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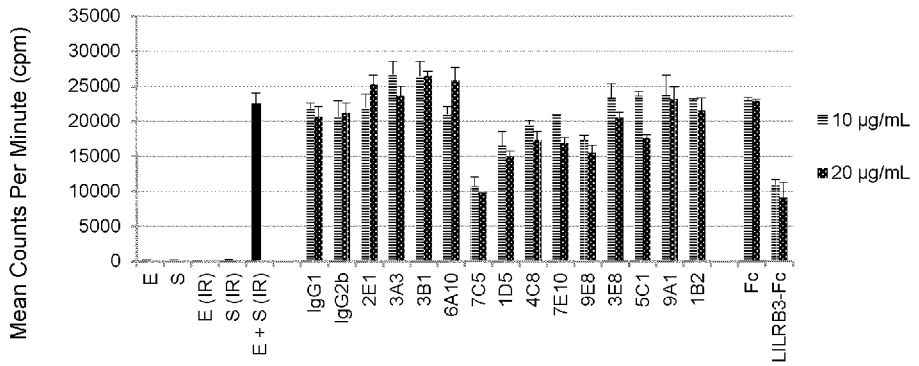
(54) Title: LILRB3-BINDING MOLECULES AND USES THEREFOR

FIGURE 2



(57) Abstract: The invention provides novel anti-LILRB3 antibodies, pharmaceutical compositions comprising such antibodies, and therapeutic methods of using such antibodies and pharmaceutical compositions for the treatment of diseases such as cancer, autoimmune disease, or allergic inflammation. This invention can also be used to modulate osteoclast differentiation.

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[Continued on next page]

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LILRB3-BINDING MOLECULES AND USES THEREFOR

CROSS REFERENCE TO RELATED APPLICATION

[0001] The present application claims the benefit of priority to U.S. Provisional Application No. 62/794,064, filed January 18, 2019, the contents of which is expressly incorporated herein in its entirety for all purposes.

SEQUENCE LISTING

[0002] The present application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on January 15, 2020, is named 011506-5022_ST25.txt and is 72 kilobytes in size.

TECHNICAL FIELD

[0003] The present disclosure relates to antibodies that specifically bind to LILRB3, e.g., human LILRB3 (hLILRB3), and pharmaceutical compositions comprising such LILRB3-binding antibodies thereof. Methods of using the antibodies of the invention to detect human LILRB3 or to modulate human LILRB3 activity in the treatment of various diseases, including inflammatory diseases, autoimmune diseases and cancer, are also encompassed by the invention.

BACKGROUND OF THE INVENTION

[0004] The human leukocyte Ig-like receptor (LILR) family belongs to the superfamily of paired receptors that have the potential to transmit stimulatory or inhibitory signals according to the presence or absence of tyrosine-based signaling motifs in their cytoplasmic tail. Human LILRs consist of five stimulatory receptors (LILRA1-5), six inhibitory receptors (LILRB1-6) and two pseudogenes. LILRs are expressed on various cells, such as lymphoid and myeloid cells, and the expression patterns are different from receptor to receptor. Polymorphism and copy-number variation contribute to diversity within humans. In general, LILR activity can result in the upregulation or downregulation of both innate and adaptive immune functions with a range of effects on different cell types. Recent studies have found that several LILRB family members are expressed by cancer cells, in particular hematopoietic cancer cells, and may support cancer development and relapse, as well as the activity of cancer stem cells.

[0005] Human LILRB3 (also called CD85A, ILT5, LIR3 or HL9) contains 4 extracellular immunoglobulin domains, a transmembrane domain and 4 cytoplasmic immunoreceptor tyrosine-based inhibition motifs (ITIMs). Expression of LILRB3 has been reported on monocytes, monocyte-derived osteoclasts, granulocytes, dendritic cells, osteoclasts and progenitor mast cells. The ligand for LILRB3 has not been identified, and little is known about the function of LILRB3. Collectively, these findings suggest that the development of agents useful in modulating signaling from LILRB3 would be of great benefit in diseases involving dysregulation of the immune system, including inflammatory diseases, autoimmune diseases and cancer.

SUMMARY OF THE INVENTION

[0006] In one aspect, the present invention relates to novel anti-LILRB3 antibodies. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:1 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:2. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:3 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:4. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:5 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:6. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:8. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:9 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:10. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:11 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:12. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:13 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:14. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:15 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:16. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:17 and a light chain variable region comprising an amino

acid sequence of SEQ ID NO:18. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:19 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:20. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:21 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:22. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:23 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:24. In some embodiments, the anti-LILRB3 antibodies include a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:25 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:26.

[0007] In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:27, a vhCDR2 comprising SEQ ID NO:28, a vhCDR3 comprising SEQ ID NO:29, a vlCDR1 comprising SEQ ID NO:30, a vlCDR2 comprising SEQ ID NO:31, and a vlCDR3 comprising SEQ ID NO:32. In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:33, a vhCDR2 comprising SEQ ID NO:34, a vhCDR3 comprising SEQ ID NO:35, a vlCDR1 comprising SEQ ID NO:36, a vlCDR2 comprising SEQ ID NO:37, and a vlCDR3 comprising SEQ ID NO:38. In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:39, a vhCDR2 comprising SEQ ID NO:40, a vhCDR3 comprising SEQ ID NO:41, a vlCDR1 comprising SEQ ID NO:42, a vlCDR2 comprising SEQ ID NO:43, and a vlCDR3 comprising SEQ ID NO:44. In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:45, a vhCDR2 comprising SEQ ID NO:46, a vhCDR3 comprising SEQ ID NO:47, a vlCDR1 comprising SEQ ID NO:48, a vlCDR2 comprising SEQ ID NO:49, and a vlCDR3 comprising SEQ ID NO:50. In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:51, a vhCDR2 comprising SEQ ID NO:52, a vhCDR3 comprising SEQ ID NO:53, a vlCDR1 comprising SEQ ID NO:54, a vlCDR2 comprising SEQ ID NO:55, and a vlCDR3 comprising SEQ ID NO:56. In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:57, a vhCDR2 comprising SEQ ID NO:58, a vhCDR3 comprising SEQ ID NO:59, a vlCDR1 comprising SEQ ID NO:60, a vlCDR2 comprising SEQ ID NO:61, and a vlCDR3 comprising SEQ ID NO:62. In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:63, a vhCDR2 comprising SEQ ID NO:64, a vhCDR3 comprising SEQ ID NO:65, a vlCDR1 comprising SEQ ID NO:66, a

vlCDR2 comprising SEQ ID NO:67, and a vlCDR3 comprising SEQ ID NO:68. In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:69, a vhCDR2 comprising SEQ ID NO:70, a vhCDR3 comprising SEQ ID NO:71, a vlCDR1 comprising SEQ ID NO:72, a vlCDR2 comprising SEQ ID NO:73, and a vlCDR3 comprising SEQ ID NO:74. In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:75, a vhCDR2 comprising SEQ ID NO:76, a vhCDR3 comprising SEQ ID NO:77, a vlCDR1 comprising SEQ ID NO:78, a vlCDR2 comprising SEQ ID NO:79, and a vlCDR3 comprising SEQ ID NO:80. In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:81, a vhCDR2 comprising SEQ ID NO:82, a vhCDR3 comprising SEQ ID NO:83, a vlCDR1 comprising SEQ ID NO:84, a vlCDR2 comprising SEQ ID NO:85, and a vlCDR3 comprising SEQ ID NO:86. In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:87, a vhCDR2 comprising SEQ ID NO:88, a vhCDR3 comprising SEQ ID NO:89, a vlCDR1 comprising SEQ ID NO:90, a vlCDR2 comprising SEQ ID NO: 91, and a vlCDR3 comprising SEQ ID NO:92. In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:93, a vhCDR2 comprising SEQ ID NO:94, a vhCDR3 comprising SEQ ID NO:95, a vlCDR1 comprising SEQ ID NO:96, a vlCDR2 comprising SEQ ID NO:97, and a vlCDR3 comprising SEQ ID NO:98. In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:99, a vhCDR2 comprising SEQ ID NO:100, a vhCDR3 comprising SEQ ID NO:101, a vlCDR1 comprising SEQ ID NO:102, a vlCDR2 comprising SEQ ID NO:103, and a vlCDR3 comprising SEQ ID NO:104.

[0008] In some embodiments, the anti-LILRB3 antibodies described herein bind human LILRB3.

[0009] In another aspect, the present invention relates to a nucleic acid composition encoding any one of the anti-LILRB3 antibodies described herein.

[0010] Another aspect of the present invention relates to an expression vector composition that includes any one of the nucleic acid compositions described herein. In some embodiments, the first nucleic acid is contained in a first expression vector and the second nucleic acid is contained in a second expression vector. In some other embodiments, the first nucleic acid and the second nucleic acid are contained in a single expression vector.

[0011] Another aspect of the present invention relates to a host cell that includes any one of the expression vectors described herein. Also presented is a method of making anti-LILRB3 antibodies, and the method includes culturing the host cell under conditions wherein the antibodies expressed, and recovering the antibodies.

[0012] In another aspect, the present invention relates to a composition that includes any one of the anti-LILRB3 antibodies described herein, and a pharmaceutical acceptable carrier or diluent.

[0013] Also described is a method of modulating an immune response in a subject, and the method includes administering to the subject an effective amount of any one of the anti-LILRB3 antibodies described herein, or any one of the compositions described herein. In some embodiments, the method includes administering to the subject an effective amount of an anti-LILRB3 antibody that serves as a LILRB3 antagonist, or a pharmaceutical composition thereof. In some embodiments, the method includes administering to the subject an effective amount of an anti-LILRB3 antibody that serves as a LILRB3 agonist, or a pharmaceutical composition thereof.

[0014] In another aspect, the present invention relates to a method of treating cancer in a subject, and the method includes administering to the subject an effective amount of an anti-LILRB3 antibody described herein or any one of the compositions described herein. In some embodiments, the cancer to be treated upregulates LILRB3 compared to the corresponding non-cancerous tissue. In some embodiments, the subject to be treated expresses a high level of LILRB3 on hematopoeitic cells. The cancer to be treated can be any cancer. In some embodiments, an anti-LILRB3 antibody is used in combination with one or more additional therapeutic agents to treat cancer. In some embodiments, such anti-cancer therapeutic agents are other immune checkpoint inhibitors, such as Ipilimumab, Nivolumab, Pembrolizumab, Avelumab, Durvalumab, and Atezolizumab.

[0015] In another aspect, the present invention relates to a method of treating an autoimmune disease in a subject, and the method includes administering to the subject an effective amount of any one of the anti-LILRB3 antibodies described herein, or any one of the compositions described herein.

[0016] In another aspect, the present invention relates to a method of treating an autoimmune disease in a subject, and the method includes administering to the subject an effective amount of an anti-LILRB3 antibody described herein, or any one of the compositions described herein.

[0017] In a further aspect, the present invention relates to a method of treating allergic inflammation in a subject, and the method includes administering to the subject an effective amount of any one of the anti-LILRB3 antibodies described herein, or any one of the compositions described herein.

[0018] In a further aspect, the present invention relates to a method of modulating osteoclast differentiation, and the method includes administering to the subject an effective amount of any one of the anti-LILRB3 antibodies described herein, or any one of the compositions described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] The invention may be best understood from the following detailed description when read in conjunction with the accompanying drawings. Included in the drawings are the following figures:

[0020] **FIGURE 1A and FIGURE 1B** show LILBR3 surface expression on various hematopoietic subsets using flow cytometry.

[0021] **FIGURE 2** shows the effect of LILRB3 antibodies or LILRB3-Fc protein on responsiveness of T cells in primary mixed lymphocyte reactions (MLR).

[0022] **FIGURE 3** shows the ability of PBMCs to regulate surface expression of activation markers in response to T cell stimulation after incubation with the LILRB3 7C5 antibody.

[0023] **FIGURE 4** shows the effect of the LILRB3 7C5 antibody on cytokine production by PBMCs in response to T cell stimulation.

[0024] **FIGURE 5** shows cytokine release of unstimulated blood when incubated with the LILRB3 7C5 antibody.

DETAILED DESCRIPTION

[0025] The present disclosure provides novel anti-LILRB3 antibodies. In some embodiments, the anti-LILRB3 antibodies act to modulate an immune response in a subject, and, for example, to treat cancer or an autoimmune disease. In some embodiments the anti-LILRB3 antibodies act to treat allergic inflammation. In some embodiments the anti-LILRB3 antibodies modulate osteoclast differentiation.

[0026] To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

[0027] As used herein, each of the following terms has the meaning associated with it in this section.

[0028] The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.,* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0029] "About" as used herein when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ±20% or ±10%, more preferably ±5%, even more preferably ±1%, and still more preferably ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

[0030] By "antigen binding domain" or "ABD" herein is meant a set of six Complementary Determining Regions (CDRs) that, when present as part of a polypeptide sequence, specifically binds a target antigen as discussed herein. Thus, an "antigen binding domain" binds a target antigen as outlined herein. As is known in the art, these CDRs are generally present as a first set of variable heavy CDRs (vhCDRs or VHCDRs or CDR-HC) and a second set of variable light CDRs (vlCDRs or VLCDRs or CDR-LC), each comprising three CDRs: vhCDR1, vhCDR2, vhCDR3 for the heavy chain and vlCDR1, vlCDR2 and vlCDR3 for the light chain. The CDRs are present in the variable heavy and variable light domains, respectively, and together form an Fv region. Thus, in some cases, the six CDRs of the antigen binding domain are contributed by a variable heavy and variable light chain. In a "Fab" format, the set of 6 CDRs are contributed by two different polypeptide sequences, the variable heavy domain (vh or VH; containing the vhCDR1, vhCDR2 and vhCDR3) and the variable light domain (vl or VL; containing the vlCDR1, vlCDR2 and vlCDR3), with the C-terminus of the vh domain being attached to the N-

terminus of the CH1 domain of the heavy chain and the C-terminus of the vl domain being attached to the N-terminus of the constant light domain (and thus forming the light chain). In a scFv format, the VH and VL domains are covalently attached, generally through the use of a linker as outlined herein, into a single polypeptide sequence, which can be either (starting from the N-terminus) vh-linker-vl or vl-linker-vh, with the former being generally preferred (including optional domain linkers on each side, depending on the format used. As is understood in the art, the CDRs are separated by framework regions in each of the variable heavy and variable light domains: for the light variable region, these are FR1-vlCDR1-FR2-vlCDR2-FR3-vlCDR3-FR4, and for the heavy variable region, these are FR1-vhCDR1-FR2-vhCDR2-FR3-vhCDR3-FR4, with the framework regions showing high identity to human germline sequences. Antigen binding domains of the invention include, Fab, Fv and scFv.

[0031] The term "antibody" is used in the broadest sense and includes, for example, an intact immunoglobulin or an antigen binding portion. Antigen binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Thus the term antibody includes traditional tetrameric antibodies of two heavy chains and two light chains, as well as antigen binding fragments such as Fv, Fab and scFvs. In some cases, the invention provides bispecific antibodies that include at least one antigen binding domain as outlined herein.

