

- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of LAG-3 mAb 6, and, respectively have the amino acid sequences: **SEQ ID NO:76**, **SEQ ID NO:77**, and **SEQ ID NO:78**;

or

- (H) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of LAG-3 hAb 6, and respectively have the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of hLAG-3 hAb 6, and respectively have the amino acid sequences: **SEQ ID NO:87**, **SEQ ID NO:77**, and **SEQ ID NO:78**.

[0014a] In one aspect, the present disclosure refers to a LAG-3-binding molecule that is capable of binding both to human LAG-3 and to cynomolgus monkey LAG-3, wherein said LAG-3-binding molecule is an antibody or comprises an antigen-binding fragment thereof that comprises a Variable Heavy Chain Domain and a Variable Light Chain Domain of an antibody that specifically binds human LAG-3 with an equilibrium binding constant (KD) of about 0.05 nM or less, wherein:

said Variable Heavy Chain Domain comprises a CDR_{H1} Domain, a CDR_{H2} Domain and a CDR_{H3} Domain, and said Variable Light Chain Domain comprises a CDR_{L1} Domain, a CDR_{L2} Domain, and a CDR_{L3} Domain, wherein:

- (A) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of LAG-3 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:8**, **SEQ ID NO:9**, and **SEQ ID NO:10**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of LAG-3 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:13**, **SEQ ID NO:14**, and **SEQ ID NO:15**;

- (B) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of hLAG-3 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:8**, **SEQ ID NO:9**, and **SEQ ID NO:10**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of hLAG-3 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:28**, **SEQ ID NO:14**, and **SEQ ID NO:15**;
- (C) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of LAG-3 mAb 6 VH1, and respectively have the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of LAG-3 mAb 6, and, respectively have the amino acid sequences: **SEQ ID NO:76**, **SEQ ID NO:77**, and **SEQ ID NO:78**;

or

- (D) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of hLAG-3 mAb 6, and respectively have the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of hLAG-3 mAb 6, and respectively have the amino acid sequences: **SEQ ID NO:87**, **SEQ ID NO:77**, and **SEQ ID NO:78**;

wherein said LAG-3-binding molecule is capable of binding both to human LAG-3 and to cynomolgus monkey LAG-3, and is capable of binding to human LAG-3 with an equilibrium binding constant (KD) of about 0.05 nM or less.

[0014b] In another aspect, the present disclosure refers to a LAG-3-binding molecule that is capable of binding both to human LAG-3 and to cynomolgus monkey LAG-3, wherein said LAG-3-binding molecule is an antibody or comprises an antigen-binding fragment thereof that comprises a Variable Heavy Chain Domain and a Variable Light Chain Domain, wherein:

- (A) (1) said Variable Heavy Chain Domain comprises the amino acid sequence of **SEQ ID NO:16** or **SEQ ID NO:18**; and
- (2) said Variable Light Chain Domain comprises the amino acid sequence of **SEQ ID NO:24** or **SEQ ID NO:26**; or
- (B) (1) said Variable Heavy Chain Domain comprises the amino acid sequence of **SEQ ID NO:79**; and
- (2) said Variable Light Chain Domain comprises the amino acid sequence of **SEQ ID NO:83**.

[0015] The disclosure further concerns the examples of such LAG-3-binding molecules wherein the Heavy Chain Variable Domain has the amino acid sequence of **SEQ ID NO:6, SEQ ID NO:29, SEQ ID NO:39, SEQ ID NO:49, or SEQ ID NO:59.**

[0016] The disclosure further concerns the examples of such LAG-3-binding molecules wherein the Light Chain Variable Domain has the amino acid sequence of **SEQ ID NO:11, SEQ ID NO:34, SEQ ID NO:44, SEQ ID NO:54, or SEQ ID NO:64.**

[0017] The disclosure further concerns the examples of such LAG-3-binding molecules wherein the Heavy Chain Variable Domain has the amino acid sequence of **SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:79, or SEQ ID NO:80.**

[0018] The disclosure further concerns the examples of such LAG-3-binding molecules wherein the Light Chain Variable Domain has the amino acid sequence of **SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:83, or SEQ ID NO:85.**

[0019] The disclosure further concerns the examples of all such LAG-3-binding molecules wherein the molecule is an antibody, and especially wherein the molecule is a chimeric antibody or a humanized antibody.

