (See for example Xie, H.H., et al. *Elevated Serum Interleukin-34 Level in Patients with Systemic Lupus Erythematosus Is Associated with Disease Activity*. Sci Rep 8, 3462 (2018). According to some more specific [embodimentexamples](#) of the methods of treating provided herein, such methods further include the steps of determining the reference value including the further steps of contacting a control

standard with a first antibody which binds the same first epitope region of IL-34 as used in contacting the patient sample; contacting the control standard with a second antibody having a detectable label and which binds the same second epitope region of IL-34 as used in contacting the patient sample; and detecting a signal provided by the detectable signal. In some specific [embodimentexamples](#), the anti-IL-34 antibody comprises a combination of LC and HC CDRs provided in Table 1. In further [embodimentexamples](#), the second antibody comprises a combination of LCVR and HCVR provided in Table 1. According to some [embodimentexamples](#), the reference value is approximately 10-30pg/mL, for example from CNS tissue lysates. In certain [embodimentexamples](#), the immune-mediated disease is one of AD; Sjogren's syndrome (SS); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD), atopic dermatitis, kidney disease, sepsis, and/or non-alcoholic fatty liver disease (NAFLD). In some [embodimentexamples](#), the patient sample is one of CSF, blood, serum, a tissue lysate, or plasma. According to some [embodimentexamples](#), the method further includes the steps of contacting the patient sample with a second anti-IL-34 antibody which binds a second epitope region of IL-34, and has a detectable label, and detecting a signal provided by the detectable signal. In further [embodimentexamples](#), the second antibody comprises a combination of LC and HC CDRs provided in Table 1. In further [embodimentexamples](#), the second antibody comprises a combination of LCVR and HCVR provided in Table 1. According to certain [embodimentexamples](#), the first and second anti-IL-34 antibodies do not bin together.

According to some [embodimentexamples](#), the present [inventiondisclosure](#) provides a method of detecting IL-34 in a patient sample comprising the steps of contacting the patient sample with a first antibody which binds a first epitope region of IL-34; contacting the patient sample with a second antibody which binds a second epitope region of IL-34 and has a detectable label; and detecting a signal provided by said detectable label. In some [embodimentexamples](#), the patient sample is one of blood, serum, a tissue lysate or plasma. According to some more specific [embodimentexamples](#), the first epitope region of IL-34 partially overlaps with the second epitope region of IL-34. Further, in some [embodimentexamples](#), said steps of contacting with the first and second antibodies occurs simultaneously. In some specific [embodimentexamples](#), the first antibody comprises a combination of LC and HC CDRs

provided in Table 1. In further [embodimentexamples](#), the first antibody comprises a combination of LCVR and HCVR provided in Table 1.

According to some [embodimentexamples](#) of the present [inventiondisclosure](#), a method of quantifying IL-34 in a patient sample is provided. Such method includes the steps of contacting the patient sample with a first antibody which binds a first epitope region of IL-34; contacting the patient sample with a second antibody which binds a second epitope region of IL-34 and said has a detectable label; and detecting the signal provided by said detectable label;

contacting a control standard with a first antibody which binds the same first epitope region of IL-34 (as used in contacting the patient sample); contacting the control standard with a second antibody which binds the same second epitope region of IL-34 (as used in contacting the patient sample) and having a detectable label; and detecting a signal provided by said detectable signal. In some [embodimentexamples](#), the patient sample is one of blood, serum or plasma, or a tissue lysate. According to some more specific [embodimentexamples](#), the first epitope region of IL-34 partially overlaps with the second epitope region of IL-34. Further, in some [embodimentexamples](#), said steps of contacting with the first and second antibodies occurs simultaneously. In some specific [embodimentexample](#), the first antibody comprises a combination of LC and HC CDRs provided in Table 1. In further [embodimentexamples](#), the first antibody comprises a combination of LCVR and HCVR provided in Table 1. In some specific [embodimentexamples](#), the second antibody comprises a combination of LC and HC CDRs provided in Table 1. In further [embodimentexamples](#), the second antibody comprises a combination of LCVR and HCVR provided in Table 1.