[0032] By "modification" herein is meant an amino acid substitution, insertion, and/or deletion in a polypeptide sequence or an alteration to a moiety chemically linked to a protein. For example, a modification may be an altered carbohydrate or PEG structure attached to a protein. By "amino acid modification" herein is meant an amino acid substitution, insertion, and/or deletion in a polypeptide sequence. For clarity, unless otherwise noted, the amino acid modification is always to an amino acid coded for by DNA, *e.g.*, the 20 amino acids that have codons in DNA and RNA.

[0033] By "amino acid substitution" or "substitution" herein is meant the replacement of an amino acid at a particular position in a parent polypeptide sequence with a different amino acid. In particular, in some embodiments, the substitution is to an amino acid that is not naturally occurring at the particular position, either not naturally occurring within the organism or in any organism. For example, the substitution M252Y refers to a variant polypeptide, in this case an Fc variant, in which the methionine at position 252 is replaced with tyrosine. For clarity, a protein which has been engineered to change the nucleic acid coding sequence but not change

the starting amino acid (for example exchanging CGG (encoding arginine) to CGA (still encoding arginine) to increase host organism expression levels) is not an "amino acid substitution"; that is, despite the creation of a new gene encoding the same protein, if the protein has the same amino acid at the particular position that it started with, it is not an amino acid substitution.

[0034] By "variant protein" or "protein variant", or "variant" as used herein is meant a protein that differs from that of a parent protein by virtue of at least one amino acid modification. Protein variant may refer to the protein itself, a composition comprising the protein, or the amino sequence that encodes it. Preferably, the protein variant has at least one amino acid modification compared to the parent protein, *e.g.,* from about one to about seventy amino acid modifications, and preferably from about one to about five amino acid modifications compared to the parent. As described below, in some embodiments the parent polypeptide, for example an Fc parent polypeptide, is a human wild type sequence, such as the Fc region from IgG1, IgG2, IgG3 or IgG4. The protein variant sequence herein will preferably possess at least about 80% identity with a parent protein sequence, and most preferably at least about 90% identity, more preferably at least about 95%-98%-99% identity. Variant protein can refer to the variant protein itself, compositions comprising the protein variant, or the DNA sequence that encodes it.

[0035] Accordingly, by "antibody variant" or "variant antibody" as used herein is meant an antibody that differs from a parent antibody by virtue of at least one amino acid modification, "IgG variant" or "variant IgG" as used herein is meant an antibody that differs from a parent IgG (again, in many cases, from a human IgG sequence) by virtue of at least one amino acid modification, and "immunoglobulin variant" or "variant immunoglobulin" as used herein is meant an immunoglobulin sequence that differs from that of a parent immunoglobulin sequence by virtue of at least one amino acid modification. "Fc variant" or "variant Fc" as used herein is meant a protein comprising an amino acid modification in an Fc domain. The Fc variants of the present invention are defined according to the amino acid modifications that compose them. Thus, for example M252Y or 252Y is an Fc variant with the substitution tyrosine at position 252 relative to the parent Fc polypeptide, wherein the numbering is according to the EU index. Likewise, M252Y/S254T/T256E defines an Fc variant with the substitutions M252Y, S254T and T256E relative to the parent Fc polypeptide. The identity of the wild type amino acid may be unspecified, in which case the aforementioned variant is referred to as 252Y/254T/256E. It is noted that the order in which substitutions are provided is arbitrary, that is to say that, for example, 252Y/254T/256E is the same Fc variant as 254T/252Y/256E, and so on. For all

positions discussed in the present invention that relate to antibodies, unless otherwise noted, amino acid position numbering is according to Kabat for the variable region numbering and is according to the EU index for the constant regions, including the Fc region. The EU index or EU index as in Kabat or EU numbering scheme refers to the numbering of the EU antibody (Edelman et al., 1969, Proc Natl Acad Sci USA 63:78-85, hereby entirely incorporated by reference.) The modification can be an addition, deletion, or substitution. Substitutions can include naturally occurring amino acids and, in some cases, synthetic amino acids.

[0036] As used herein, "protein" herein is meant at least two covalently attached amino acids, which includes proteins, polypeptides, oligopeptides and peptides. The peptidyl group may comprise naturally occurring amino acids and peptide bonds.

[0037] By "Fab" or "Fab region" as used herein is meant the polypeptide that comprises the VH, CH1, VL, and CL immunoglobulin domains. Fab may refer to this region in isolation, or this region in the context of a full length antibody, antibody fragment or Fab fusion protein.

By "Fv" or "Fv fragment" or "Fv region" as used herein is meant a polypeptide that comprises the VL and VH domains of a single antigen binding domain (ABD). As will be appreciated by those in the art, these generally are made up of two chains, or can be combined (generally with a linker as discussed herein) to form a scFv.

[0038] By "amino acid" and "amino acid identity" as used herein is meant one of the 20 naturally occurring amino acids that are coded for by DNA and RNA.

[0039] By "parent polypeptide" as used herein is meant a starting polypeptide that is subsequently modified to generate a variant. The parent polypeptide may be a naturally occurring polypeptide, or a variant or engineered version of a naturally occurring polypeptide. Parent polypeptide may refer to the polypeptide itself, compositions that comprise the parent polypeptide, or the amino acid sequence that encodes it. Accordingly, by "parent immunoglobulin" as used herein is meant an unmodified immunoglobulin polypeptide that is modified to generate a variant, and by "parent antibody" as used herein is meant an unmodified antibody that is modified to generate a variant antibody. It should be noted that "parent antibody" includes known commercial, recombinantly produced antibodies as outlined below.

[0040] By “heavy constant region” herein is meant the CH1-hinge-CH2-CH3 portion of an antibody, generally from human IgG1, IgG2 or IgG4.

[0041] By "target antigen" as used herein is meant the molecule that is bound specifically by the variable region of a given antibody. In the present case, the target antigen is a LILRB3 protein.

[0042] By "target cell" as used herein is meant a cell that expresses a target antigen.

[0043] By "variable region" as used herein is meant the region of an immunoglobulin that comprises one or more Ig domains substantially encoded by any of the V.kappa., V.lamda., and/or VH genes that make up the kappa, lambda, and heavy chain immunoglobulin genetic loci respectively.

[0044] By "wild type or WT" herein is meant an amino acid sequence or a nucleotide sequence that is found in nature, including allelic variations. A WT protein has an amino acid sequence or a nucleotide sequence that has not been intentionally modified.

[0045] By "position" as used herein is meant a location in the sequence of a protein. Positions may be numbered sequentially, or according to an established format, for example the EU index for antibody numbering.

[0046] By "residue" as used herein is meant a position in a protein and its associated amino acid identity. For example, Asparagine 297 (also referred to as Asn297 or N297) is a residue at position 297 in the protein sequence.

[0047] The antibodies of the present invention are generally recombinant. “Recombinant” means the antibodies are generated using recombinant nucleic acid techniques in exogenous host cells.

[0048] "Percent (%) amino acid sequence identity" with respect to a protein sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific (parental) sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. One particular

program is the ALIGN-2 program outlined at paragraphs [0279] to [0280] of US Pub. No. 20160244525, hereby incorporated by reference. Another approximate alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman, Advances in Applied Mathematics, 2:482-489 (1981). This algorithm can be applied to amino acid sequences by using the scoring matrix developed by Dayhoff, Atlas of Protein Sequences and Structure, M.O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA, and normalized by Gribskov, Nucl. Acids Res. 14(6):6745-6763 (1986).

[0049] An example of an implementation of this algorithm to determine percent identity of a sequence is provided by the Genetics Computer Group (Madison, WI) in the "BestFit" utility application. The default parameters for this method are described in the Wisconsin Sequence Analysis Package Program Manual, Version 8 (1995) (available from Genetics Computer Group, Madison, WI). Another method of establishing percent identity in the context of the present invention is to use the MPSRCH package of programs copyrighted by the University of Edinburgh, developed by John F. Collins and Shane S. Sturrok, and distributed by IntelliGenetics, Inc. (Mountain View, CA). From this suite of packages, the Smith-Waterman algorithm can be employed where default parameters are used for the scoring table (for example, gap open penalty of 12, gap extension penalty of one, and a gap of six). From the data generated the "Match" value reflects "sequence identity." Other suitable programs for calculating the percent identity or similarity between sequences are generally known in the art, for example, another alignment program is BLAST, used with default parameters. For example, BLASTN and BLASTP can be used using the following default parameters: genetic code = standard; filter = none; strand = both; cutoff = 60; expect = 10; Matrix = BLOSUM62; Descriptions = 50 sequences; sort by = HIGH SCORE; Databases = non-redundant, GenBank + EMBL + DDBJ + PDB + GenBank CDS translations + Swiss protein + Spupdate + PIR. Details of these programs can be found at the internet address located by placing http:// in front of blast.ncbi.nlm.nih.gov/Blast.cgi.

[0050] The degree of identity between an amino acid sequence of the present invention ("invention sequence") and the parental amino acid sequence is calculated as the number of exact matches in an alignment of the two sequences, divided by the length of the "invention sequence," or the length of the parental sequence, whichever is the shortest. The result is expressed in percent identity.

[0051] In some embodiments, two or more amino acid sequences are at least 50%, 60%, 70%, 80%, or 90% identical. In some embodiments, two or more amino acid sequences are at least 95%, 97%, 98%, 99%, or even 100% identical.

[0052] "Specific binding" or "specifically binds to" or is "specific for" a particular antigen or an epitope means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target.

[0053] The term "Kassoc" or "Ka", as used herein, is intended to refer to the association rate of a particular antibody-antigen interaction, whereas the term "Kdis" or "Kd," as used herein, is intended to refer to the dissociation rate of a particular antibody-antigen interaction. The term "K_D", as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of Kd to Ka (*i.e.*, Kd/Ka) and is expressed as a molar concentration (M). K_D values for antibodies can be determined using methods well established in the art. In some embodiments, the method for determining the K_D of an antibody is by using surface plasmon resonance, for example, by using a biosensor system such as a BIACORE® system. In some embodiments, the K_D of an antibody is determined by Bio-Layer Interferometry. In some embodiments, the K_D value is measured with the immobilized. In other embodiments, the K_D value is measured with the antibody (*e.g.*, parent mouse antibody, chimeric antibody, or humanized antibody variants) immobilized. In certain embodiments, the K_D value is measured in a bivalent binding mode. In other embodiments, the K_D value is measured in a monovalent binding mode.

[0054] A "disease" includes a state of health of an animal, including a human, wherein the animal cannot maintain homeostasis, and wherein if the disease is not ameliorated then the animal's health continues to deteriorate.

[0055] In contrast, a "disorder" in an animal, including a human, includes a state of health in which the animal is able to maintain homeostasis, but in which the animal's state of health is less favorable than it would be in the absence of the disorder. Left untreated, a disorder does not necessarily cause a further decrease in the animal's state of health.

[0056] The terms "treatment", "treating", "treat", and the like, refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely

or partially preventing a disease or symptom thereof or reducing the likelihood of a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease. "Treatment", as used herein, covers any treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, *i.e.,* arresting its development or progression; and (c) relieving the disease, *i.e.,* causing regression of the disease and/or relieving one or more disease symptoms. "Treatment" is also meant to encompass delivery of an agent in order to provide for a pharmacologic effect, even in the absence of a disease or condition. For example, "treatment" encompasses delivery of a composition that can elicit an immune response or confer immunity in the absence of a disease condition, *e.g.,* in the case of a vaccine.

[0057] As used herein, the term "mammal" refers to any mammal, including, but not limited to, mammals of the order Rodentia, such as mice and hamsters, and mammals of the order Logomorpha, such as rabbits. In some embodiments, the mammals are from the order Carnivora, including felines (cats) and canines (dogs). In some embodiments, the mammals are from the order Artiodactyla, including bovines (cows) and swines (pigs) or of the order Perssodactyla, including Equines (horses). It is most preferred that the mammals are of the order Primates, Ceboids, or Simoids (monkeys) or of the order Anthropoids (humans and apes). In some embodiments, the mammal is a human. In some embodiments, the mammal is cynomolgus monkey.

[0058] The term "regression," as well as words stemming therefrom, as used herein, does not necessarily imply 100% or complete regression. Rather, there are varying degrees of regression of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the disclosed methods can provide any amount of any level of regression of a cancer in a mammal. Furthermore, the regression provided by the inventive method can include regression of one or more conditions or symptoms of the disease, *e.g.,* a cancer. Also, for purposes herein, "regression" can encompass delaying the onset of the disease, delaying the onset of a symptom, and/or delaying the onset of a condition thereof. With respect to progressive diseases and disorders, "regression" can encompass slowing the progression of the disease or disorder, slowing the progression of a symptom of the disease or disorder, and/or slowing the progression of a condition thereof.

[0059] An "effective amount" or "therapeutically effective amount" of a composition includes that amount of the composition which is sufficient to provide a beneficial effect to the subject to which the composition is administered. An "effective amount" of a delivery vehicle includes that amount sufficient to effectively bind or deliver a composition.

[0060] By "individual" or "host" or "subject" or "patient" is meant any mammalian subject for whom diagnosis, treatment, or therapy is desired, particularly humans. Other subjects may include cynomolgus monkey, cattle, dogs, cats, guinea pigs, rabbits, rats, mice, horses, and so on.

[0061] The term "in combination with" as used herein refers to uses where, for example, a first therapy is administered during the entire course of administration of a second therapy; where the first therapy is administered for a period of time that is overlapping with the administration of the second therapy, *e.g.*, where administration of the first therapy begins before the administration of the second therapy and the administration of the first therapy ends before the administration of the second therapy ends; where the administration of the second therapy begins before the administration of the first therapy and the administration of the second therapy ends before the administration of the first therapy ends; where the administration of the first therapy begins before administration of the second therapy begins and the administration of the second therapy ends before the administration of the first therapy ends; where the administration of the second therapy begins before administration of the first therapy begins and the administration of the first therapy ends before the administration of the second therapy ends. As such, "in combination" can also refer to regimen involving administration of two or more therapies. "In combination with" as used herein also refers to administration of two or more therapies which may be administered in the same or different formulations, by the same or different routes, and in the same or different dosage form type.

[0062] The term "allergic inflammation" as used herein refers to a local or general hypersensitivity reaction to at least one particular allergens. "Allergic inflammation" symptoms can vary greatly in effects and intensity.

[0063] "Encoding" includes the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (*i.e.*, rRNA, tRNA and mRNA) or a defined sequence of amino acids and the

biological properties resulting therefrom. Thus, a gene encodes a protein if, for example, transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

[0064] The term "nucleic acid" includes RNA or DNA molecules having more than one nucleotide in any form including single-stranded, double-stranded, oligonucleotide or polynucleotide. The term "nucleotide sequence" includes the ordering of nucleotides in an oligonucleotide or polynucleotide in a single-stranded form of nucleic acid.

[0065] By "nucleic acid construct" it is meant a nucleic acid sequence that has been constructed to comprise one or more functional units not found together in nature. Examples include circular, linear, double-stranded, extrachromosomal DNA molecules (plasmids), cosmids (plasmids containing COS sequences from lambda phage), viral genomes including non-native nucleic acid sequences, and the like.

