

**[0012]** Accordingly, in one example, the disclosure pertains to an isolated monoclonal antibody (e.g., a human, mouse, chimeric or humanized antibody), or an antigen-binding portion thereof, that binds Siglec15, having i) a heavy chain variable region that may comprise a VH CDR1 region, a VH CDR2 region and a VH CDR3 region, wherein the VH CDR1 region, the VH CDR2 region and the VH CDR3 region may comprise amino acid sequences having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to (1) SEQ ID NOs: 1, 2 (X1=D, X2=Q) and 3, respectively; (2) SEQ ID NOs: 1, 2 (X1=E, X2=Q) and 3, respectively; (3) SEQ ID NOs: 1, 2 (X1=D, X2=K) and 3, respectively; (4) SEQ ID NOs: 9, 10 and 11, respectively; or (5) SEQ ID NOs: 33, 34 and 35, respectively; and/or ii) a light chain variable region that may comprise a VL CDR1 region, a VL CDR2 region and a VL CDR3 region, wherein the VL CDR1 region, the VL CDR2 region, and the VL CDR3 region may comprise amino acid sequences having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to (1) SEQ ID NOs: 4, 5 and 6, respectively; (2) SEQ ID NOs: 12, 13 and 14, respectively; or (3) SEQ ID NOs: 36, 37 and 38, respectively. In one aspect, the present disclosure refers to an isolated monoclonal antibody or an antigen-binding portion thereof, binding to Siglec15, comprising i) a heavy chain variable region that comprises a VH CDR1 region, a VH CDR2 region and a VH CDR3 region, wherein the VH CDR1 region, the VH CDR2 region and the VH CDR3 region comprise the amino acid sequences of (1) SEQ ID NOs: 1, 2 (X1=D, X2=Q) and 3, respectively; (2) SEQ ID NOs: 1, 2 (X1=E, X2=Q) and 3, respectively; or (3) SEQ ID NOs: 1, 2 (X1=D, X2=K) and 3, respectively; and ii) a light chain variable region that comprises a VL CDR1 region, a VL CDR2 region and a VL CDR3 region, wherein the VL CDR1 region, the VL CDR2 region, and the VL CDR3 region comprise the amino acid sequences of SEQ ID NOs: 4, 5 and 6, respectively.

**[0013]** The antibody or antigen-binding portion thereof of the disclosure may comprise a heavy chain variable region that may comprise a VH CDR1 region, a VH CDR2 region and a VH CDR3 region, and a light chain variable region that may comprise a VL CDR1 region, a VL CDR2 region and a VL CDR3 region, wherein the VH CDR1 region, the VH CDR2 region, the VH CDR3 region, the VL CDR1 region, the VL CDR2 region, and the VL CDR3 region may comprise amino acid sequences having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to (1) SEQ ID NOs: 1, 2 (X1=D, X2=Q), 3, 4, 5 and 6, respectively; (2) SEQ ID NOs: 1, 2 (X1=E, X2=Q), 3, 4, 5 and 6, respectively; (3) SEQ ID NOs: 1, 2 (X1=D, X2=K), 3, 4, 5 and 6, respectively; (4) SEQ ID NOs: 9, 10, 11, 12, 13 and 14, respectively; or (5) SEQ ID NOs: 33, 34, 35, 36, 37 and 38, respectively, wherein the antibody or antigen-binding fragment thereof binds to Siglec15.

**[0014]** The heavy chain variable region of the antibody or antigen-binding portion thereof of the disclosure may comprise an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to SEQ ID NOs: 7 (X1=D, X2=Q; X1=E, X2=Q; or X1=D, X2=K), 15, 39, 40 or 41, wherein the antibody or antigen-binding fragment thereof binds to Siglec15. The amino acid sequence of SEQ ID NO: 7 (X1=D, X2=Q) may be encoded by the nucleotide sequence of SEQ ID NOs: 27, and the amino acid sequence of SEQ ID NO: 15 may be encoded by the nucleotide sequence of SEQ ID NO: 29.