According to some [embodimentexamples](#), a method of diagnosing an immune-mediated disease is provided. Such method comprises the steps of contacting a patient sample with an anti-IL-34 antibody and detecting binding between IL-34 in the patient sample and the antibody. According to some specific [embodimentexample](#), the method of diagnosing includes diagnosing the patient as having; at risk for; in need of treatment for; and/or at risk of symptoms relating to an immune-mediated disease when the presence of IL-34 in the patient sample is detected as above a reference value. According to some more specific [embodimentexamples](#), such methods further include the steps of determining the reference value including the steps of contacting a control standard with a first antibody which binds the

same first epitope region of IL-34 as used in contacting the patient sample; contacting the control standard with a second antibody having a detectable label and which binds the same second epitope region of IL-34 as used in contacting the patient sample; and detecting a signal provided by the detectable signal. In some [embodimentexamples](#), the first antibody comprises a combination of LC and HC CDRs provided in Tables 1. Some [embodimentexamples](#) of the method of diagnosing an immune-mediated disease, provided herein, further includes the steps of contacting the patient sample with a second anti-IL-34 antibody which binds a second epitope region of IL-34 and has a detectable label; and detecting a signal provided by the detectable label. In some specific [embodimentexamples](#), the anti-IL-34 antibody comprises a combination of LC and HC CDRs provided in Table 1. In further [embodimentexamples](#), the antibody comprises a combination of LCVR and HCVR provided in Table 1. According to specific [embodimentexamples](#), the first epitope region of IL-34 partially overlaps with the second epitope region of IL-34. According to certain [embodimentexamples](#), the first and second antibodies do not bin together. According to further [embodimentexamples](#), the reference value is approximately a range from 10-30 pg/mL from CNS tissue lysates, and/ or as determined by the skilled artisan for the appropriate reference group and sample source. In further [embodimentexamples](#), the immune-mediated disease is one of AD; a tauopathy; Sjogren's syndrome (SS); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD), atopic dermatitis, kidney disease, sepsis, and/or non-alcoholic fatty liver disease (NAFLD).

In an [embodimentexample](#) the present [inventiondisclosure](#) provides a method of determining the human IL-34 level in a bodily fluid comprising: (a) contacting the bodily fluid with an anti-human IL-34 diagnostic monoclonal antibody, or antigen-binding fragment thereof, that specifically binds to human IL-34 consisting of the amino acid sequence as in SEQ ID NO: 41, the antibody, or antigen-binding fragment thereof, comprising: light chain complementarity determining regions LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences (SEQ ID NO: 8), (SEQ ID NO: 9), and (SEQ ID NO: 10), respectively, and heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences (SEQ ID NO: 15), (SEQ ID NO: 16), and (SEQ ID NO: 17), respectively; (b) optionally, removing any non-specifically bound

monoclonal antibody or, antigen-binding fragment thereof; and (c) detecting and/or quantifying the amount of monoclonal antibody, or antigen-binding fragment thereof, which is specifically bound to human IL-34. Preferably, wherein said bodily fluid is blood, serum or plasma, or cerebrospinal fluid, and said contacting occurs ex vivo.

Tauopathy diseases include but are not limited to, Alzheimer's disease (AD), Pick's disease (PiD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease, Down's Syndrome, chronic traumatic encephalopathy (CTE), traumatic brain injury (TBI), frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17), Parkinsonism-dementia complex of Guam, Niemann-Pick disease type C, myotonic dystrophy (See Li, C., Götz, J. *Tau-based therapies in neurodegeneration: opportunities and challenges*. Nat Rev Drug Discov 16, 863–883 (2017)).

In embodiment examples of the invention disclosure a patient is a human who has been diagnosed as having a medical risk, condition or disorder, such as one of the diseases or disorders described herein, in need of treatment with an antibody described herein. In those instances where the disorders which can be treated by the methods of the present invention disclosure are known by established and accepted classifications, such as Alzheimer's Disease; a tauopathy disease; Sjogren's syndrome (SS); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD), atopic dermatitis, kidney disease, sepsis, and/or non-alcoholic fatty liver disease (NAFLD), their classifications can be found in various well-known medical texts. For example, at present, the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), provides a diagnostic tool for identifying certain disorders described herein. Also, the International Classification of Diseases, Tenth Revision (ICD-10), provides classifications for certain disorders described herein. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for diseases and disorders described herein, including those as described in the DSM-5 and ICD-10, and that terminology and classification systems evolve with medical scientific progress.