[0066] The term "operably linked" as used herein includes a polynucleotide in functional relationship with a second polynucleotide, *e.g.,* a single-stranded or double-stranded nucleic acid moiety comprising the two polynucleotides arranged within the nucleic acid moiety in such a manner that at least one of the two polynucleotides is able to exert a physiological effect by which it is characterized, upon the other. By way of example, a promoter operably linked to the coding region of a gene is able to promote transcription of the coding region. The order specified when indicating operably linkage is not important. For example, the phrases: "the promoter is operably linked to the nucleotide sequence" and "the nucleotide sequence is operably linked to the promoter" are used interchangeably herein and are considered equivalent. In some cases, when the nucleic acid encoding the desired protein further comprises a promoter/regulatory sequence, the promoter/regulatory sequence is positioned at the 5' end of the desired protein coding sequence such that it drives expression of the desired protein in a cell.

[0067] The terms "oligonucleotide," "polynucleotide," and "nucleic acid molecule", used interchangeably herein, refer to a polymeric forms of nucleotides of any length, either ribonucleotides or deoxyribonucleotides. Thus, this term includes, but is not limited to, single-, double-, or multi-stranded DNA or RNA, genomic DNA, cDNA, DNA-RNA hybrids, or a

polymer comprising purine and pyrimidine bases or other natural, chemically or biochemically modified, non-natural, or derivatized nucleotide bases. The backbone of the polynucleotide can comprise sugars and phosphate groups (as may typically be found in RNA or DNA), or modified or substituted sugar or phosphate groups.

[0068] The term "osteoclast" as used herein is a large multinucleated cell with abundant acidophilic cytoplasm derived from hematopoietic stem cells, functioning in the absorption and removal of osseous tissue.

[0069] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use in vivo or ex vivo.

[0070] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.,* such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, see *e.g.,* Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[0071] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0072] Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section.

I. Antibodies

[0073] The present disclosure provides novel anti-LILRB3 antibodies. Such antibodies bind to and/or affect the functional properties of human LILRB3. Table 1 lists peptide sequences of heavy chain variable regions and light chain variable regions that, in combination as designated in Table 1, are LILRB3 antibodies. In some embodiments, the heavy chain variable region and

the light chain variable region are arranged in a Fab format. In some embodiments, the heavy chain variable region and the light chain variable region are fused together to from an scFv.

Table 1		
Clone	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
2E1	MEWPCIFLFLLSVTEGVHSQVQL QQSGPELVKPGASVKISCKASDY AFSSSWMNWVKQRPGKGLEWIG RIYPGDGDTNYNGKFKGKATLT ADKSSSTAYMQLSSLTSEDSAVY FCAREIYYDYDGYFDVWGTGTT VTVSSAKTTPPSVYPLAPGSAAQ TNSMVTLGCLVKGYFPEPVTVT WNSGSLSSGVHTFPAVLQSDLYT LSSSVTVPSSTWPSQTVTCNVAH PASSTKVDKKIVPRDCGCKPCIC TVPEVSSVFIFPPKPKDVLTITLTP KVTCVVVDISKDDQ SEQ ID NO: 1 (IgG1) CDR1 (SEQ ID NO: 27)- DYAFSSSW CDR2 (SEQ ID NO: 28)- IYPGDGDT CDR3 (SEQ ID NO: 29)- AREIYYDYDGYFDV	MHFQVQIFSFLLISASVIMSRGQ IVLTQSPAIMSASPGEKVTITCS ASSSVNYMHWFQQKSGTSPKL WIYSTSNLASGVPARFSGSGSG TSYSLTISRMEAEDAATYYCQQ RSSYPYTFGGGTKLEIKRADAA PTVSIFPPSSEQLTSGGASVVCF LNNFYPRDINVKWKIDGSERQN GVLNSWTDQDSKDSTYSMSST LTLTKDEYERHNSYTCEATHKT STSPR SEQ ID NO: 2 (kappa) CDR1 (SEQ ID NO: 30)- SSVNY CDR2 (SEQ ID NO: 31)- STS CDR3 (SEQ ID NO: 32)- CQQRSSYPY
3A3	MEWTWVFLFLLSVTAGVHSQVQ LQQSRTELMKPGASVKLSCKAT GYTFTGYWIEWVKQRPGHGLEW IGEILPGSTNINYNERFKGKATIT ADTSSNTAYMQLSSLTTEDSAIY YCARWASVVVGDYWGQGATLT VSSAKTTPPSVYPLAPGSAAQTN SMVTLGCLVKGYFPEPVTVTWN	MDFQVQIFSFLLISASVIMSRGQ IVLTQSPAIMSASLGERVTMTC TASSSVSSSYLHWYQQKPGSSP KLWIYSTSNLASGVPARFSGSG SGTSYSLTISSMEAEDAATYYC HQYHRSPPTFGGGTKLEIKRAD AAPTVSIFPPSSEQLTSGGASVV CFLNNFYPRDINVKWKIDGSER

	SGSLSSGVHTFPAVLQSDLYTLSS SVTVPSSTWPSQTVTCNVAHPAS STKVDKKIVPRDCGCKPCICTVP EVSSVFIFPPKPKDVLTITLTPKVT CVVVDISKDDQG SEQ ID NO: 3 (IgG1) CDR1 (SEQ ID NO: 33)- GYTFTGYW CDR2 (SEQ ID NO: 34)- ILPGSTNI CDR3 (SEQ ID NO: 35) ARWASVVVGDY	QNGVLNSWTDQDSKDSTYSMS STLTLTKDEYERHNSYT SEQ ID NO: 4 (kappa) CDR1 (SEQ ID NO: 36)- SSVSSSY CDR2 (SEQ ID NO: 37)- STS CDR3 (SEQ ID NO: 38)- HQYHRSPPT
3B1	MKVLSLLYLLTAIPGILSDVQLQ ESGPGLVKPSQSLSLTCSVTGYSI TSAYYWNWIRQFPENKLEWMG YISHDGSNTYNPSLKNRISITRDT SKNQFFLKLNSVTTEDTATYYC ATFDSDEVYWGQGTLVTVSAA KTTPPSVYPLAPGCGDTTGSSVT LGCLVKGYFPESVTVTWNSGSL SSSVHTFPALLQSGLYTMSSSVT VPSSTWPSQTVTCSVAHPASSTT VDKKLEPSGPISTINPCPPCKECH KCPAPNLEGGPSVFIFPPKG SEQ ID NO: 5 (IgG2b) CDR1 (SEQ ID NO: 39)- YSITSAYY CDR2 (SEQ ID NO: 40)- ISHDGSN CDR3 (SEQ ID NO: 41)- ATFDSDEVY	MSVLTQVLALLLLWLTGARCD IQMTQSPASLSASVGETVTITCR ASGNIHNFLAWYQQKQGRSPQ LLVYNAKTLADGVPSRFSGSGS GAQYSLKVNSLQPEDFGNYYC QHFWSTPFTFGSGTKLEAKRAD AAPTVSIFPPSSEQLTSGGASVV CFLNNFYPRDINVKWKIDGSER QNGVLNSWTDQDSKDSTYSMS STLTLTKDEYERHNSYT SEQ ID NO: 6 (kappa) CDR1 (SEQ ID NO: 42)- GNIHNF CDR2 (SEQ ID NO: 43)- NAK CDR3 (SEQ ID NO: 44)- QHFWSTPFT
6A10	MGWSWIFLLFLSGTAGVLSEVQ LQQSGPELVKPGASVKIPCKASG	MESQTQVFLSLLLWVSGTCGNI MMTQSPSSLAVSAGEKVTMSC

	YTFTDYNMDWVKQSHGKSLEW IGDINPNNGGTIYNQKFKGKATL TVDKSSSTAYMELRSLTSEDTA VYYCARRGIYYGSSYAMDYWG QGTSVTVSSAKTTPPSVYPLAPG SAAQTNSMVTLGCLVKGYFPEP VTVTWNSGSLSSGVHTFPAVLQ SDLYTLSSSVTVPSSTWPSQTVT CNVAHPASSTKVDKKIVPRDCG CKPCICTVPEVSSVFIFPPKPKDV LTITLTPKVTCVVVDISKDDQG SEQ ID NO: 7 (IgG1) CDR1 (SEQ ID NO: 45)- GYTFTDYN CDR2 (SEQ ID NO: 46)- INPNNGGT CDR3 (SEQ ID NO: 47)- ARRGIYYGSSYAMDY	KSSQSVLYSSNQKNYLAWYQQ KPGQSPKLLIYWASTRESGVPD RFTGSGSGTDFTLTISRVQAEDL AVYYCHQYLSPYTFGGGTKLEI KRADAAPTVSIFPPSSEQLTSGG ASVVCFLNNFYPRDINVKWKID GSERQNGVLNSWTDQDSKDST YSMSSTLTLTKDEYERHNSYT SEQ ID NO: 8 (kappa) CDR1 (SEQ ID NO: 48)- QSVLYSSNQKNY CDR2 (SEQ ID NO: 49)-WAS CDR3 (SEQ ID NO: 50)- HQYLSPYT
7C5	MEWELSLIFIFALLKDVQCDVQL LETGGGLVQPGGSRGLSCEGSG FTFSGFWMSWVRQTPGKTLEWI GDINSDGTAINYAPSIKDRFTIFR DNDKSTLYLQMSNVRSEDTATY FCMRSYGSGPWCFDVWGTGTT VTVSSAKTTAPSVYPLAPVCGG TTGSSVTLGCLVKGYFPEPVTLT WNSGSLSSGVHTFPALLQSGLY TLSSSVTVTSNTWPSQTITCNVA HPASSTKVDKKIEPRVPITQNPC PPLKECPPCAAPDLLGGPSVFIFP SEQ ID NO: 9 (IgG2c) CDR1 (SEQ ID NO: 51)- GFTFSGF	MDFQVQIFSFLLISASVIMSRGQ IVLTQSPAIMSASLGERVTMTC TASSSVSSAYLHWYQQKPGSSP KLWIYSTSNLASGVPTRFSGSG SGTSYSLTISSMEAEDAATYYC HQYHRSPFTFGAGTKLELKRAD AAPTVSIFPPSSEQLTSGGASVV CFLNNFYPKDKGEF SEQ ID NO: 10 (kappa) CDR1 (SEQ ID NO: 54)- SSVSSAY CDR2 (SEQ ID NO: 55)- STS CDR3 (SEQ ID NO: 56)- QYHRSPFT

	CDR2 (SEQ ID NO: 52)- INSDGTAI CDR3 (SEQ ID NO: 53)- MRSYGSGPWCFDV	
1D5	MEWTWVFLFLLSVTAGVHSQV QLQQSGAELMKPGASVKLSCKS TDYTFTGYWIEWVKQRPGHGLE WIGEILFGSGTNNYNEKFNGKA TFTADTSSNTAYMQLSSLTTEDS AIYYCARRNNFYFDYWGQGTTL TVSSAKTTPPSVYPLAPGSAAQT NSMVTLGCLVKGYFPEPVTVTW NSGSLSSGVHTFPAVLQSDLYTL SSSVTVPSSTWPSQTVTCNVAHP ASSTKVDKKIVPRDCGCKPCICT VPEVSSVFIFPPKPKDVLTITLTP KVTCVVVDISKDDQG SEQ ID NO: 11 (IgG1) CDR1 (SEQ ID NO: 57)- DYTFTGYW CDR2 (SEQ ID NO: 58)- ILFGSGTN CDR3 (SEQ ID NO: 59)- CARRNNFYFDY	MDFQVQIFSFLLISASVIMSRGQ IVLTQSPAIMSASLGERVTMTC TASSSVSSTYLHWYQQKPGSSP KLWIYSTSNLASGVPARFSGSG SGTSYSLTITTMETEDAATYYC HQYHRSPFTFGSGTKLEIKRAD AAPTVSIFPPSSEQLTSGGASVV CFLNNFYPRDINVKWKIDGSER QNGVLNSWTDQDSKDSTYSMS STLTLTKDEYERHNSYTCEATH KTSTSPR SEQ ID NO: 12 (kappa) CDR1 (SEQ ID NO: 60)- SSVSST CDR2 (SEQ ID NO: 61)- STS CDR3 (SEQ ID NO: 62)- HQYHRSPFT
4C8	MEWTWVFLFLLSVTAGVHSQV QLQQSGGELMKPGASVKLSCKA TEYTFTGYWIEWIKQRPGHGLE WIGEILFGNGVTNYNENFKGKA TFTADASSNTAYMQLSSLTTEDS AIYYCARRTYFYFDYWGQGTTL TVSSAKTTPPSVYPLAPGSAAQT NSMVTLGCLVKGYFPEPVTVTW NSGSLSSGVHTFPAVLQSDLYTL	MDFQVQIFSFLLISASVIMSRGQ IVLTQSPAIMSASLGERVTMTC TASSSVSSSYLHWYQQKPGSSP KLWIYSTSNLASGVPARFSGSG SGTSYSLTISSMEAEDAATYYC HQYHRSPFTFGSGTKLEIKRAD AAPTVSIFPPSSEQLTSGGASVV CFLNNFYPRDINVKWKIDGSER QNGVLNSWTDQDSKDSTYSMS

	SSSVTVPSSTWPSQTVTCNVAHP ASSTKVDKKIVPRDCGCKPCICT VPEVSSVFIFPPKPKDVLTITLTP KVTCVVVDISKDDQG SEQ ID NO: 13 (IgG1) CDR1 (SEQ ID NO: 63)- EYTFTGYW CDR2 (SEQ ID NO: 64)- ILFGNGVT CDR3 (SEQ ID NO: 65)- ARRTYFYFDY	STLTLTKDEYERHNSYT SEQ ID NO: 14 (kappa) CDR1 (SEQ ID NO: 66)- SSVSSSY CDR2 (SEQ ID NO: 67)- STS CDR3 (SEQ ID NO: 68)- HQYHRSPFT
7E10	MEWTWVFLFLLSVTAGVHSQV QLQQSGAELMKPGASVKLSCKA SGYTFTGYWIEWVKQRPGHGLE WIGEILPGNGYTNYNEKFEGKA TFTADTSSNTAYIQLNSLTTEDS AIYYCARRGSWTMDFWGQGTS VTVSSAKTTPPSVYPLAPGSAAQ TNSMVTLGCLVKGYFPEPVTVT WNSGSLSSGVHTFPAVLQSDLY TLSSSVTVPSSTWPSQTVTCNVA HPASSTKVDKKIVPRDCGCKPCI CTVPEVSSVFIFPPKPKDVLTITL TPKVTCVVVDISKDDKG SEQ ID NO: 15 (IgG1) CDR1 (SEQ ID NO: 69)- GYTFTGYW CDR2 (SEQ ID NO: 70)- ILPGNGYT CDR3 (SEQ ID NO: 71)- ARRGSWTMDF	MDFQVQIFSFLLISASVIMSRGQ IVLTQSPAIMSASLEERVTMTCT ASSSVSSSYLHWFQQKPGSSPK LWIYSTSNLASGVPARFSGSGS GTSYSLTISSMEAEDAATYYCH QYHRSPHTFGGGTKLEIKRADA APTVSIFPPSSEQLTSGGASVVC FLNNFYPRDINVKWKIDGSERQ NGVLNSWTDQDSKDSTYSMSS TLTLTKDEYERHNSYT SEQ ID NO:16 (kappa) CDR1 (SEQ ID NO: 72)- SSVSSSY CDR2 (SEQ ID NO: 73)- STS CDR3 (SEQ ID NO: 74)- HQYHRSPHT
9E8	MEWIWILLFILSGTAGVQSQVQL QQSGAELARPGASVKLSCKASG	MHFQVQIFSFLLISASVIMSRGQ IVLTQSPAIMSASPGEKVTITCS