**[0015]** The light chain variable region of the antibody or antigen-binding portion thereof of the disclosure may comprise an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to SEQ ID NOs: 8, 16, 42 or 43, wherein the antibody or antigen-binding fragment thereof binds to Siglec15. The amino acid sequences of SEQ ID NO: 8 and 16 may be encoded by nucleotide sequences of SEQ ID NOs: 28 and 30.

**[0016]** The antibody or antigen-binding portion thereof of the disclosure may comprise a heavy chain variable region and a light chain variable region having amino acid sequences having at least 85%,

**[0020]** Nucleic acid molecules encoding the antibody, or the antigen-binding portion thereof, of the disclosure are also encompassed by the disclosure, as well as expression vectors that may comprise such nucleic acids and host cells that may comprise such expression vectors. In one aspect, the present disclosure refers to a nucleotide encoding any one of the isolated monoclonal antibody or the antigen-binding portion thereof as disclosed herein. In one aspect, the present disclosure refers to a vector containing the nucleotide as disclosed herein. In one aspect, the present disclosure refers to a host cell containing the vector as disclosed herein. A method for preparing the anti-Siglec15 antibody or the antigen-binding portion thereof of the disclosure using the host cell is also provided, that may comprise steps of (i) expressing the antibody in the host cell and (ii) isolating the antibody from the host cell or its cell culture.

**[0021]** Compositions that may comprise the antibody, or the antigen-binding portion thereof, the immunoconjugate, the bispecific molecule, the oncolytic virus, the CAR, the CAR-T cell, the nucleic acid molecule, the expression vector or the host cells of the disclosure, and a pharmaceutically acceptable carrier, are also provided. In one aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody or antigen-binding portion thereof as disclosed herein, and a pharmaceutically acceptable carrier. In certain examples, the pharmaceutical composition may further contain a therapeutic agent such as an anti-cancer agent.

**[0021a]** In one aspect, the present disclosure refers to use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating cancer in a subject.

**[0022]** In yet another example, the disclosure provides a method of modulating an immune response in a subject comprising administering to the subject a therapeutically effective amount of the antibody or antigen-binding portion thereof, of the disclosure, or alternatively a nucleic acid molecule capable of expressing the same in the subject, such that the immune response in the subject is modulated. Preferably, the antibody or antigen-binding portion thereof of the disclosure enhances, stimulates or increases the immune response in the subject, e.g., by reversing Siglec15 mediated T cell suppression. In some examples, the method comprises administering a bispecific molecule, an immunoconjugate, a CAR-T cell, or an antibody-encoding or antibody-bearing oncolytic virus of the disclosure.

**[0023]** In one aspect, the present disclosure refers to use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating osteoporosis in a subject. In yet another example, the disclosure provides a method of inhibiting bone loss or increasing bone mass in a subject comprising administering to the subject a therapeutically effective amount of the antibody, or antigen-binding portion thereof, of the disclosure, or alternatively a nucleic acid molecule capable of expressing the same.

**[0024]** In a further example, the disclosure provides a method of inhibiting tumor growth in a subject in need thereof, comprising administering to a subject a therapeutically effective amount of the antibody or antigen-binding portion thereof, of the disclosure, or alternatively a nucleic acid molecule capable of expressing the same in the subject. In some examples, the method comprises administering a bispecific molecule, an immunoconjugate, a CAR-T cell, or an antibody-encoding or antibody-bearing oncolytic virus of the disclosure. The tumor may be a solid or non-solid tumor. In certain examples, the tumor is solid tumor, including, but not limited to, non-small cell lung cancer, ovarian cancer, melanoma, colorectal cancer, breast cancer (including triple-negative breast cancer), head and neck squamous cell carcinoma, endometrial cancer, and squamous cell carcinoma. In some examples, at least one additional anti-cancer antibody can be administered with the antibody, or an antigen-binding portion thereof, of the disclosure, such as an anti-VISTA antibody, an anti-PD-1 antibody, an anti-PD-L1 antibody, an anti-LAG-3 antibody, an anti-CTLA-4 antibody, an anti-TIM-3 antibody, an anti-STAT3 antibody, and/or an anti-ROR1 antibody. In yet another example, an antibody, or an antigen-binding portion thereof, of the disclosure is administered with a cytokine (e.g., IL-2, IL-21, GM-CSF and/or IL-4), or a costimulatory antibody (e.g., an anti-CD137 and/or anti-GITR antibody). In another example, an antibody, or an antigen-binding portion thereof, of the