What Is Claimed Is:

Claim 1. A LAG-3-binding molecule that is capable of binding both to human LAG-3 and to cynomolgus monkey LAG-3, wherein said LAG-3-binding molecule is an antibody or comprises an antigen-binding fragment thereof that comprises a Variable Heavy Chain Domain and a Variable Light Chain Domain of an antibody that specifically binds human LAG-3 with an equilibrium binding constant (KD) of about 0.05 nM or less, wherein:

said Variable Heavy Chain Domain comprises a CDR_{H1} Domain, a CDR_{H2} Domain and a CDR_{H3} Domain, and said Variable Light Chain Domain comprises a CDR_{L1} Domain, a CDR_{L2} Domain, and a CDR_{L3} Domain, wherein:

- (A) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of LAG-3 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:8**, **SEQ ID NO:9**, and **SEQ ID NO:10**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of LAG-3 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:13**, **SEQ ID NO:14**, and **SEQ ID NO:15**;
- (B) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of hLAG-3 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:8**, **SEQ ID NO:9**, and **SEQ ID NO:10**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of hLAG-3 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:28**, **SEQ ID NO:14**, and **SEQ ID NO:15**;
- (C) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of LAG-3 mAb 6 VH1, and respectively have the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**; and

- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of LAG-3 mAb 6, and, respectively have the amino acid sequences: **SEQ ID NO:76**, **SEQ ID NO:77**, and **SEQ ID NO:78**;

or

- (D) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of hLAG-3 mAb 6, and respectively have the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of hLAG-3 mAb 6, and respectively have the amino acid sequences: **SEQ ID NO:87**, **SEQ ID NO:77**, and **SEQ ID NO:78**;

wherein said LAG-3-binding molecule is capable of binding both to human LAG-3 and to cynomolgus monkey LAG-3, and is capable of binding to human LAG-3 with an equilibrium binding constant (KD) of about 0.05 nM or less.

Claim 2. The LAG-3-binding molecule of claim 1, wherein:

- (A) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of LAG-3 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:8**, **SEQ ID NO:9**, and **SEQ ID NO:10**; and
- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of LAG-3 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:13**, **SEQ ID NO:14**, and **SEQ ID NO:15**; or
- (B) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of hLAG-3 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:8**, **SEQ ID NO:9**, and **SEQ ID NO:10**; and

- (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of hLAG-3 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:28**, **SEQ ID NO:14**, and **SEQ ID NO:15**.

Claim 3. The LAG-3-binding molecule of claim 1, wherein:

- (A) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of LAG-3 mAb 6, and respectively have the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**; and
 - (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of hLAG-3 mAb 6, and respectively have the amino acid sequences: **SEQ ID NO:76**, **SEQ ID NO:77**, and **SEQ ID NO:78**; or
- (B) (1) the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain are the Heavy Chain CDRs of hLAG-3 mAb 6, and respectively have the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**; and
 - (2) the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain are the Light Chain CDRs of hLAG-3 mAb 6, and respectively have the amino acid sequences: **SEQ ID NO:87**, **SEQ ID NO:77**, and **SEQ ID NO:78**.

Claim 4. A LAG-3-binding molecule that is capable of binding both to human LAG-3 and to cynomolgus monkey LAG-3, wherein said LAG-3-binding molecule is an antibody or comprises an antigen-binding fragment thereof that comprises a Variable Heavy Chain Domain and a Variable Light Chain Domain, wherein:

- (A) (1) said Variable Heavy Chain Domain comprises the amino acid sequence of **SEQ ID NO:16** or **SEQ ID NO:18**; and
 - (2) said Variable Light Chain Domain comprises the amino acid sequence of **SEQ ID NO:24** or **SEQ ID NO:26**; or
- (B) (1) said Variable Heavy Chain Domain comprises the amino acid sequence of **SEQ ID NO:79**; and

- (2) said Variable Light Chain Domain comprises the amino acid sequence of **SEQ ID NO:83**.

Claim 5. The LAG-3-binding molecule of any one of claims 1-4, wherein said molecule comprises:

- (1) a Heavy Chain Variable Domain comprising the amino acid sequence of **SEQ ID NO:16** or **SEQ ID NO:18**; and
- (2) a Light Chain Variable Domain comprising the amino acid sequence of **SEQ ID NO:24** or **SEQ ID NO:26**.

Claim 6. The LAG-3-binding molecule of any one of claims 1-4, wherein said molecule comprises:

- (1) a Heavy Chain Variable Domain comprising the amino acid sequence of **SEQ ID NO:79**; and
- (2) a Light Chain Variable Domain comprising the amino acid sequence of **SEQ ID NO:83**.

Claim 7. The LAG-3-binding molecule of claim 5, wherein said molecule comprises a Heavy Chain Variable Domain comprising the amino acid sequence of **SEQ ID NO:16**, and a Light Chain Variable Domain comprising the amino acid sequence of **SEQ ID NO:24**,

Claim 8. The LAG-3-binding molecule of claim 5, wherein said molecule comprises a Heavy Chain Variable Domain comprising the amino acid sequence of **SEQ ID NO:16**, and a Light Chain Variable Domain comprising the amino acid sequence of **SEQ ID NO:26**,

Claim 9. The LAG-3-binding molecule of any one of claims 1-8, wherein said molecule is an antibody.