	YTFTSNGISWVKQTTGQGLEWI GLIYPRSGNTYYNERFKGKATL TADKSSSTAYMELRRLTSEDSA VYFCLRERETGLFDFWGQGTTL TVSSAKTTPPSVYPLAPGSAAQT NSMVTLGCLVKGYFPEPVTVTW NSGSLSSGVHTFPAVLQSDLYTL SSSVTVPSSTWPSQTVTCNVAHP ASSTKVDKKIVPRDCGCKPCICT VPEVSSVFIFPPKPKDVLTITLTP KVTCVVVDISKDDQG SEQ ID NO: 17 (IgG1) CDR1 (SEQ ID NO: 75)- GYTFTSNG CDR2 (SEQ ID NO: 76)- IYPRSGNT CDR3 (SEQ ID NO: 77)- LRERETGLFDF	ASSSVSYMHWFQQKPGTSPKL WIYTTSNLASGVPARFSGSGSG TSYSLTISRMEAEDAATYYCQQ RSSYPPTFGGGTKLEVKRADAA PTVSIFPPSSEQLTSGGASVVCF LNNFYPRDINVKWKIDGSERQN GVLNSWTDQDSKDSTYSMSST LTLTKDEYERHNSYT SEQ ID NO: 18 (kappa) CDR1 (SEQ ID NO: 78)- SSVSY CDR2 (SEQ ID NO: 79)- TTS CDR3 (SEQ ID NO: 80)- QQRSSYPPT
3E8	MEWTWVFLFLLSVTAGVHSQVQ LQQSGAELMKPGASVRLSCKAT GYTFTGYWIEWVKQRPGHGLEW IGEILPGSGSSNYNEKFKGKATIT ADTSSNTSDMQLNSLTTEDSAIY YCARWGHPFDYWGLGTTLTVSS AKTTPPSVYPLAPGSAAQTNSMV TLGCLVKGYFPEPVTVTWNSGSL SSGVHTFPAVLQSDLYTLSSSVT VPSSTWPSQTVTCNVAHPASSTK VDKKIVPRDCGCKPCICTVPEVS SVFIFPPKPKDVLTITLTPKVTCV VVDISKDDQG SEQ ID NO: 19 (IgG1) CDR1 (SEQ ID NO: 81)-	MDFQVQIFSFLLISASVIMSRGQ IVLTQSPAIMSASLGERVTMTC TASSSVSSSYLHWYQQKPGSSP KLWIYSTSNLASGVPARFSGSG SGTSYSLTISSMEAEDAATYYC HQYHRSPRTFGGGTKLEIKRAD AAPTVSIFPPSSEQLTSGGASVV CFLNNFYPRDINVKWKIDGSER QNGVLNSWTDQDSKDSTYSMS STLTLTKDEYERHNSYT SEQ ID NO: 20 (kappa) CDR1 (SEQ ID NO: 84)- SSVSSSY CDR2 (SEQ ID NO: 85)- STS CDR3 (SEQ ID NO: 86)-

	GYTFTGYW CDR2 (SEQ ID NO: 82)- ILPGSGSS CDR3 (SEQ ID NO: 83)- RWGHPFDY	HQYHRSPRT
5C1	MEWTWVFLFLLSVTAGVHSQVQ LQQSGAELMKPGASVKLSCKAT DYTFTGYWIEWVKQRPGHGLEW IGQILPGSAYSNYNEKFQGKATFT ADTSSDTAFMQLSSLTAEDSAIY YCARRDYYTMDYWGQGTSVTV SSAKTTAPSVYPLAPVCGGTTGS SVTLGCLVKGYFPEPVTLTWNSG SLSSGVHTFPALLQSGLYTLSSSV TVTSNTWPSQTITCNVAHPASST KVDKKIEPRVPITQNPCPPLKECP PCAAPDLLGGPSVFIFPPKIKDVL MISLSPMVTCVVVDVSEDDQG SEQ ID NO: 21 (IgG2c) CDR1 (SEQ ID NO: 87)- DYTFTGYW CDR2 (SEQ ID NO: 88)- ILPGSAYS CDR3 (SEQ ID NO: 89)- ARRDYYTMDY	MDFQVQIFSFLLISASVIMSRGQ IVLTQSPAIMSASLGERVTMTC TASSSVSSTYLHWYQQKPGSSP KLWIYSTSNLASGVPPRFSGSG SGTSYSLTISSMEAEDAATYYC HQYHRSPFTFGSGTKLEIERAD AAPTVSIFPPSSEQLTSGGASVV CFLNNFYPRDINVKWKIDGSER QNGVLNSWTDQDSKDSTYSMS STLTLTKDEYERHNSYT SEQ ID NO: 22 (kappa) CDR1 (SEQ ID NO: 90)- SSVSSTY CDR2 (SEQ ID NO: 91)- STS CDR3 (SEQ ID NO: 92)- HQYHRSPFT
9A1	MEWTWVFLFLLSVTAGVHSQVQ LQQSGAELMKPGASVKLSCKAT GSTFTGYWIEWVKQRPGHGLEW IGEILPGSGYTNYNENFKGKATIT ADTSSNTAYMQLSSLTTEDSAIY YCARREWYYFDYWGQGTTLIVS SAKTTPPSVYPLAPGSAAQTNSM VTLGCLVKGYFPEPVTVTWNSG	MDFQVQIFSFLLISASVIMSRGQ IVLTQSPAIMSASLGERVTMTC TASSSVSSSYLHWYQQKPGSSP KLWIYSTSNLASGVPVRFSGSG SGTSYSLTISIMEAEDAATYYC HQYHRSPFTFGSGTKLDIKRAD AAPTVSIFPPSSEQLTSGGASVV CFLNNFYPRDINVKWKIDGSER

	SLSSGVHTFPAVLQSDLYTLSSSV TVPSSTWPSQTVTCNVAHPASST KVDKKIVPRDCGCKPCICTVPEV SSVFIFPPKPKDVLTITLTPKVTCV VVDISKDDQG SEQ ID NO: 23 (IgG1) CDR1 (SEQ ID NO: 93)- STFTGYW CDR2 (SEQ ID NO: 94)- ILPGSGYT CDR3 (SEQ ID NO: 95)- ARREWYYFDY	QNGVLNSWTDQDSKDSTYSMS STLTLTKDEYERHNSYT SEQ ID NO: 24 (kappa) CDR1 (SEQ ID NO: 96)- SSVSSSY CDR2 (SEQ ID NO: 97)- STS CDR3 (SEQ ID NO: 98)- HQYHRSPFT
1B2	MEWTWVFLFLLSVTAGVHSQVQ LQQSGAELMKPGASVKLSCKAT GYTFTVYWIEWVKQRPGHGLEW IGEILPGSGSINYIEKFKGKATITA DTSSNTAYMQLSSLTTEDSAIYY CARRTWYYFDYWGQGTTLTVSS AKTTPPSVYPLAPGSAAQTNSMV TLGCLVKGYFPEPVTVTWNSGSL SSGVHTFPAVLQSDLYTLSSSVT VPSSTWPSQTVTCNVAHPASSTK VDKKIVPRDCGCKPCICTVPEVS SVFIFPPKPKDVLTITLTPKVTCV VVDISKDDQG SEQ ID NO: 25 (IgG1) CDR1 (SEQ ID NO: 99)- GYTFTVYW CDR2 (SEQ ID NO: 100)- ILPGSGSI CDR3 (SEQ ID NO; 101)- ARRTWYYFDY	MDFQVQIFSFLLISASVIMSRGQ IVLTQSPAIMSASLGERVTMTC TASSSVSSSYLHWYQQKPGSSP QLWIYSTSNLASGVPTRFSGSG SGTSYSLTISSMEAEDAATYYC HQYHRSPFTFGSGTKLEIKRAD AAPTVSIFPPSSEQLTSGGASVV CFLNNFYPRDINVKWKIDGSER QNGVLNSWTDQDSKDSTYSMS STLTLTKDEYERHNSYT SEQ ID NO: 26 (kappa) CDR1 (SEQ ID NO: 102)- SSVSSSY CDR2 (SEQ ID NO: 103)- STS CDR3 (SEQ ID NO: 104)- HQYHRSPFT

[0074] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:1 and a light chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:2.

[0075] In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:27, a vhCDR2 comprising SEQ ID NO:28, a vhCDR3 comprising SEQ ID NO:29, a vlCDR1 comprising SEQ ID NO:30, a vlCDR2 comprising SEQ ID NO:31, and a vlCDR3 comprising SEQ ID NO:32. In some embodiments, one or more of such 6 CDRs have from 1, 2, 3, 4 or 5 amino acid modifications. In further embodiments, a single CDR contains 1 or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[0076] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:3 and a light chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:4.

[0077] In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:33, a vhCDR2 comprising SEQ ID NO:34, a vhCDR3 comprising SEQ ID NO:35, a vlCDR1 comprising SEQ ID NO:36, a vlCDR2 comprising SEQ ID NO:37, and a vlCDR3 comprising SEQ ID NO:38. In further embodiments, a single CDR contains 1 or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[0078] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:5 and a light chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:6.

[0079] In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:39, a vhCDR2 comprising SEQ ID NO:40, a vhCDR3 comprising SEQ ID NO:41,

a vlCDR1 comprising SEQ ID NO:42, a vlCDR2 comprising SEQ ID NO:43, and a vlCDR3 comprising SEQ ID NO:44. In some embodiments, one or more of such 6 CDRs have from 1, 2, 3, 4 or 5 amino acid modifications. In further embodiments, a single CDR contains 1 or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[0080] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:7 and a light chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:8.

[0081] In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:45, a vhCDR2 comprising SEQ ID NO:46, a vhCDR3 comprising SEQ ID NO:47, a vlCDR1 comprising SEQ ID NO:48, a vlCDR2 comprising SEQ ID NO:49, and a vlCDR3 comprising SEQ ID NO:50. In some embodiments, one or more of such 6 CDRs have from 1, 2, 3, 4 or 5 amino acid modifications. In further embodiments, a single CDR contains 1 or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[0082] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:9 and a light chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:10.

[0083] In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:51, a vhCDR2 comprising SEQ ID NO:52, a vhCDR3 comprising SEQ ID NO:53, a vlCDR1 comprising SEQ ID NO:54, a vlCDR2 comprising SEQ ID NO:55, and a vlCDR3 comprising SEQ ID NO:56. In some embodiments, one or more of such 6 CDRs have from 1, 2, 3, 4 or 5 amino acid modifications. In further embodiments, a single CDR contains 1 or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[0084] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%,

99%, or 100%) identical to SEQ ID NO:11 and a light chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:12.

[0085] In some embodiments, the anti-LILRB3 antibodies that include a vhCDR1 comprising SEQ ID NO:57, a vhCDR2 comprising SEQ ID NO:58, a vhCDR3 comprising SEQ ID NO:59, a vlCDR1 comprising SEQ ID NO:60, a vlCDR2 comprising SEQ ID NO:61, and a vlCDR3 comprising SEQ ID NO:62. In some embodiments, one or more of such 6 CDRs have from 1, 2, 3, 4 or 5 amino acid modifications. In further embodiments, a single CDR contains 1 or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[0086] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:13 and a light chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:14.

[0087] In some embodiments, the anti-LILRB3 antibodies that include a vhCDR1 comprising SEQ ID NO:63, a vhCDR2 comprising SEQ ID NO:64, a vhCDR3 comprising SEQ ID NO:65, a vlCDR1 comprising SEQ ID NO:66, a vlCDR2 comprising SEQ ID NO:67, and a vlCDR3 comprising SEQ ID NO:68. In some embodiments, one or more of such 6 CDRs have from 1, 2, 3, 4 or 5 amino acid modifications. In further embodiments, a single CDR contains 1 or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[0088] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:15 and a light chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:16.

[0089] In some embodiments, the anti-LILRB3 antibodies that include a vhCDR1 comprising SEQ ID NO:69, a vhCDR2 comprising SEQ ID NO:70, a vhCDR3 comprising SEQ ID NO:71, a vlCDR1 comprising SEQ ID NO:72, a vlCDR2 comprising SEQ ID NO:73, and a vlCDR3 comprising SEQ ID NO:74. In some embodiments, one or more of such 6 CDRs have from 1, 2,

3, 4 or 5 amino acid modifications. In further embodiments, a single CDR contains 1 or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[0090] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:17 and a light chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:18.

[0091] In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:75, a vhCDR2 comprising SEQ ID NO:76, a vhCDR3 comprising SEQ ID NO:77, a vlCDR1 comprising SEQ ID NO:78, a vlCDR2 comprising SEQ ID NO:79, and a vlCDR3 comprising SEQ ID NO:80. In some embodiments, one or more of such 6 CDRs have from 1, 2, 3, 4 or 5 amino acid modifications. In further embodiments, a single CDR contains 1 or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[0092] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:19 and a light chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:20.

[0093] In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:81, a vhCDR2 comprising SEQ ID NO:82, a vhCDR3 comprising SEQ ID NO:83, a vlCDR1 comprising SEQ ID NO:84, a vlCDR2 comprising SEQ ID NO:85, and a vlCDR3 comprising SEQ ID NO:86. In some embodiments, one or more of such 6 CDRs have from 1, 2, 3, 4 or 5 amino acid modifications. In further embodiments, a single CDR contains 1 or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[0094] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:21 and a light chain variable region having an amino

acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:22.

[0095] In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:87, a vhCDR2 comprising SEQ ID NO:88, a vhCDR3 comprising SEQ ID NO:89, a vlCDR1 comprising SEQ ID NO:90, a vlCDR2 comprising SEQ ID NO:91, and a vlCDR3 comprising SEQ ID NO:92. In some embodiments, one or more of such 6 CDRs have from 1, 2, 3, 4 or 5 amino acid modifications. In further embodiments, a single CDR contains 1 or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[0096] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:23 and a light chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:24.

[0097] In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:93, a vhCDR2 comprising SEQ ID NO:94, a vhCDR3 comprising SEQ ID NO:95, a vlCDR1 comprising SEQ ID NO:96, a vlCDR2 comprising SEQ ID NO:97, and a vlCDR3 comprising SEQ ID NO:98. In some embodiments, one or more of such 6 CDRs have from 1, 2, 3, 4 or 5 amino acid modifications. In further embodiments, a single CDR contains 1 or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[0098] In some embodiments, the anti-LILRB3 antibodies in the present disclosure include a heavy chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:25 and a light chain variable region having an amino acid sequence at least 80% (*e.g.*, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:26.

[0099] In some embodiments, the anti-LILRB3 antibodies include a vhCDR1 comprising SEQ ID NO:99, a vhCDR2 comprising SEQ ID NO:100, a vhCDR3 comprising SEQ ID NO:101, a vlCDR1 comprising SEQ ID NO:102, a vlCDR2 comprising SEQ ID NO:103, and a vlCDR3 comprising SEQ ID NO:104. In some embodiments, one or more of such 6 CDRs have from 1, 2, 3, 4 or 5 amino acid modifications. In further embodiments, a single CDR contains 1

or 2 amino acid substitutions, and the modified anti-LILRB3 antibodies retain binding to human LILRB3.