**We claim:**

1. An isolated monoclonal antibody or an antigen-binding portion thereof, binding to Siglec15, comprising

i) a heavy chain variable region that comprises a VH CDR1 region, a VH CDR2 region and a VH CDR3 region,

wherein the VH CDR1 region, the VH CDR2 region and the VH CDR3 region comprise the amino acid sequences of (1) SEQ ID NOs: 1, 2 (X1=D, X2=Q) and 3, respectively; (2) SEQ ID NOs: 1, 2 (X1=E, X2=Q) and 3, respectively; or (3) SEQ ID NOs: 1, 2 (X1=D, X2=K) and 3, respectively;

and ii) a light chain variable region that comprises a VL CDR1 region, a VL CDR2 region and a VL CDR3 region,

wherein the VL CDR1 region, the VL CDR2 region, and the VL CDR3 region comprise the amino acid sequences of SEQ ID NOs: 4, 5 and 6, respectively.

2. The isolated monoclonal antibody or the antigen-binding portion thereof, of claim 1

wherein the heavy chain variable region comprises an amino acid sequence having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to SEQ ID NO: 7 (X1=D, X2=Q; X1=E, X2=Q; or X1=D, X2=K).

3. The isolated monoclonal antibody or the antigen-binding portion thereof of claim 1,

wherein the light chain variable region comprises having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to SEQ ID NO: 8.

4. The isolated monoclonal antibody or an antigen-binding portion thereof of claim 2, wherein the heavy chain variable region and the light chain variable region comprise amino acid sequences having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identity to

(1) SEQ ID NO: 7 (X1=D, X2=Q) and 8, respectively;

(2) SEQ ID NO: 7 (X1=E, X2=Q) and 8, respectively; or

(3) SEQ ID NO: 7 (X1=D, X2=K) and 8, respectively.

5. The isolated monoclonal antibody or an antigen-binding portion thereof of claim 1, comprising a heavy chain constant region having an amino acid sequence of SEQ ID NO: 17, linked to the heavy chain variable region, and a light chain constant region having an amino acid sequence of SEQ ID NO: 18, linked to the light chain variable region.

6. The isolated monoclonal antibody or the antigen-binding portion thereof of claim 1, which (a) binds human Siglec15; (b) binds monkey Siglec15; (c) binds mouse Siglec15; (d) blocks Siglec15 binding to LRRC4C; and/or (e) reverses Siglec15 mediated T cell suppression.

7. The isolated monoclonal antibody or the antigen-binding portion thereof of claim 1, which is a mouse, human, chimeric or humanized antibody.

8. The isolated monoclonal antibody or the antigen-binding portion thereof of claim 1, which is an IgG1, IgG2 or IgG4 isotype.

9. A nucleotide encoding the isolated monoclonal antibody or the antigen-binding portion thereof of any one of claims 1 to 8.

10. A vector containing the nucleotide of claim 9.

11. A host cell containing the vector of claim 10.

12. A pharmaceutical composition comprising the antibody or antigen-binding portion thereof of claim 1, and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition of claim 12, further comprising an anti-tumor agent or an osteoporosis drug.

14. Use of the pharmaceutical composition of claim 12 or 13 in the manufacture of a medicament for treating cancer in a subject.

15. The use of claim 14, wherein the cancer disease is a solid tumor.

16. The use of claim 15, wherein the cancer is non-small cell lung cancer, ovarian cancer, melanoma, colorectal cancer, breast cancer, endometrial cancer, or squamous cell carcinoma.

17. Use of the pharmaceutical composition of claim 12 or 13 in the manufacture of a medicament for treating osteoporosis in a subject.