

CLAIMS

1. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an IGSF8 (Immunoglobulin Super Family 8) antagonist.
2. The method of claim 1, further comprising administering to the subject an effective amount of a second therapeutic agent selected from the group consisting of: an immune checkpoint inhibitor, a chemotherapeutic agent, an anti-angiogenesis agent, a growth inhibitory agent, an immune-oncology agent, and an anti-neoplastic composition.
3. The method of claim 1 or 2, wherein the IGSF8 antagonist is an anti-IGSF8 antibody, or an antigen-binding portion / fragment thereof.
4. The method of claim 3, wherein the antibody is a chimeric antibody, a humanized antibody, or a human antibody.
5. The method of claim 3 or 4, wherein the antigen-binding portion / fragment is an Fab, Fab', F(ab')₂, F_d, single chain Fv or scFv, disulfide linked F_v, V-NAR domain, IgNar, intrabody, IgGΔCH₂, minibody, F(ab')₃, tetrabody, triabody, diabody, single-domain antibody, DVD-Ig, Fcab, mAb₂, (scFv)₂, or scFv-Fc.
6. The method of any one of claims 1 to 5, wherein the cancer is melanoma (including skin cutaneous melanoma), cervical cancer, lung cancer (*e.g.*, non-small cell lung cancer, lung adenocarcinoma, lung squamous cell carcinoma), colorectal cancer, lymphoma (including DLBCL), leukemia (including CLL), BLCA tumor, breast cancer, head-neck squamous cell carcinoma, PRAD, THCA, or UCEC, thyroid cancer, unitary tract cancer, esophagus cancer, liver cancer, or ganglia cancer.
7. The method of any one of claims 1 to 6, wherein the IGSF8 antagonist promotes expression, secretion, or otherwise increases activity of a cytokine or a target gene selected from the group consisting of: CXCL10, CXCL9, TNF α , CD8b, CD8a, Prf1, IFN γ , Gzma, Gzmb, CD274, PDCD1, PDCD1 Ig2, LAG3, Havcr2, Tigit, or CTLA4.
8. The method of any one of claims 1 to 7, wherein expression, secretion, or otherwise increased activity of said cytokine or said target gene occurs within tumor microenvironment.

9. The method of any one of claims 1 to 8, wherein expression, secretion, or otherwise increased activity of said cytokine or said target gene is due to immune cell (*e.g.*, T lymphocytes or NK cells) infiltration into tumor microenvironment.
10. The method of any one of claims 1 to 9, wherein the IGSF8 antagonist is an immunostimulatory molecule.
11. The method of claim 10, wherein the IGSF8 antagonist stimulates T cell or NK cell activation and/or infiltration into tumor microenvironment.
12. The method of any one of claims 1 to 11, wherein the immune checkpoint inhibitor is an antibody or antigen-binding fragment thereof specific for PD-1 or PD-L1.
13. The method of claim 12, wherein the antibody is an anti-PD-1 antibody, such as cemiplimab, nivolumab, or pembrolizumab.
14. The method of claim 12, wherein the antibody is an anti-PD-L1 antibody, such as avelumab, durvalumab, atezolizumab, KN035, or CK-301.
15. The method of any one of claims 1 to 11, wherein the immune checkpoint inhibitor is a (non-antibody) peptide inhibitor of PD-1/PD-L1, such as AUNP12; a small molecule inhibitor of PD-L1 such as CA-170, or a macrocyclic peptide such as BMS-986189.
16. Use of an IGSF8 antagonist for treating cancer in a subject.
17. The use of claim 16, for combination use with a second therapeutic agent of any one of claims 2 and 12-16.
18. A composition comprising an IGSF8 antagonist for use in any of the preceding method claims 1-15.
19. An antibody which specifically bind IGSF8 for use in a method of treating cancer, preferably through stimulating T cell and/or NK cell activation.
20. An antibody which specifically bind IGSF8 for use in a method of treating cancer, preferably through combination with a second therapeutic agent of any one of claims 2 and 12-16.
21. A monoclonal antibody or an antigen-binding fragment thereof specific for IGSF8, wherein said monoclonal antibody comprises:
 - (1) a heavy chain variable region (HCVR), comprising HCVR CDR1 - CDR3

- sequences of any one of antibodies C1-C29, such as C1-C12; and,
- (2) a light chain variable region (LCVR), comprising LCVR CDR1 - CDR3 sequences of said any one of antibodies C1-C29, such as C1-C12.
22. The monoclonal antibody or antigen-binding fragment thereof of claim 21, comprising:
- (a) the HCVR sequence of said any one of antibodies C1-C29, such as C1-C12; and/or,
- (b) the LCVR sequence of said any one of antibodies C1-C29, such as C1-C12.
23. The monoclonal antibody or antigen-binding fragment thereof of claim 21 or 22, which is a human-mouse chimeric antibody, a humanized antibody, a human antibody, a CDR-grafted antibody, or a resurfaced antibody.
24. The monoclonal antibody or antigen-binding fragment thereof of any one of claims 21-23, wherein said antigen-binding fragment thereof is an Fab, Fab', F(ab')₂, F_d, single chain Fv or scFv, disulfide linked F_v, V-NAR domain, IgNar, intrabody, IgGACH₂, minibody, F(ab')₃, tetrabody, triabody, diabody, single-domain antibody, DVD-Ig, Fcab, mAb₂, (scFv)₂, or scFv-Fc.
25. The monoclonal antibody or antigen-binding fragment thereof of any one of claims 21-24, wherein said monoclonal antibody or antigen-binding fragment thereof binds IGSF8 with a K_d of less than about 25 nM, 20 nM, 15 nM, 10 nM, 5 nM, 2 nM, or 1 nM.
26. A monoclonal antibody or an antigen-binding fragment thereof, which competes with the monoclonal antibody or antigen-binding fragment thereof of any one of claims 21-25 for binding to IGSF8.
27. A method of stimulating T cell and/or NK cell activation in a tumor microenvironment (TME), the method comprising contacting said T cell and/or NK cell with an IGSF8 (Immuno Globulin Super Family 8) antagonist, such as an antibody or antigen-binding fragment thereof that specifically binds IGSF8.
28. The method of claim 27, further comprising contacting said T cell and/or NK cell with an immune checkpoint inhibitor, such as an antibody or antigen-binding fragment thereof specific for PD-1 or PD-L1.