[00100] In addition to the sequence variants described herein in the heavy chain and light chain variable regions and/or CDRs, changes in the framework region(s) of the heavy and/or light variable region(s) can be made. In some embodiments, variants in the framework regions (*e.g.,* excluding the CDRs) retain at least about 80, 85, 90 or 95% identity to a germline sequence. Variants can be made to retain at least about 80, 85, 90 or 95% identity to any one of the light chain V-GENE, light chain J-GENE, heavy chain V-GENE, heavy chain J-GENE, and heavy chain D-GENE alleles.

[00101] In some embodiments, variations are made in the framework regions that retain at least 80, 85, 90 or 95% identity to the germline gene sequences, while keeping 6 CDRs unchanged.

[00102] In some embodiments, variations are made in both the framework regions that retain at least 80, 85, 90 or 95% identity to germline gene sequences. The CDRs can have amino acid modifications (*e.g.,* from 1, 2, 3, 4 or 5 amino acid modifications in the set of CDRs (that is, the CDRs can be modified as long as the total number of changes in the set of 6 CDRs is less than 6 amino acid modifications, with any combination of CDRs being changed; *e.g.,* there may be one change in vlCDR1, two in vhCDR2, none in vhCDR3, etc.).

[00103] By selecting amino acid sequences of CDRs and/or variable regions of a heavy chain and a light chain from those described herein and combining them with amino acid sequences of framework regions and/or constant regions of a heavy chain and a light chain of an antibody as appropriate, a person skilled in the art will be able to design an anti-LILRB3 antibody according to the present invention. The antibody framework regions and/or constant region (Fc domain) described in the current invention can derive from an antibody of any species, such as from human, rabbit, dog, cat, mouse, horse or monkey.

[00104] In some embodiments, the constant region is derived from human, and includes a heavy chain constant region derived from those of IgG, IgA, IgM, IgE, and IgD subtypes or variants thereof, and a light chain constant region derived from kappa or lambda subtypes or variants thereof. In some embodiments, the heavy chain constant region is derived from a human IgG, including IgG1, IgG2, IgG3, and IgG4. In some embodiments, the amino acid sequence of the heavy chain constant region is at least 80%, 85%, 90%, or 95% identical to a human IgG1,

IgG2, IgG3, or IgG4 constant region. In some other embodiments, the amino acid sequence of the constant region is at least 80%, 85%, 90%, or 95% identical to an antibody constant region from another mammal, such as rabbit, dog, cat, mouse, horse or monkey. In some embodiments, the antibody constant region includes a hinge, a CH2 domain, a CH3 domain and optionally a CH1 domain.

[00105] In some embodiments, the antibodies described herein can be derived from a mixture from different species, *e.g.,* forming a chimeric antibody and/or a humanized antibody. In general, both "chimeric antibodies" and "humanized antibodies" refer to antibodies that combine regions from more than one species. For example, "chimeric antibodies" traditionally comprise variable region(s) from a mouse (or rat, in some cases) and the constant region(s) from a human. "Humanized antibodies" generally refer to non-human antibodies that have had the variable-domain framework regions swapped for sequences found in human antibodies. Generally, in a humanized antibody, the entire antibody, except the CDRs, is encoded by a polynucleotide of human origin or is identical to such an antibody except within its CDRs. The CDRs, some or all of which are encoded by nucleic acids originating in a non-human organism, are grafted into the beta-sheet framework of a human antibody variable region to create an antibody, the specificity of which is determined by the engrafted CDRs. The creation of such antibodies is described in, *e.g.,* WO 92/11018, Jones, 1986, Nature 321:522-525, Verhoeyen et al., 1988, Science 239:1534-1536, all entirely incorporated by reference. "Backmutation" of selected acceptor framework residues to the corresponding donor residues is often required to regain affinity that is lost in the initial grafted construct (US 5530101; US 5585089; US 5693761; US 5693762; US 6180370; US 5859205; US 5821337; US 6054297; US 6407213, all entirely incorporated by reference). The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region, typically that of a human immunoglobulin, and thus will typically comprise a human Fc region. Humanized antibodies can also be generated using mice with a genetically engineered immune system, as described for example in Roque et al., 2004, Biotechnol. Prog. 20:639-654, entirely incorporated by reference. A variety of techniques and methods for humanizing and reshaping non-human antibodies are well known in the art (See Tsurushita & Vasquez, 2004, Humanization of Monoclonal Antibodies, Molecular Biology of B Cells, 533-545, Elsevier Science (USA), and references cited therein, all entirely incorporated by reference). Humanization methods include but are not limited to methods described in Jones et al., 1986, Nature 321:522-525; Riechmann et al.,1988; Nature 332:323-329; Verhoeyen et al., 1988, Science, 239:1534-1536; Queen et al., 1989, Proc Natl Acad Sci, USA 86:10029-33; He et

al., 1998, J. Immunol. 160: 1029-1035; Carter et al., 1992, Proc Natl Acad Sci, USA 89:4285-9, Presta et al., 1997, Cancer Res. 57(20):4593-9; Gorman et al., 1991, Proc. Natl. Acad. Sci. USA 88:4181-4185; O'Connor et al., 1998, Protein Eng 11:321-8, all entirely incorporated by reference. Humanization or other methods of reducing the immunogenicity of nonhuman antibody variable regions may include resurfacing methods, as described for example in Roguska et al., 1994, Proc. Natl. Acad. Sci. USA 91:969-973, entirely incorporated by reference. Other humanization methods may involve the grafting of only parts of the CDRs, including but not limited to methods described in Tan et al., 2002, J. Immunol. 169:1119-1125; De Pascalis et al., 2002, J. Immunol. 169:3076-3084, all entirely incorporated by reference.

[00106] In some embodiments, the antibodies of the current invention comprise a heavy chain variable region derived from a particular human germline heavy chain immunoglobulin gene and/or a light chain variable region derived from a particular human germline light chain immunoglobulin gene. Such antibodies may contain amino acid differences as compared to the human germline sequences, due to, for example, naturally-occurring somatic mutations or intentional introduction of site-directed mutation. However, a humanized antibody typically is at least 80% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that identify the antibody as being derived from human sequences when compared to the germline immunoglobulin amino acid sequences of other species (*e.g.,* murine germline sequences). In certain cases, a humanized antibody may be at least 95, 96, 97, 98 or 99%, or even at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the human germline immunoglobulin gene. Typically, a humanized antibody derived from a particular human germline sequence will display no more than 10-20 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene. In certain cases, the humanized antibody may display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene.

[00107] In some embodiments, the antibodies of the current disclosure are humanized and affinity matured, as is known in the art. Structure-based methods may be employed for humanization and affinity maturation, for example as described in US Patent No 7,657,380. Selection based methods may be employed to humanize and/or affinity mature antibody variable regions, including but not limited to methods described in Wu et al., 1999, J. Mol. Biol. 294:151-162; Baca et al., 1997, J. Biol. Chem. 272(16):10678-10684; Rosok et al., 1996, J. Biol.

Chem. 271(37): 22611-22618; Rader et al., 1998, Proc. Natl. Acad. Sci. USA 95: 8910-8915; Krauss et al., 2003, Protein Engineering 16(10):753-759, all entirely incorporated by reference.

II. Characteristics of the antibodies

[00108] In some embodiments, the anti-LILRB3 antibodies described herein bind to human LILRB3. In some embodiments, binding of the anti-LILBR3 antibodies to human LILRB3 is measured by Flow cytometry, such as the exemplary assay described in Example 1.

[00109] In some embodiments, the anti-LILRB3 antibodies display low immunogenicity when administered into human subjects. These antibodies can contain an Fc domain derived from human IgG1, human IgG2 or human IgG3. In some embodiments, these antibodies are humanized using the framework regions derived from human immunoglobulins.

[00110] In some embodiments, the anti-LILRB3 antibodies affect the responsiveness of T cells. In some embodiments the anti-LILRB3 antibodies regulate surface expression of activation markers in response to different types of T cell stimulation, such as the exemplary assay described in Example 3. In some embodiments the anti-LILRB3 antibodies regulate cytokine production by PBMCs in response to T cell stimulation, such as the exemplary assay described in Example 4.

[00111] In some embodiments, anti-LILRB3 antibodies described act as LILRB3 antagonists. As a result, such anti-LILRB3 antibodies inhibit the activity of LILRB3.

[00112] In some other embodiments, anti-LIRB3 antibodies described herein act as LILRB3 agonists. As a result, such anti-LILRB3 antibodies promote the activity of LILRB3.

[00113] Effects of the anti-LILRB3 antibodies on T cell function can be assayed using a variety of methods known in the art and described herein. Accordingly, the anti-LILRB3 antibodies can serve as LILRB3 antagonists or LILRB3 agonists.

III. Nucleic acids of the invention

[00114] Nucleic acids encoding the anti-LILRB3 antibodies described herein are also encompassed by the present disclosure, as well as expression vectors containing such nucleic acids and host cells transformed with such nucleic acids and/or expression vectors. As will be appreciated by those in the art, the protein sequences depicted herein can be encoded by any

number of possible nucleic acid sequences due to the degeneracy of the genetic code, and one of skill in the art could readily identify such nucleic acid sequences based on the amino acid sequences provided herein.

[00115] In some embodiments, nucleic acid compositions encoding the anti-LILRB3 antibodies and/or LILRB3-binding domains are also encompassed by the invention. As will be appreciated by those in the art, in the case of antigen binding domains, the nucleic acid compositions generally include a first nucleic acid encoding the heavy chain variable region and a second nucleic acid encoding the light chain variable region. In the case of scFvs, a single nucleic acid encoding the heavy chain variable region and light chain variable region, separated by a linker described herein, can be made. In the case of traditional antibodies, the nucleic acid compositions generally include a first nucleic acid encoding the heavy chain and a second nucleic acid encoding the light chain, which will, upon expression in a cell, spontaneously assemble into the "traditional" tetrameric format of two heavy chains and two light chains.

[00116] In some embodiments, the nucleic acid compositions encoding the anti-LILRB3 antibodies and/or LILRB3-binding domains are codon optimized versions or variants.

[00117] As is known in the art, the nucleic acids encoding the components of the invention can be incorporated into expression vectors, and depending on the host cells, used to produce the antibodies of the invention. These two nucleic acids can be incorporated into a single expression vector or into two different expression vectors. Generally, the nucleic acids can be operably linked to any number of regulatory elements (promoters, origin of replication, selectable markers, ribosomal binding sites, inducers, etc.) in an expression vector. The expression vectors can be extra-chromosomal or integrating vectors.

[00118] The nucleic acids and/or expression vectors of the current invention can be introduced into any type of host cells, which are well known in the art, including mammalian, bacterial, yeast, insect and fungal cells. After transfection, single cell clones can be isolated for cell bank generation using methods known in the art, such as limited dilution, ELISA, FACS, microscopy, or Clonepix. Clones can be cultured under conditions suitable for bio-reactor scale-up and maintained expression of the antibodies. The antibodies can be isolated and purified using methods known in the art including centrifugation, depth filtration, cell lysis, homogenization, freeze-thawing, affinity purification, gel filtration, ion exchange chromatography, hydrophobic interaction exchange chromatography, and mixed-mode chromatography.

IV. Therapeutic Applications

[00119] The current disclosure provides a method of modulating an immune response in a subject, and the method includes administering to the subject an effective amount of an anti-LILRB3 antibody described herein, or a pharmaceutical composition containing an anti-LILRB3 antibody.

[00120] In some embodiments, the methods of modulating an immune response encompassed by the present disclosure comprises inhibiting LILRB3 activity in a subject, and in further embodiments, such methods comprise administering to the subject an effective amount of an anti-LILRB3 antibody that acts as a LILRB3 antagonist, or by administering a pharmaceutical composition containing an antagonistic anti-LILRB3 antibody.

In some embodiments, the methods of modulating an immune response encompassed by the present disclosure comprises promoting LILRB3 activity in a subject, and in further embodiments, such methods comprise administering to the subject an effective amount of an anti-LILRB3 antibody that acts as a LILRB3 agonist, or by administering a pharmaceutical composition containing an agonistic anti-LILRB3 antibody.

In some embodiments, an antagonist may stimulate and immune response. In other embodiments an antagonistic may inhibit an immune response. In some embodiments an agonist may stimulate an immune response. In other embodiments an agonist may inhibit an immune response.

[00121] The present disclosure also provides methods of treating cancer in a subject, and such methods include administering to the subject an effective amount of an anti-LILRB3 antibody, or a pharmaceutical composition containing such anti-LILRB3 antibody. In some embodiments, the cancer to be treated expresses LILRB3 on the cancer cell surface. In some embodiments, the cancer to be treated upregulates LILRB3 compared to the corresponding non-cancerous tissue. In some embodiments, the subject to be treated expresses LILRB3 on one or more types of immune cells including lymphoid cells, myeloid cells, monocytes, monocyte-derived osteoclasts, granulocytes, dendritic cells, osteoclasts, and progenitor mast cells. In some embodiments, the subject to be treated expresses a high level of LILRB3 on one or more types of immune cells including monocytes, monocyte-derived osteoclasts, granulocytes, dendritic cells, osteoclasts, and progenitor mast cells. In some embodiments, the subject to be treated expresses a high level of LILRB3 on hematopoietic cancer cells. In some embodiments, the

cancer to treated is non-responsive to existing immune-modulating antibodies targeting other immune checkpoints, such as CTLA-4, PD-1 or PD-L1.

[00122] In some embodiments, the cancer is myeloid leukemia, B lymphoid leukemia, or myeloma.

[00123] In some other embodiments, the cancer is brain cancer, bladder cancer, breast cancer, cervical cancer, endometrial cancer, esophageal cancer, leukemia, lung cancer, liver cancer, melanoma, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, renal cancer, testicular cancer, or uterine cancer. In yet other embodiments, the cancer is a vascularized tumor, squamous cell carcinoma, adenocarcinoma, small cell carcinoma, neuroblastoma, sarcoma (*e.g.,* an angiosarcoma or chondrosarcoma), larynx cancer, parotid cancer, biliary tract cancer, thyroid cancer, acral lentiginous melanoma, actinic keratoses, acute lymphocytic leukemia, acute myeloid leukemia, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, anal canal cancer, anal cancer, anorectum cancer, astrocytic tumor, bartholin gland carcinoma, basal cell carcinoma, biliary cancer, bone cancer, bone marrow cancer, bronchial cancer, bronchial gland carcinoma, carcinoid, cholangiocarcinoma, chondosarcoma, choroid plexus papilloma/carcinoma, chronic lymphocytic leukemia, chronic myeloid leukemia, clear cell carcinoma, connective tissue cancer, cystadenoma, digestive system cancer, duodenum cancer, endocrine system cancer, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, endothelial cell cancer, ependymal cancer, epithelial cell cancer, Ewing's sarcoma, eye and orbit cancer, female genital cancer, focal nodular hyperplasia, gallbladder cancer, gastric antrum cancer, gastric fundus cancer, gastrinoma, glioblastoma, glucagonoma, heart cancer, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatobiliary cancer, hepatocellular carcinoma, Hodgkin's disease, ileum cancer, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, intrahepatic bile duct cancer, invasive squamous cell carcinoma, jejunum cancer, joint cancer, Kaposi's sarcoma, pelvic cancer, large cell carcinoma, large intestine cancer, leiomyosarcoma, lentigo maligna melanomas, lymphoma, male genital cancer, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, meningeal cancer, mesothelial cancer, metastatic carcinoma, mouth cancer, mucoepidermoid carcinoma, multiple myeloma, muscle cancer, nasal tract cancer, nervous system cancer, neuroepithelial adenocarcinoma nodular melanoma, non-epithelial skin cancer, oat cell carcinoma, oligodendroglial cancer, oral cavity cancer, osteosarcoma, papillary serous adenocarcinoma, penile cancer, pharynx cancer, pituitary tumors, plasmacytoma,

pseudosarcoma, pulmonary blastoma, rectal cancer, renal cell carcinoma, respiratory system cancer, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, sinus cancer, skin cancer, small cell carcinoma, small intestine cancer, smooth muscle cancer, soft tissue cancer, somatostatin-secreting tumor, spine cancer, squamous cell carcinoma, striated muscle cancer, submesothelial cancer, superficial spreading melanoma, T cell leukemia, tongue cancer, undifferentiated carcinoma, ureter cancer, urethra cancer, urinary bladder cancer, urinary system cancer, uterine cervix cancer, uterine corpus cancer, uveal melanoma, vaginal cancer, verrucous carcinoma, VIPoma, vulva cancer, well-differentiated carcinoma, or Wilms tumor.