The term "treating" (or "treat" or "treatment") refers to slowing, interrupting, arresting, alleviating, stopping, reducing, or reversing the progression or severity of an existing symptom, disorder, condition, or disease.

As used herein, the term "innate immunity" includes the arm of the immune response which, in contrast to the adaptive arm of the immune response, is required to initiate and maintain an adaptive immune response (antibody and T cell responses).

"Effective amount" means the amount of an anti-human IL-34 antibody of the present ~~invention~~disclosure, or a pharmaceutical composition comprising such an antibody, that will elicit the biological or medical response of or desired therapeutic effect on a tissue, system, or human, that is being sought by the treating health professional. As used herein, the term "effective response" of a patient or a patient's responsiveness to treatment refers to the clinical or therapeutic benefit imparted to a patient upon administration an antibody of the present disclosure. An effective amount of the antibody may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody to elicit a desired response in the individual. An effective amount is also one in which any toxic or detrimental effect of the antibody is outweighed by the therapeutically beneficial effects. Such benefit includes any one or more of: a decreased level of inflammation or immune activation, stabilized immune-mediated disease or disorder; or improving signs or symptoms of an immune-mediated disorder. Alternatively, such benefit includes any one or more of the following: an increased immune tolerance of transplanted organs; stabilized autoimmune disease or disorder; or improving signs or symptoms of an autoimmune disorder.

A potential advantage of methods disclosed herein is the possibility of producing marked and/or prolonged relief in a patient suffering from an immune-mediated disorder, or neuroinflammatory disorder, with an acceptable safety profile including acceptable tolerability, toxicities and/or adverse events, so that the patient benefits from the treatment method overall. The efficacy of the treatment of the present disclosure can be measured by various endpoints that are commonly used in evaluating treatments for various immune-mediated disorders. Other approaches to determining efficacy of any particular therapy of the present ~~invention~~disclosure can be optionally employed, including, for

example, immune cell activation markers, measures of inflammation, cell-cycle dependent biomarker measurement and visualization, and/or measurement of response through various inflammation or immune or tissue specific biomarker assessments.

An effective amount can be readily determined by one skilled in the art, using known techniques, and by observing results obtained under analogous circumstances. An effective amount of an anti-human IL-34 antibody of the present ~~invention~~disclosure may be administered in a single dose or in multiple doses. Furthermore, an effective amount of an antibody of the ~~invention~~disclosure may be administered in multiple doses of amounts that would be less than an effective amount if not administered more than once. In determining the effective amount for a patient, a number of factors are considered by the attending medical practitioner, including, but not limited to: the patient's size (e.g., weight or mass), body surface area, age, and general health; the specific disease or disorder involved; the degree of, or involvement, or the severity of the disease or disorder; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances known to medical practitioners.

A weekly, every two week, monthly, or quarterly parenteral (including, but not limited to, subcutaneous, intramuscular, and/or intravenous) dose can be from about 0.5 mg/kg to about 50 mg/kg.

A weekly, every two week, monthly, or quarterly parenteral (including, but not limited to, subcutaneous, intramuscular, and/or intravenous) dose can be from about 0.5 mg/kg to about 10 mg/kg, from about 1 mg/kg to about 10 mg/kg, from about 2 mg/kg to about 10 mg/kg, from about 3 mg/kg to about 10 mg/kg, from about 4 mg/kg to about 10 mg/kg, from about 5 mg/kg to about 10 mg/kg, from about 6 mg/kg to about 10 mg/kg, from about 7 mg/kg to about 10 mg/kg from about 8 mg/kg to about 10 mg/kg, from about 1 mg/kg to about 8 mg/kg, from about 2 mg/kg to about 8 mg/kg, from about 3 mg/kg to about 8 mg/kg, from about 4 mg/kg to about 8 mg/kg, from about 5 mg/kg to about 8 mg/kg, from about 6 mg/kg to about 8 mg/kg, from about 1 mg/kg to about 6 mg/kg, from about 2 mg/kg to about 6 mg/kg, from about 3 mg/kg to about 6 mg/kg, from