Claim 10. The LAG-3-binding molecule of claim 9, wherein said molecule is a chimeric antibody or a humanized antibody.

- Claim 11. The LAG-3-binding molecule of any one of claims 1-8, wherein said molecule is a bispecific binding molecule, capable of simultaneously binding to human LAG-3 and to a second epitope.
- Claim 12. The LAG-3-binding molecule of claim 11, wherein said second epitope is an epitope of a molecule involved in regulating an immune check point present on the surface of an immune cell.
- Claim 13. The LAG-3-binding molecule of claim 11, wherein said second epitope is an epitope of B7-H3, B7-H4, BTLA, CD40, CD40L, CD47, CD70, CD80, CD86, CD94, CD137, CD137L, CD226, CTLA-4, Galectin-9, GITR, GITRL, HHLA2, ICOS, ICOSL, KIR, LAG-3, LIGHT, MHC class I or II, NKG2a, NKG2d, OX40, OX40L, PD1H, PD-1, PD-L1, PD-L2, PVR, SIRPa, TCR, TIGIT, TIM-3 or VISTA.
- Claim 14. The LAG-3-binding molecule of claim 13, wherein said second epitope is an epitope of PD-1.
- Claim 15. The LAG-3-binding molecule of any one of claims 11-14, wherein said molecule is:
- (a) a diabody, said diabody being a covalently bonded complex that comprises two, or three or four different polypeptide chains; or
 - (b) a trivalent binding molecule, said trivalent binding molecule being a covalently bonded complex that comprises three, four, or five polypeptide chains.
- Claim 16. The LAG-3-binding molecule of any one of claims 1-15, wherein said molecule comprises an Fc Region.
- Claim 17. The LAG-3-binding molecule of any one of claims 1-16, wherein said molecule comprises an Albumin-Binding Domain (ABD).
- Claim 18. The LAG-3-binding molecule of claim 17, wherein said ABD is a deimmunized ABD.

- Claim 19. The LAG-3-binding molecule of claim 16, wherein said Fc Region is a variant Fc Region that comprises:
- (a) one or more amino acid modifications that reduce(s) the affinity of said variant Fc Region for an Fc γ R; and/or
 - (b) one or more amino acid modifications that enhance(s) the serum half-life of said variant Fc Region.
- Claim 20. The LAG-3-binding molecule of claim 19, wherein:
- (a) said modifications that reduce(s) the affinity of the variant Fc Region for an Fc γ R comprise the substitutions:
 - (1) L234A; L235A; or
 - (2) L234A and L235A;
 - and
 - (b) said modifications that enhance(s) the serum half-life of the variant Fc Region comprise the substitutions:
 - (1) M252Y and S254T;
 - (2) M252Y and T256E;
 - (3) M252Y, S254T and T256E; or
 - (4) K288D and H435K,
- wherein said numbering is that of the EU index according to Kabat.
- Claim 21. A pharmaceutical composition comprising an effective amount of the LAG-3-binding molecule of any one of claims 1-20, and a pharmaceutically acceptable carrier.
- Claim 22. The LAG-3-binding molecule of any one of claims 1-20, or the pharmaceutical composition of claim 21, for use in stimulating a T-cell-mediated immune response of a subject in need thereof.
- Claim 23. The LAG-3-binding molecule of any one of claims 1-20, or the pharmaceutical composition of claim 21, for use in treating a disease or condition associated with a suppressed immune system.
- Claim 24. The LAG-3-binding molecule of claim 23, wherein the disease or condition is cancer or an infection.
- Claim 25. The LAG-3-binding molecule of claim 24, wherein disease or condition is a cancer selected from the group consisting of: an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a

chondrosarcoma, a chordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a pheochromocytoma, a pituitary tumor, a prostate cancer, a posterior uveal melanoma, a renal metastatic cancer, a rhabdoid tumor, a rhabdomyosarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine cancer.

Claim 26. The LAG-3-binding molecule of claim 24, wherein said disease or condition is selected from the group consisting of: colorectal cancer, hepatocellular carcinoma, glioma, kidney cancer, breast cancer, multiple myeloma, bladder cancer, neuroblastoma, sarcoma, non-Hodgkin's lymphoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer, rectal cancer, acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), acute B lymphoblastic leukemia (B-ALL), chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), non-Hodgkin's lymphoma (NHL), including mantle cell leukemia (MCL), and small lymphocytic lymphoma (SLL), Hodgkin's lymphoma, systemic mastocytosis, and Burkitt's lymphoma.

Claim 27. The LAG-3-binding molecule of any one of claims 1-20, or the pharmaceutical composition of claim 21, wherein said molecule is detectably labeled for use in the detection of LAG-3.