[00124] In some other embodiments, the cancer to be treated is a non-Hodgkin's lymphoma, such as a B-cell lymphoma or a T-cell lymphoma. In certain embodiments, the non-Hodgkin's lymphoma is a B-cell lymphoma, such as a diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, follicular lymphoma, small lymphocytic lymphoma, mantle cell lymphoma, marginal zone B-cell lymphoma, extranodal marginal zone B-cell lymphoma, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma, hairy cell leukemia, or primary central nervous system (CNS) lymphoma. In certain other embodiments, the non-Hodgkin's lymphoma is a T-cell lymphoma, such as a precursor T-lymphoblastic lymphoma, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, angioimmunoblastic T-cell lymphoma, extranodal natural killer/T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, anaplastic large cell lymphoma, or peripheral T-cell lymphoma.

[00125] The present disclosure also provides methods of treating autoimmune or inflammatory disorders in a subject, and the method includes administering to the subject an effective amount of an anti-LILRB3 antibody that acts as a modulator of LILRB3. In some embodiments, the subject to be treated expresses LILRB3 on one or more types of immune cells including lymphoid cells, myeloid cells, monocytes, monocyte-derived osteoclasts, granulocytes, dendritic cells, osteoclasts, and progenitor mast cells. In some embodiments, the subject to be treated expresses a high level of LILRB3 on one or more types of immune cells including lymphoid cells, myeloid cells, monocytes, monocyte-derived osteoclasts, granulocytes, dendritic cells, osteoclasts, and progenitor mast cells. In some embodiments, LILRB3 is expressed in the subject at a high level on autoreactive immune cells (*e.g.,* T cells, B cells, natural killer cells, dendritic cells, endothelial cells, and macrophages at sites where the autoimmune disease develops, for example, lymph nodes and central nervous system in the subject suffering from multiple sclerosis, joints in the subject suffering from Rheumatoid arthritis, and gastrointestinal

tract in the subject suffering from Celiac disease). Administering an anti-LILRB3 antibody that acts as a LILRB3 antagonist can inhibit LILRB3 activity. Administering an anti-LILRB3 antibody that acts as a LILRB3 agonist can promote LILRB3 activity.

[00126] In some embodiments, the autoimmune or inflammatory disorder to treated is asthma, multiple sclerosis, Addison's disease, amyotrophic lateral sclerosis, Crohn's disease, Cushing's Syndrome, diabetes mellitus type 1, graft versus host disease, Graves' disease, Guillain-Barré syndrome, lupus erythematosus, psoriasis, psoriatic arthritis, rheumatoid arthritis, sarcoidosis, scleroderma, systemic lupus erythematosus, transplant rejection, or vasculitis.

[00127] In some other embodiments, the autoimmune disorders to be treated include, but are not limited to, Acute disseminated encephalomyelitis (ADEM), Agammaglobulinemia, Alopecia areata, Ankylosing Spondylitis, Antiphospholipid syndrome, Antisynthetase syndrome, Atopic allergy, Atopic dermatitis, Autoimmune aplastic anemia, Autoimmune cardiomyopathy, Autoimmune enteropathy, Autoimmune hemolytic anemia, Autoimmune hepatitis, Autoimmune inner ear disease, Autoimmune lymphoproliferative syndrome, Autoimmune pancreatitis, Autoimmune peripheral neuropathy, Autoimmune polyendocrine syndrome, Autoimmune progesterone dermatitis, Autoimmune thrombocytopenic purpura, Autoimmune urticaria, Autoimmune uveitis, Balo disease/Balo concentric sclerosis, Behcet's disease, Berger's disease, Bickerstaffs encephalitis, Blau syndrome, Bullous pemphigoid, Cancer, Castleman's disease, Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy, Chronic inflammatory demyelinating polyneuropathy, Chronic obstructive pulmonary disease, Chronic recurrent multifocal osteomyelitis, Churg-Strauss syndrome, Cicatricial pemphigoid, Cogan syndrome, Cold agglutinin disease, Complement component 2 deficiency, Contact dermatitis, Cranial arteritis, CREST syndrome, Cutaneous leukocytoclastic angiitis, Dego's disease, Dercum's disease, Dermatitis herpetiformis, Dermatomyositis, Diffuse cutaneous systemic sclerosis, Discoid lupus erythematosus, Dressler's syndrome, Drug-induced lupus, Eczema, Endometriosis, Eosinophilic fasciitis, Eosinophilic gastroenteritis, Eosinophilic pneumonia, Epidermolysis bullosa acquisita, Erythema nodosum, Erythroblastosis fetalis, Essential mixed cryoglobulinemia, Evan's syndrome, Fibrodysplasia ossificans progressiva, Fibrosing alveolitis (or Idiopathic pulmonary fibrosis), Gastritis, Gastrointestinal pemphigoid, Glomerulonephritis, Goodpasture's syndrome, Hashimoto's encephalopathy, Hashimoto's thyroiditis, Henoch-Schonlein purpura, Herpes gestationis aka Gestational Pemphigoid, Hidradenitis suppurativa, Hughes-Stovin syndrome, Hypogammaglobulinemi, Idiopathic inflammatory demyelinating diseases, Idiopathic pulmonary fibrosis, Idiopathic thrombocytopenic purpura, IgA nephropathy,

Inclusion body myositis, Interstitial cystitis, Juvenile idiopathic arthritis aka Juvenile rheumatoid arthritis, Kawasaki's disease, Lambert-Eaton myasthenic syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Linear IgA disease, Lupoid hepatitis aka Autoimmune hepatitis, Majeed syndrome, Microscopic colitis, Microscopic polyangiitis, Miller-Fisher syndrome, Mixed connective tissue disease, Morphea, Mucha-Habermann disease aka Pityriasis lichenoides et varioliformis acuta, Multiple sclerosis, Myasthenia gravis, Myositis, Ménière's disease, Narcolepsy, Neuromyelitis optica, Neuromyotonia, Occular cicatricial pemphigoid, Opsoclonus myoclonus syndrome, Ord's thyroiditis, Palindromic rheumatism, PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcus), Paraneoplastic cerebellar degeneration, Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis, Parsonage-Turner syndrome, Pemphigus vulgaris, Perivenous encephalomyelitis, Pernicious anaemia, POEMS syndrome, Polyarteritis nodosa, Polymyalgia rheumatica, Polymyositis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progressive inflammatory neuropathy, Pure red cell aplasia, Pyoderma gangrenosum, Rasmussen's encephalitis, Raynaud phenomenon, Reiter's syndrome, Relapsing polychondritis, Restless leg syndrome, Retroperitoneal fibrosis, Rheumatic fever, Schizophrenia, Schmidt syndrome, Schnitzler syndrome, Scleritis, Serum Sickness, Sjögren's syndrome, Spondyloarthropathy, Stiff person syndrome, Still's disease, Subacute bacterial endocarditis (SBE), Susac's syndrome, Sweet's syndrome, Sydenham chorea, Sympathetic ophthalmia, Takayasu's arteritis, Temporal arteritis, Thrombocytopenia, Tolosa-Hunt syndrome, Transverse myelitis, Ulcerative colitis, Undifferentiated spondyloarthropathy, Urticarial vasculitis, Vitiligo, Wegener's granulomatosis.

[00128] The present disclosure also provides methods of treating allergic inflammation in a subject, and the method includes administering to the subject an effective amount of any one of the anti-LILRB3 antibodies described herein, or any one of the compositions described herein.

[00129] In some embodiments, the allergic inflammation to be treated may be related to allergic asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis.

[00130] The present disclosure also provides methods of modulating osteoclast differentiation, and the method includes administering to the subject an effective amount of any one of the anti-LILRB3 antibodies described herein, or any one of the compositions described herein.

In some embodiments, modulating osteoclast differentiation may be particularly useful to treat bone loss or bone resorption in patients suffering or susceptible of suffering from a condition

selected from the group consisting of osteoporosis, osteodystrophy, osteopenia, osteomalacia, hyperparathyroidism, hyperthyroidism, hypogonadism, thyrotoxicosis, systemic mastocytosis, adult hypophosphatasia, hyperadrenocorticism, osteogenesis imperfecta, Paget's disease, Cushing's disease/syndrome, Tumer syndrome, Gaucher disease, Ehlers-Danlos syndrome, Marfan's syndrome, Menkes' syndrome, Fanconi's syndrome, multiple myeloma, hypercalcemia, hypocalcemia, arthritides, periodontal disease, rickets (including vitamin D dependent, type I and II, and x-linked hypophosphatemic rickets) or other form of vitamin D deficiency such as vitamin D deficiency associated with chronic kidney disease or kidney failure, fibrogenesis imperfecta ossium, osteosclerotic disorders such as pycnodysostosis and damage caused by macrophage-mediated inflammatory processes.

V. Combination therapy

[00131] Anti-LILRB3 antibodies described herein can be used in combination with additional therapeutic agents to treat cancer, autoimmune disorders, and allergic inflammation. Anti-LILRB3 antibodies can also be used in combination with additional therapeutic agents to modulate osteoclast differentiation

[00132] Exemplary therapeutic agents that may be used as part of a combination therapy in treating cancer, include, for example, radiation, mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine, flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma, colony stimulating factor-1, colony stimulating factor-2, denileukin diftitox, interleukin-2, luteinizing hormone releasing factor and variations of the aforementioned agents that may exhibit differential binding to its cognate receptor, and increased or decreased serum half-life.

[00133] An additional class of agents that may be used as part of a combination therapy in treating cancer is immune checkpoint inhibitors. Exemplary immune checkpoint inhibitors

include agents that inhibit one or more of (i) cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), (ii) programmed cell death protein 1 (PD1), (iii) PDL1, (iv) LAG3, (v) B7-H3, (vi) B7-H4, and (vii) TIM3, such as Ipilimumab, Nivolumab, Pembrolizumab, Avelumab, Durvalumab, and Atezolizumab.

[00134] Yet other agents that may be used as part of a combination therapy in treating cancer are monoclonal antibody agents that target non-checkpoint targets (*e.g.*, herceptin) and non-cytotoxic agents (*e.g.*, tyrosine-kinase inhibitors).

[00135] Yet other categories of anti-cancer agents include, for example: (i) an inhibitor selected from an ALK Inhibitor, an ATR Inhibitor, an A2A Antagonist, a Base Excision Repair Inhibitor, a Bcr-Abl Tyrosine Kinase Inhibitor, a Bruton's Tyrosine Kinase Inhibitor, a CDC7 Inhibitor, a CHK1 Inhibitor, a Cyclin-Dependent Kinase Inhibitor, a DNA-PK Inhibitor, an Inhibitor of both DNA-PK and mTOR, a DNMT1 Inhibitor, a DNMT1 Inhibitor plus 2-chloro-deoxyadenosine, an HDAC Inhibitor, a Hedgehog Signaling Pathway Inhibitor, an IDO Inhibitor, a JAK Inhibitor, a mTOR Inhibitor, a MEK Inhibitor, a MELK Inhibitor, a MTH1 Inhibitor, a PARP Inhibitor, a Phosphoinositide 3-Kinase Inhibitor, an Inhibitor of both PARP1 and DHODH, a Proteasome Inhibitor, a Topoisomerase-II Inhibitor, a Tyrosine Kinase Inhibitor, a VEGFR Inhibitor, and a WEE1 Inhibitor; (ii) an agonist of OX40, CD137, CD40, GITR, CD27, HVEM, TNFRSF25, or ICOS; and (iii) a cytokine selected from IL-12, IL-15, GM-CSF, and G-CSF. Antibodies of the invention can also be used as an adjunct to surgical removal of cancer from the primary lesion.

[00136] Exemplary therapeutic agents that may be used as a part of a combination therapy with the anti-LILRB3 antibodies for treating, delaying the progression of, preventing a relapse of, or alleviating a symptom of an autoimmune or inflammatory disorder, include, for example, any of a variety of known anti-inflammatory and/or immunosuppressive therapy. In some embodiments, the anti-inflammatory and/or immunosuppressive therapies include, but are not limited to methotrexate, cyclosporin A (including, for example, cyclosporin microemulsion), tacrolimus, corticosteroids, statins, interferon beta, non-steroidal anti-inflammatory agents, and 6-MP (Mercaptopurine, also called 6-Mercaptopurine, or Purinethol).

[00137] In some embodiments, the anti-inflammatory and/or immunosuppressive therapies for combining with the anti-LILRB3 antibodies include, but are not limited to a TOPK inhibitor (e.g., OTS964 ((R)-9-(4-(1-(dimethylamino)propan-2-yl)phenyl)-8-hydroxy-6-methylthieno[2,3-

c] quinolin-4(5H)-one) (Oncotherapy Science)), a tyrosine kinase inhibitor (e.g., axitinib, dasatinib, icotinib), a topoisomerase inhibitor (e.g., topotecan), a sphingosine-1-phosphate receptor agonist (e.g., fingolimod, KRP-203), anti-T cell immunoglobulin (e.g. AtGam), anti-IL-2 receptor antibody (e.g. daclizumab), amides (CTX), ifosfamide (IFO), adriamycin (ADM), daunorubicin (DNR), vincristine (VCR), vinblastine (VBL), etoposide (VP16), vermeer (Vumon), carboplatin (CBP), tacrolimus, sirolimus, everolimus, azathioprine, brequinar, leflunomide, LEA-29Y, anti-CD3 antibody (e.g. OKT3), aspirin, B7-CD28 blocking molecules (e.g. belatacept, abatacept), CD40-CD154 blocking molecules (anti-CD40 antibodies), acetaminophen, ibuprofen, naproxen, piroxicam, and anti-inflammatory steroids (e.g. prednisolone or dexamethasone).