A potential advantage of methods disclosed herein is the possibility of producing marked and/or prolonged relief in a patient suffering from an immune-mediated disorder, or neuroinflammatory disorder, with an acceptable safety profile including acceptable tolerability, toxicities and/or adverse events, so that the patient benefits from the treatment method overall, and more particularly the antibodies of the present ~~invention~~disclosure will provide effective treatment while avoiding clinically undesirable immunosuppression and/or immune associated adverse events such as “cytokine storm” or significant cytokine release. Antibodies of the present ~~invention~~disclosure may be useful for the treatment of cytokine storm, or otherwise adverse cytokine release. As used herein, “significant cytokine release” refers to a significant increase in measurable cytokines that can be detected by methods known to persons of ordinary skill. For example, significant cytokine release may be detected in human blood samples by ELISA, wherein cytokine levels from unstimulated blood are compared to cytokine levels with blood incubated with antibody. In some such studies, for example, a significant cytokine release may be detected if the levels of IL-6, or IL-8, or IFN- γ are at least three-fold higher in blood incubated with antibody compared to levels in unstimulated blood. Preferably, treatment of an immune-mediated disorder as described in the ~~embodiment~~examples herein will occur wherein the patient will not experience significant cytokine release.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows Antibody 1 neutralization of human IL-34 induced luciferase reporter activity in hCSF1R expressing 293 SRE cells.

FIGURE 2 shows the ability of Antibody 1 to neutralize the dimerization of CSF1R in the PathHunter eXpress Dimerization Assay.

FIGURE 3 shows the ability of Antibody 1 to inhibit ERK phosphorylation in NIH-3T3/CSF1R cells.

FIGURE 4 shows the ability of anti-IL34 antibodies to inhibit IL-34 induced expression of CD163 in human monocytes by flow cytometry.

EXAMPLES

The following examples are offered to illustrate, but not to limit, the claimed invention. The results of the following assays demonstrate that the exemplified

We Claim:

1. An antibody that binds human IL-34 wherein the antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions (HCDR) HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions (LCDR) LCDR1, LCDR2, and LCDR3, wherein
 - the HCDR1 comprises SEQ ID NO: 5,
 - the HCDR2 comprises SEQ ID NO: 6,
 - the HCDR3 comprises SEQ ID NO: 7,
 - the LCDR1 comprises SEQ ID NO: 8,
 - the LCDR2 comprises SEQ ID NO: 9, and
 - the LCDR3 comprises SEQ ID NO: 10.
2. The antibody of claim 1, wherein the VH comprises SEQ ID NO: 3 and the VL comprises SEQ ID NO: 4.
3. The antibody of claim 1 or 2, wherein the antibody comprises a heavy chain (HC) comprising SEQ ID NO: 1 and a light chain (LC) comprising SEQ ID NO: 2.
4. An antibody that binds human IL-34 comprising a VH and a VL, wherein the VH comprises HCDR1, HCDR2, and HCDR3, and the VL comprises LCDR1, LCDR2, and LCDR3, wherein
 - the HCDR1 comprises SEQ ID NO: 15,
 - the HCDR2 comprises SEQ ID NO: 16,
 - the HCDR3 comprises SEQ ID NO: 17,
 - the LCDR1 comprises SEQ ID NO: 8,
 - the LCDR2 comprises SEQ ID NO: 9, and
 - the LCDR3 comprises SEQ ID NO: 10.

5. The antibody of claim 4, wherein the VH comprises SEQ ID NO: 14 and the VL comprises SEQ ID NO: 4.
6. The antibody of claim 4 or 5, wherein the antibody comprises a HC comprising SEQ ID NO: 13 and a LC comprising SEQ ID NO: 2.
7. An antibody that binds murine IL-34 wherein the antibody comprises a VH and a VL, wherein the VH comprises HCDR1, HCDR2, and HCDR3, and the VL comprises LCDR1, LCDR2, and LCDR3, wherein
 - the HCDR1 comprises SEQ ID NO: 23,
 - the HCDR2 comprises SEQ ID NO: 24,
 - the HCDR3 comprises SEQ ID NO: 25,
 - the LCDR1 comprises SEQ ID NO: 26,
 - the LCDR2 comprises SEQ ID NO: 27, and
 - the LCDR3 comprises SEQ ID NO: 28.
8. The antibody of claim 7, wherein the VH comprises SEQ ID NO: 21 and the VL comprises SEQ ID NO: 22.
9. The antibody of claim 7 or 8, wherein the antibody comprises a HC comprising SEQ ID NO: 19 and a LC comprising SEQ ID NO: 20.
10. A nucleic acid comprising a sequence encoding a SEQ ID NO selected from one or more of the group consisting of: 11, 12, 18, 29, and 30.
11. A vector comprising the nucleic acid of claim 10.
12. The vector of claim 11, wherein the vector comprises a first nucleic acid sequence encoding SEQ ID NO: 11 or 18, and a second nucleic acid sequence encoding SEQ ID NO: 12.

13. The vector of claim 11, wherein the vector comprises a first nucleic acid sequence encoding SEQ ID NO: 29, and a second nucleic acid sequence encoding SEQ ID NO: 30.

14. A composition comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 11 or 18, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 12.

15. A composition comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 29, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 30.

16. A cell comprising the vector of claim 12 or 13.

17. A cell comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 11 or 18, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 12.

18. A cell comprising a first vector comprising a nucleic acid sequence encoding SEQ ID NO: 29, and a second vector comprising a nucleic acid sequence encoding SEQ ID NO: 30.

19. The cell of any one of claims 16-18, wherein the cell is a mammalian cell.

20. A process of producing an antibody comprising culturing the cell of any one of claims 16-19 under conditions such that the antibody is expressed and recovering the expressed antibody from the culture medium.

21. An antibody produced by the process of claim 20.

22. A pharmaceutical composition comprising the antibody of any one of claims 1-9 or 21, and a pharmaceutically acceptable excipient, diluent or carrier.

~~23. A method of treating an immune-mediated disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the antibody of any one of claims 1-9 or 21, or the pharmaceutical composition of claim 22.~~

~~24. The method of claim 23, wherein the immune-mediated disease is selected from the group consisting of Alzheimer's Disease; a tauopathy disease; Sjogren's syndrome (SS); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD); atopic dermatitis; kidney disease; sepsis, and/or non-alcoholic fatty liver disease (NAFLD).~~

~~25. The method of claim 23, wherein the immune-mediated disease is Alzheimer's Disease.~~

~~26~~23. The antibody of any one of claims 1-9 or 21 for use in therapy.

~~27~~24. The antibody of any one of claims 1-9 or 21, or the pharmaceutical composition of claim 22, for use in the treatment of an immune-mediated disease.

~~28~~25. The antibody or pharmaceutical composition for use of claim ~~27~~24, wherein the ~~an~~ immune-mediated disease is selected from the group consisting of Alzheimer's Disease; a tauopathy disease; Sjogren's syndrome (SS); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD), atopic dermatitis, kidney disease, sepsis, and/or non-alcoholic fatty liver disease (NAFLD).

~~29~~26. The antibody or pharmaceutical composition for use of claim ~~27~~24, wherein the immune-mediated disease is Alzheimer's Disease.

~~3027~~. Use of the antibody of any one of claims 1-9 or 21, in the manufacture of a medicament for the treatment of an immune-mediated disease.

~~3128~~. The use of claim ~~3027~~, wherein the immune-mediated disease is selected from the group consisting of Alzheimer's Disease; a tauopathy disease; Sjogren's syndrome (SS); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD), atopic dermatitis, kidney disease, sepsis, and/or non-alcoholic fatty liver disease (NAFLD).

~~3229~~. The use of claim ~~3027~~, wherein the immune-mediated disease is Alzheimer's Disease.

~~3330~~. A method of determining the human IL-34 level in a bodily fluid comprising:

- (a) contacting the bodily fluid with an anti-human IL-34 diagnostic monoclonal antibody, or antigen-binding fragment thereof, that specifically binds to human IL-34 consisting of the amino acid sequence as in SEQ ID NO: 41, the antibody, or antigen-binding fragment thereof, comprising: light chain complementarity determining regions LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences (SEQ ID NO: 8), (SEQ ID NO: 9), and (SEQ ID NO: 10), respectively, and heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences (SEQ ID NO: 15), (SEQ ID NO: 16), and (SEQ ID NO: 17), respectively;
- (b) optionally, removing any non-specifically bound monoclonal antibody or, antigen-binding fragment thereof, wherein said contacting occurs *ex vivo*;
and
- (c) detecting and/or quantifying the amount of monoclonal antibody, or antigen-binding fragment thereof, which is specifically bound to human IL-34.

~~3431~~. The method of claim ~~3330~~, wherein said bodily fluid is blood, serum or plasma, or cerebrospinal fluid, ~~and said contacting occurs *ex vivo*~~.