[00138] In some embodiments, the anti-inflammatory and/or immunosuppressive therapies for combining with the anti-LILRB3 antibodies include ablation of autoimmune cells, for example, by administration of TNF-alpha, CFA, interleukin-1 (IL-1), proteasome inhibitors, NFκB inhibitors, anti-inflammatory drugs, tissue plasminogen activator (TPA), lipopolysaccharide, UV light, and an intracellular mediator of the TNF-alpha signaling pathway. Such agents induce the apoptosis of autoreactive lymphocytes by interrupting the pathway downstream from TNF-alpha receptor signaling or act downstream of TNF-alpha receptor binding. (Baldwin et al., Ann. Rev. Immunol.(1996) 12:141; Baltimore, Cell (1996) 87:13).

[00139] In some embodiments, the anti-LILRB3 antibodies are used in conjunction with a surgical method of treating or otherwise alleviating autoimmune diseases.

[00140] Exemplary therapeutic agents that may be used as a part of a combination therapy with the anti-LILRB3 antibodies for treating, delaying the progression of, preventing a relapse of, or alleviating a symptom of allergic inflammation, include, for example, any of a variety of known anti-inflammatory and/or immunosuppressive therapies. In some embodiments, the anti-inflammatory and/or immunosuppressive therapies for combining with anti-LILRB3 antibodies include but are not limited to: short-acting β2-agonists, long-acting β2-agonists, anticholinergics, corticosteroids, systemic corticosteroids, mast cell stabilizers, leukotriene modifiers, methylxanthines, β2-agonists, albuterol, levalbuterol, pirbuterol, artformoterol, formoterol, salmeterol, anticholinergics including ipratropium and tiotropium; corticosteroids including beclomethasone, budesonide, flunisolide, fluticasone, mometasone, triamcinolone, methyprednisolone, prednisolone, prednisone; leukotriene modifiers including montelukast, zafirlukast, and zileuton; mast cell stabilizers including cromolyn and nedocromil;

methylxanthines including theophylline; combination drugs including ipratropium and albuterol, fluticasone and salmeterol, budesonide and formoterol; antihistamines including hydroxyzine, diphenhydramine, loratadine, cetirizine, and hydrocortisone; immune system modulating drugs including tacrolimus and pimecrolimus; cyclosporine; azathioprine; mycophenolatemofetil; and combinations thereof.

[00141] In other embodiments, therapeutic agents that may be used as a part of a combination therapy with the anti-LILRB3 antibodies for treating, delaying the progression of, preventing a relapse of, or alleviating a symptom of allergic inflammation, may also include those therapeutic agents specified for autoimmune or inflammatory disorders.

[00142] Exemplary therapeutic agents that may be used as a part of a combination therapy with the anti-LILRB3 antibodies for modulating osteoclast activity include but are not limited to bisphosphonates, calcitonin, estrogen replacement, sclerostin antibodies, RANKL antibodies, parathyroid peptides, strontiumranelate, TNFα inhibitors, colony-stimulating factor-1 inhibitors, colony-stimulating factor-1 receptor inhibitors, cathepsin K inhibitors, V-ATPase inhibitors, and Glucagon-like peptide 2.

[00143] The amount of the antibodies and additional therapeutic agents and the relative timing of administration may be selected in order to achieve a desired combined therapeutic effect. For example, when administering a combination therapy to a patient in need of such administration, the therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. Further, for example, a multi-specific binding protein may be administered during a time when the additional therapeutic agent(s) exerts its prophylactic or therapeutic effect, or vice versa.

VI. Pharmaceutical composition and administration

[00144] The present disclosure also features pharmaceutical compositions/formulations that contain a therapeutically effective amount of an anti-LILRB3 antibody described herein. The composition can be formulated for use in a variety of drug delivery systems. One or more physiologically acceptable excipients or carriers can also be included in the composition for proper formulation. Suitable formulations for use in the present disclosure are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed.,

1985. For a brief review of methods for drug delivery, see, *e.g.,* Langer (Science 249:1527-1533, 1990).

[00145] The antibodies of the present disclosure can exist in a lyophilized formulation or liquid aqueous pharmaceutical formulation. The aqueous carrier of interest herein is one which is pharmaceutically acceptable (safe and non-toxic for administration to a human) and is useful for the preparation of a liquid formulation. Illustrative carriers include sterile water for injection (SWFI), bacteriostatic water for injection (BWFI), a pH buffered solution (*e.g.,* phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

[00146] The antibodies of the present disclosure could exist in a lyophilized formulation including the proteins and a lyoprotectant. The lyoprotectant may be sugar, *e.g.,* disaccharides. In certain embodiments, the lyoprotectant is sucrose or maltose. The lyophilized formulation may also include one or more of a buffering agent, a surfactant, a bulking agent, and/or a preservative.

[00147] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. It may be administered in the range of 0.1 mg to 1 g and preferably in the range of 0.5 mg to 500 mg of active antibody per administration for adults. Alternatively, a patient's dose can be tailored to the approximate body weight or surface area of the patient. Other factors in determining the appropriate dosage can include the disease or condition to be treated or prevented, the severity of the disease, the route of administration, and the age, sex and medical condition of the patient. Further refinement of the calculations necessary to determine the appropriate dosage for treatment is routinely made by those skilled in the art, especially in light of the dosage information and assays disclosed herein. The dosage can also be determined through the use of known assays for determining dosages used in conjunction with appropriate dose-response data. An individual patient's dosage can be adjusted as the progress of the disease is monitored. Blood levels of the targetable construct or complex in a patient can be measured to see if the dosage needs to be adjusted to reach or maintain an effective concentration. Pharmacogenomics may be used to determine which targetable constructs and/or complexes, and dosages thereof, are most likely to be effective for a given individual (Schmitz et al., Clinica Chimica Acta 308: 43-53, 2001; Steimer et al., Clinica Chimica Acta 308: 33-41, 2001).

[00148] Doses may be given once or more times daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measured residence times and concentrations of the targetable construct or complex in bodily fluids or tissues. Administration of the present invention could be intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, intrapleural, intrathecal, intracavitary, by perfusion through a catheter or by direct intralesional injection. This may be administered once or more times daily, once or more times weekly, once or more times monthly, and once or more times annually.

EXAMPLES

[00149] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and is not intended to limit the invention.

Example 1 – LILRB3 surface expression on hematopoietic cell subsets

[00150] LILRB3 surface expression was measured on various hematopoietic subsets in the form of two-dimensional flow cytometry (FCM) representations called quantile contour plots (probability plots). Peripheral blood mononuclear cells (PBMCs) from a healthy human donor were stained with the LILRB3 3A3 antibody as well as antibodies specific for the indicated cell subset. FIGURE 1A plots depict LILRB3 expression by gated CD3+CD4+ T cells, CD3+CD8+ T cells or CD11b+ monocytes. In FIGURE 1B, fresh whole blood from a healthy human donor was stained as in FIGURE 1A. Plots depict LILRB3 expression by gated CD3+CD4+ T cells, CD3+CD8+ T cells, CD11b+ monocytes or CD11b+ granulocytes. Percentages of gated cells and of LILRB3+ cells within the gated population are depicted inside the plots (first and second numbers, respectively). LILRB3 expression is demonstrated on monocytes and granulocytes, and low LILRB3 expression is demonstrated on CD4+ or CD8+ T cells. Specificity of the LILRB3 staining was determined by staining all of the above cell subsets with an IgG1 isotype control antibody. Data are representative of several independent experiments utilizing different human blood samples.

Example 2 – The Effect of LILRB3 antibodies or LILRB3-Fc protein on T cell responsiveness in primary mixed lymphocyte reactions (MLR)

[00151] CD3+ T cells [$1x10^5$ cells, effector (E) population] and irradiated (IR) allogenic CD14+ monocytes [$2x10^5$ cells, stimulator (S) population] from healthy human donors were co-cultured in the presence or absence of the indicated amounts of IgG1 or IgG2b isotype control antibodies, LILRB3 antibodies, Fc protein or Fc-LILRB3 protein. After 3 days, the cells were labeled with 3H-thymidine for an additional 18 hours to measure T cell proliferation. The LILRB3 7C5 antibody and LILRB3 Fc proteins inhibited T cell proliferation (Fi 2). Data shown are representative of several independent experiments utilizing different effector/stimulator pairs, and are reported as the mean counts per minute (cpm) ± standard error of triplicate wells.

Example 3 – PBMC incubated with LILRB3 7C5 antibody are unable to fully regulate the surface expression of activation markers in response to T cell stimulation

[00152] PBMCs ($2x10^5$ cells) from a healthy human donor were cultured in the presence or absence of 7C5 or isotype control antibody (20 μg/mL) and the indicated amounts of anti-CD3 and anti-CD28 antibodies. After 24 hours, the cells were stained with antibodies specific for the indicated cell subset and activation markers. In Panel A, plots depict CD69, CD25 and CD62L expression by gated CD3+CD4+ T cells (FIGURE 3A). In Panel B, plots depict CD69, CD25 and CD62L expression by gated CD3+CD8+ T cells (FIGURE 3B). The LILRB3 7C5 antibody inhibits the activation of CD4+ and CD8+ T cells by anti-CD3 and anti-CD28 antibodies as shown by reduced expression of CD69 (type II C-lectin receptor) and CD25 (IL-2 receptor), and reduced shedding of CD62L (L-selectin). Data are representative of several independent experiments utilizing different human PBMC samples, and are reported as the mean fluorescence intensity (MFI) ± standard error of triplicate wells.

Example 4 – LILRB3 antibodies alter cytokine production by PBMC in response to T cell stimulation.

[00153] PBMCs ($2x10^5$ cells) from a healthy human donor were cultured in the presence or absence of 7C5 or isotype control antibody (20 μg/mL), and anti-CD3 (1 ng/mL) and anti-CD28 (100 ng/mL) antibodies. After 24 hours, cytokine levels in culture supernatants were determined by a BioLegend LEGENDplex Human Th Cytokine Panel by manufacturer's instructions. In the presence of 7C5, the level of certain cytokines, including IL-2, IL-4, IL-5, IL-13, IL-17 and IFNγ were decreased, while the level IL-6, IL-10 and TNF were increased (FIGURE 4). Data are representative of several independent experiments utilizing different human PBMC samples,

and are reported as the fold change for 7C5 relative to the isotype control antibody of duplicate wells.

Example 5 – LILRB3 7C5 antibody causes no significant release of cytokines from unstimulated whole blood.

[00154] Fresh blood from healthy human donors (n=4) was diluted 4:1 with RPMI 1640 medium and cultured for 4 hours in the presence of 7C5 or isotype control antibody (50 μg/mL). LPS (1 μg/mL) was used as a positive control. Cytokine levels in serum samples were determined by a BioLegend LEGENDplex Human Th Cytokine Panel by manufacturer's instructions. The LILRB3 7C5 antibody showed no significant stimulatory effect in the absence of a T cell receptor stimulus (FIGURE 5). Data are representative of several independent experiments, and are reported as the mean fold change for 7C5 relative to the isotype control antibody of duplicate wells.

INCORPORATION BY REFERENCE

[00155] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[00156] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

Claims

What Is Claimed Is:

1. An antibody comprising:

a) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:1 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:2;

b) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:3 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:4;

c) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:5 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:6;

d) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:7 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:8;

e) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:9 a light chain variable region comprising an amino acid sequence of SEQ ID NO:10;

f) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:11 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:12;

g) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:13 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:14;

h) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:15 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:16;

i) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:17 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:18;

j) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:19 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:20;

k) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:21 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:22;

l) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:23 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:24;

m) a heavy chain variable region comprising an amino acid sequence of SEQ ID NO:25 and a light chain variable region comprising an amino acid sequence of SEQ ID NO:26;

2. An antibody comprising:

a) a vhCDR1 comprising SEQ ID NO:27, a vhCDR2 comprising SEQ ID NO:28, a vhCDR3 comprising SEQ ID NO:29, a vlCDR1 comprising SEQ ID NO:30, a vlCDR2 comprising SEQ ID NO:31, and a vlCDR3 comprising SEQ ID NO:32;

b) a vhCDR1 comprising SEQ ID NO:33, a vhCDR2 comprising SEQ ID NO:34, a vhCDR3 comprising SEQ ID NO:35, a vlCDR1 comprising SEQ ID NO:36, a vlCDR2 comprising SEQ ID NO:37, and a vlCDR3 comprising SEQ ID NO:38;

c) a vhCDR1 comprising SEQ ID NO:39, a vhCDR2 comprising SEQ ID NO:40, a vhCDR3 comprising SEQ ID NO:41, a vlCDR1 comprising SEQ ID NO:42, a vlCDR2 comprising SEQ ID NO:43, and a vlCDR3 comprising SEQ ID NO:44;

d) a vhCDR1 comprising SEQ ID NO:45, a vhCDR2 comprising SEQ ID NO:46, a vhCDR3 comprising SEQ ID NO:47, a vlCDR1 comprising SEQ ID NO:48, a vlCDR2 comprising SEQ ID NO:49, and a vlCDR3 comprising SEQ ID NO:50;

e) a vhCDR1 comprising SEQ ID NO:51, a vhCDR2 comprising SEQ ID NO:52, a vhCDR3 comprising SEQ ID NO:53, a vlCDR1 comprising SEQ ID NO:54, a vlCDR2 comprising SEQ ID NO:55, and a vlCDR3 comprising SEQ ID NO:56;

f) a vhCDR1 comprising SEQ ID NO:57, a vhCDR2 comprising SEQ ID NO:58, a vhCDR3 comprising SEQ ID NO:59, a vlCDR1 comprising SEQ ID NO:60, a vlCDR2 comprising SEQ ID NO:61, and a vlCDR3 comprising SEQ ID NO:62;

g) a vhCDR1 comprising SEQ ID NO:63, a vhCDR2 comprising SEQ ID NO:64, a vhCDR3 comprising SEQ ID NO:65, a vlCDR1 comprising SEQ ID NO:66, a vlCDR2 comprising SEQ ID NO:67, and a vlCDR3 comprising SEQ ID NO:68;

h) a vhCDR1 comprising SEQ ID NO:69, a vhCDR2 comprising SEQ ID NO:70, a vhCDR3 comprising SEQ ID NO:71, a vlCDR1 comprising SEQ ID NO:72, a vlCDR2 comprising SEQ ID NO:73, and a vlCDR3 comprising SEQ ID NO:74;

i) a vhCDR1 comprising SEQ ID NO:75, a vhCDR2 comprising SEQ ID NO:76, a vhCDR3 comprising SEQ ID NO:77, a vlCDR1 comprising SEQ ID NO:78, a vlCDR2 comprising SEQ ID NO:79, and a vlCDR3 comprising SEQ ID NO:80;

j) a vhCDR1 comprising SEQ ID NO:81, a vhCDR2 comprising SEQ ID NO:82, a vhCDR3 comprising SEQ ID NO:83, a vlCDR1 comprising SEQ ID NO:84, a vlCDR2 comprising SEQ ID NO:85, and a vlCDR3 comprising SEQ ID NO:86;

k) a vhCDR1 comprising SEQ ID NO:87, a vhCDR2 comprising SEQ ID NO:88, a vhCDR3 comprising SEQ ID NO:89, a vlCDR1 comprising SEQ ID NO:80, a vlCDR2 comprising SEQ ID NO:81, and a vlCDR3 comprising SEQ ID NO:82;

l) a vhCDR1 comprising SEQ ID NO:93, a vhCDR2 comprising SEQ ID NO:94, a vhCDR3 comprising SEQ ID NO:95, a vlCDR1 comprising SEQ ID NO:96, a vlCDR2 comprising SEQ ID NO:97, and a vlCDR3 comprising SEQ ID NO:98;

m) a vhCDR1 comprising SEQ ID NO:99, a vhCDR2 comprising SEQ ID NO:100, a vhCDR3 comprising SEQ ID NO:101, a vlCDR1 comprising SEQ ID NO:102, a vlCDR2 comprising SEQ ID NO:103, and a vlCDR3 comprising SEQ ID NO:104;

3. The antibody according to any of the previous claims, wherein the antibody binds human LILRB3.

4. The antibody according to any one of the previous claims, wherein the antibody comprises a constant region with an amino acid sequence at least 90% identical to a human IgG.

5. The antibody according to claim 4, wherein the human IgG is selected from a group consisting of IgG1, IgG2, IgG3 and IgG4.

6. The antibody according to claim 5, wherein the IgG is an IgG1.

7. The antibody according to claim 5, wherein the IgG is an IgG2.

8. A nucleic acid composition encoding the antibody according to any of the previous claims.

9. An expression vector composition comprising the nucleic acid composition according to claim 8, wherein the first nucleic acid is contained in a first expression vector and the second nucleic acid is contained in a second expression vector.

10. An expression vector composition comprising the nucleic acid composition according to claim 8, wherein the first nucleic acid and the second nucleic acid are contained in a single expression vector.

11. A host cell comprising the expression vector composition of claim 9 or 10.

12. A method of making an antibody comprising culturing said host cell of claim 11 under conditions wherein the antibody is expressed, and recovering the antibody.

13. A composition comprising the antibody according to any one of claims 1-7, and a pharmaceutical acceptable carrier or diluent.

14. A method of modulating an immune response in a subject, the method comprising administering to the subject an effective amount of the antibody according to any one of the claims 1-7 or the composition according to claim 13.

15. A method of treating cancer in a subject comprising administering to the subject an effective amount of the antibody according to any one of the claims 1-7 or the composition according to claim 13.

16. The method of claim 15, wherein the cancer upregulates LILRB3.

17. The method of claim 15 or 16, wherein the subject has a high level of LILRB3 on hematopoietic cancer cells.

18. The method according to any one of the claims 15-17, wherein the cancer is leukemia.

19. The method according to any one of the claims 15-17, wherein the cancer is myeloma.

20. The method according to any one of the claims 15-19, wherein the antibody is combined with one or more additional therapeutic agents to treat cancer.

21. The method of claim 20, wherein the additional therapeutic agents are other immune checkpoint inhibitors.

22. The method of claim 21, wherein the other immune checkpoint inhibitors are selected from the group consisting of Ipilimumab, Nivolumab, Pembrolizumab, Avelumab, Durvalumab, and Atezolizumab.

23. A method of treating an autoimmune disease in a subject comprising administering to the subject an effective amount of the antibody according to any one of the claims 1-7 or the composition according to claim 13.

24. A method according to claim 23, wherein the antibody is combined with one or more additional therapeutic agents to treat autoimmune disease.

25. A method of treating allergic inflammation in a subject comprising administering to the subject an effective amount of the antibody according to any one of the claims 1-7 or the composition according to claim 13.

26. A method according to claim 25, wherein the antibody is combined with one or more additional therapeutics to treat allergic inflammation.

27. A method of modulating differentiation of osteoclasts in a subject comprising administering to the subject an effective amount of the antibody according to any one of the claims 1-7 or the composition according to claim 13.

28. A method according to claim 27, wherein the antibody is combined with one or more additional therapeutics to modulate differentiation of osteoclasts.

FIGURE 1A

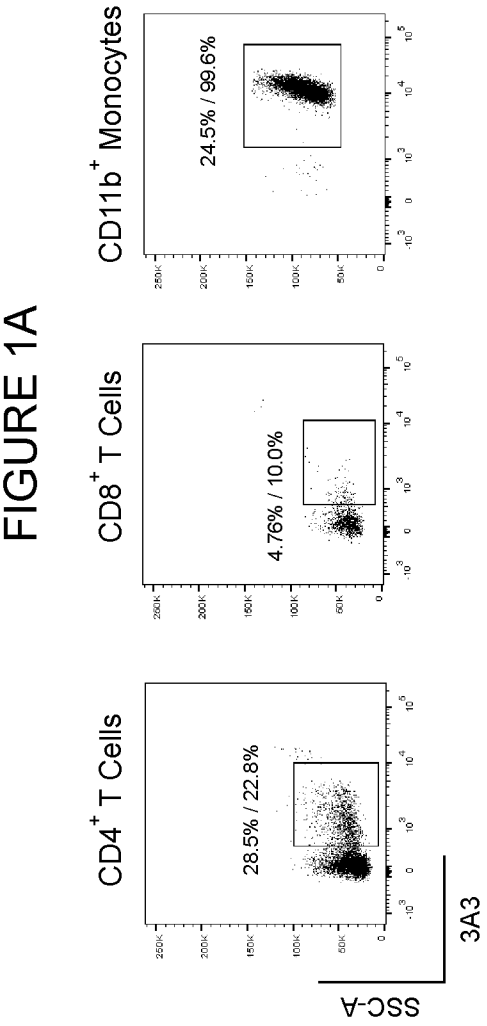


FIGURE 1B

FIGURE 2

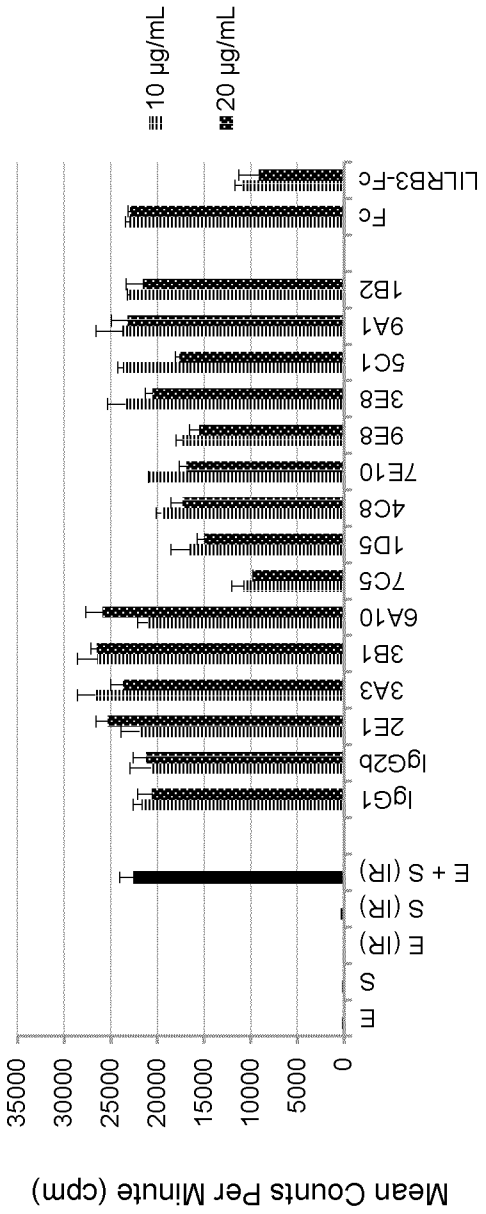

10 µg/mL
20 µg/mL
Mean Counts Per Minute (cpm)
35000
30000
25000
20000
15000
10000
5000
0
E
S
E (IR)
S (IR)
E + S (IR)
IgG1
IgG2b
2E1
3A3
3B1
6A10
7C5
1D5
4C8
7E10
9E8
3E8
5C1
9A1
1B2
Fc
LILRB3-Fc

FIGURE 3A

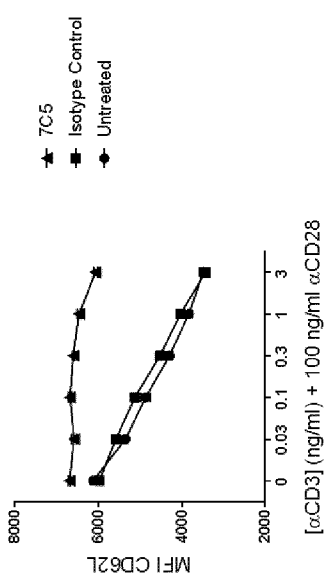


FIGURE 3B

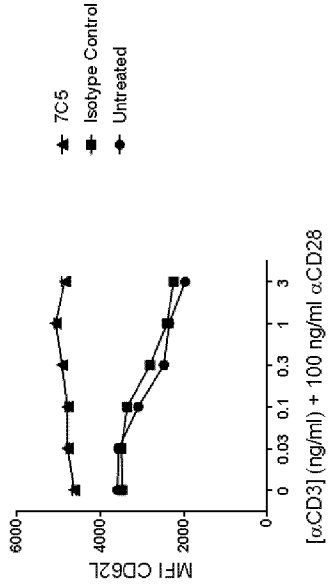
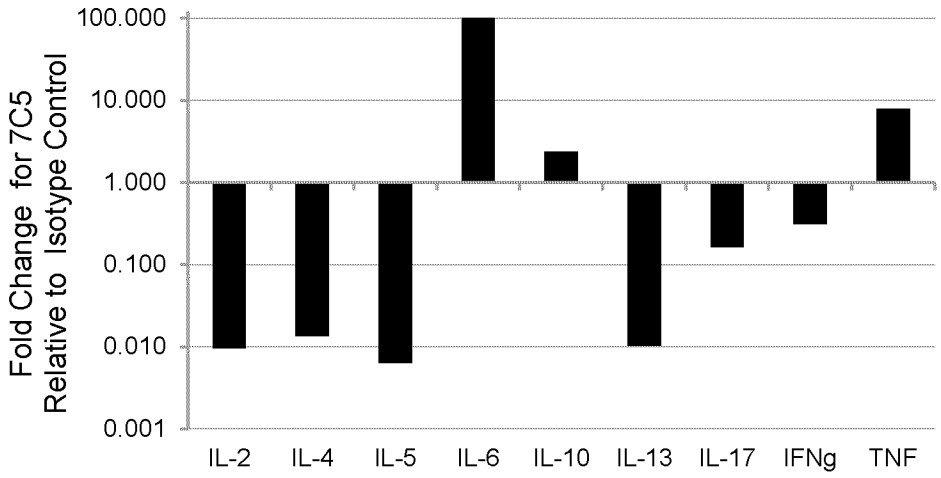


FIGURE 4


Fold Change for 7C5
Relative to Isotype Control
100.000
10.000
1.000
0.100
0.010
0.001
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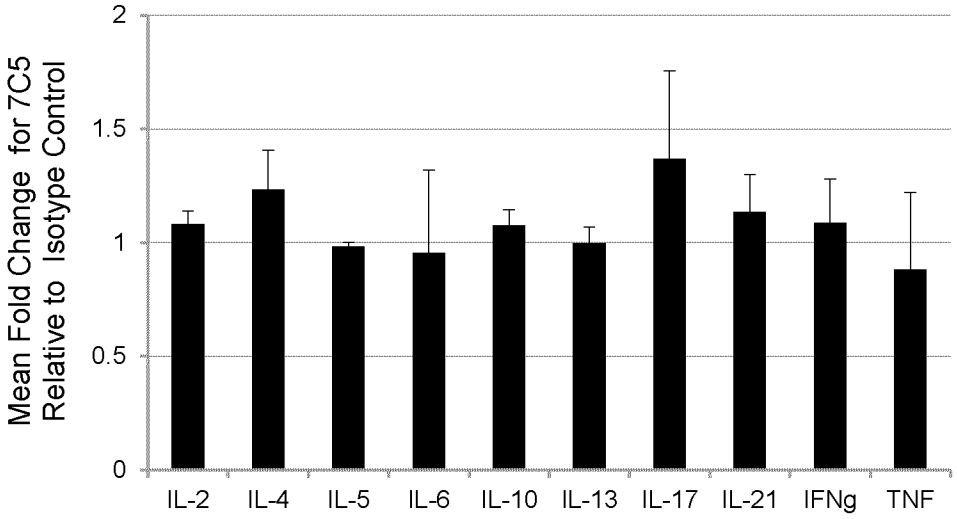
IL-4
IL-5
IL-6
IL-10
IL-13
IL-17
IFNg
TNF

FIGURE 5


Mean Fold Change for 7C5
Relative to Isotype Control
2
1.5
1
0.5
0
IL-2
IL-4
IL-5
IL-6
IL-10
IL-13
IL-17
IL-21
IFNg
TNF

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2020/050042

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07K 16/28*** (2006.01), ***A61K 39/395*** (2006.01), ***A61P 29/00*** (2006.01), ***A61P 35/00*** (2006.01), ***A61P 35/02*** (2006.01), ***A61P 37/02*** (2006.01), ***A61P 37/06*** (2006.01), ***C12N 15/13*** (2006.01), ***C12P 21/08*** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: ***C07K 16/28*** (2006.01), ***A61K 39/395*** (2006.01), ***A61P 29/00*** (2006.01), ***A61P 35/00*** (2006.01), ***A61P 35/02*** (2006.01), ***A61P 37/02*** (2006.01), ***A61P 37/06*** (2006.01), ***C12N 15/13*** (2006.01), ***C12P 21/08*** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Databases: CIPO library discovery tool, Scopus, PubmedCentral, Questel-Orbit, GQPAT, GeneSeq Protein, Uniprot, RefSeq, GenPept, IPI, IGBLAST Protein, PDB protein, ENSEMBL.

Keywords: Leukocyte Ig-like inhibitory receptor, LILRB3, CD85A, ILT5, LIR3, HL9, binding, antibody, Mab 7C5, modulating immune response, cancer, allergic inflammation. SEQ ID NOS: 1-104.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/119425 A2, CHEN SH et al. 28 June 2018 (28-06-2018). *the whole document*	1-28
A	WO 2016/127247 A1, BLASER H et al. 18 August 2016 (18-08-2016). *the whole document*	1-28

☐ Further documents are listed in the continuation of Box C.

☑ See patent family annex.

*	Special categories of cited documents:
"A"	document defining the general state of the art which is not considered to be of particular relevance
"D"	document cited by the applicant in the international application
"E"	earlier application or patent but published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search 12 February 2020 (12-02-2020)	Date of mailing of the international search report 26 March 2020 (26-03-2020)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Mostapha Bayaa (819) 639-7743

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2020/050042

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2018119425A2	28 June 2018 (28-06-2018)	WO2018119425A3	09 August 2018 (09-08-2018)
		CA3047833A1	28 June 2018 (28-06-2018)
		CN110366563A	22 October 2019 (22-10-2019)
		EP3559042A2	30 October 2019 (30-10-2019)
WO2016127247A1	18 August 2016 (18-08-2016)	AU2016218900A1	24 August 2017 (24-08-2017)
		CA2976130A1	18 August 2016 (18-08-2016)
		EP3256163A1	20 December 2017 (20-12-2017)
		EP3256163A4	10 October 2018 (10-10-2018)
		US2018201676A1	19 July 2018 (19-07-2018)