CLAIMS

1. An isolated antibody against human gremlin1 (hGREM1) or an antigen-binding fragment thereof, having at least one of the following characteristics:

a) capable of reducing hGREM1-mediated inhibition on BMP signaling selectively in a cancer cell over a non-cancer cell;

b) exhibiting no more than 50% reduction of hGREM1-mediated inhibition on BMP signaling in a non-cancer cell;

c) capable of binding to a chimeric hGREM1 comprising an amino acid sequence of SEQ ID NO: 68;

d) capable of binding to hGREM1 but not specifically binding to mouse gremlin1, or alternatively is cross-reactive to mouse gremlin1;

e) binding to hGREM1 at an epitope comprising residue Gln27 and/or residue Asn33, wherein residue number is according to SEQ ID NO: 69, or binds to a hGREM1 fragment comprising residue Gln27 and/or residue Asn33, optionally the hGREM1 fragment has a length of at least 3 (e.g. 4, 5, 6, 7, 8, 9, or 10) amino acid residues;

f) capable of binding to hGREM1 at a K_D of no more than 1 nM as measured by Fortebio;

gh) capable of blocking the binding of hGREM1 to BMP7 at a maximal blocking percentage of more than 50% as measured by ELISA;

hi) capable of blocking interaction of GREM1 to FGFR; and/or

ij) capable of binding to both hGREM1 and DAN, optionally wherein the epitope is a linear epitope or a conformational epitope.

~~2. The isolated antibody against hGREM1 or an antigen-binding fragment thereof of claim 1, wherein the epitope is a linear epitope or a conformational epitope.~~

23. An isolated antibody against human gremlin1 (hGREM1) or an antigen-binding fragment thereof, comprising a heavy chain variable (VH) region and/or a light chain variable (VL) region, wherein the heavy chain variable region comprises:

a) a HCDR1 comprises a sequence selected from the group consisting of SEQ ID NOs: 1, 11, 21, 31, 114, 119 and 123,

b) a HCDR2 comprises a sequence selected from the group consisting of SEQ ID NOs: 2, 12, 22, 32 and 115, and

c) a HCDR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 3, 13, 23, 33, 116, 120 and 124, and/or

wherein the light chain variable region comprises:

d) a LCDR1 comprises a sequence selected from the group consisting of SEQ ID NOs: 4, 14, 24, 34, 117, 121, 122 and 125,

e) a LCDR2 comprises a sequence selected from the group consisting of SEQ ID NOs: 5, 15, 25 and 35, and

f) a LCDR3 comprises a sequence selected from the group consisting of SEQ ID NOs: 6, 16, 26, 36 and 118.

34. The antibody or an antigen-binding fragment thereof of any one of the preceding claims, wherein the heavy chain variable region is selected from the group consisting of:

a) a heavy chain variable region comprising a HCDR1 comprising the sequence of SEQ ID NO: 1, a HCDR2 comprising the sequence of SEQ ID NO: 2, and a HCDR3 comprising the sequence of SEQ ID NO: 3; or

b) a heavy chain variable region comprising a HCDR1 comprising the sequence of SEQ ID NO: 11, a HCDR2 comprising the sequence of SEQ ID NO: 12, and a HCDR3 comprising the sequence of SEQ ID NO: 13; or

c) a heavy chain variable region comprising a HCDR1 comprising the sequence of SEQ ID NO: 21, a HCDR2 comprising the sequence of SEQ ID NO: 22, and a HCDR3 comprising the sequence of SEQ ID NO: 23; or

d) a heavy chain variable region comprising a HCDR1 comprising the sequence of SEQ ID NO: 31, a HCDR2 comprising the sequence of SEQ ID NO: 32, and a HCDR3 comprising the sequence of SEQ ID NO: 33; or

e) a heavy chain variable region comprising a HCDR1 comprising the sequence of SEQ ID NO: 114, a HCDR2 comprising the sequence of SEQ ID NO: 115, and a HCDR3 comprising the sequence of SEQ ID NO: 116; or~~and~~

f) a heavy chain variable region comprising a HCDR1 comprising the sequence of SEQ ID NO: 119, a HCDR2 comprising the sequence of SEQ ID NO: 115, and a HCDR3 comprising the sequence of SEQ ID NO: 120; or~~and~~

g) a heavy chain variable region comprising a HCDR1 comprising the sequence of SEQ ID NO: 123, a HCDR2 comprising the sequence of SEQ ID NO: 115, and a HCDR3 comprising the sequence of SEQ ID NO: 124, and/or~~.~~

~~5. The antibody or an antigen-binding fragment thereof of any of the preceding claims,~~ wherein the light chain variable region is selected from the group consisting of:

h~~a~~) a light chain variable region comprising a LCDR1 comprising the sequence of SEQ ID NO: 4, a LCDR2 comprising the sequence of SEQ ID NO: 5, and a LCDR3 comprising the sequence of SEQ ID NO: 6; or

i~~b~~) a light chain variable region comprising a LCDR1 comprising the sequence of SEQ ID NO: 14, a LCDR2 comprising the sequence of SEQ ID NO: 15, and a LCDR3 comprising the sequence of SEQ ID NO: 16; or

j~~c~~) a light chain variable region comprising a LCDR1 comprising the sequence of SEQ ID NO: 24, a LCDR2 comprising the sequence of SEQ ID NO: 25, and a LCDR3 comprising the sequence of SEQ ID NO: 26; or

k~~d~~) a light chain variable region comprising a LCDR1 comprising the sequence of SEQ ID NO: 34, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 36; or

l~~e~~) a light chain variable region comprising a LCDR1 comprising the sequence of SEQ ID NO: 117, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 118; or

m~~f~~) a light chain variable region comprising a LCDR1 comprising the sequence of SEQ ID NO: 121, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 118; or

n~~i~~) a light chain variable region comprising a LCDR1 comprising the sequence of SEQ ID NO: 122, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 118; or~~and~~

oj) a light chain variable region comprising a LCDR1 comprising the sequence of SEQ ID NO: 125, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 118.

46. The antibody or an antigen-binding fragment thereof of any one of the preceding claims, wherein:

a) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 1, a HCDR2 comprising the sequence of SEQ ID NO: 2, and a HCDR3 comprising the sequence of SEQ ID NO: 3; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 4, a LCDR2 comprising the sequence of SEQ ID NO: 5, and a LCDR3 comprising the sequence of SEQ ID NO: 6; or

b) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 11, a HCDR2 comprising the sequence of SEQ ID NO: 12, and a HCDR3 comprising the sequence of SEQ ID NO: 13; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 14, a LCDR2 comprising the sequence of SEQ ID NO: 15, and a LCDR3 comprising the sequence of SEQ ID NO: 16; or

c) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 21, a HCDR2 comprising the sequence of SEQ ID NO: 22, and a HCDR3 comprising the sequence of SEQ ID NO: 23; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 24, a LCDR2 comprising the sequence of SEQ ID NO: 25, and a LCDR3 comprising the sequence of SEQ ID NO: 26; or

d) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 31, a HCDR2 comprising the sequence of SEQ ID NO: 32, and a HCDR3 comprising the sequence of SEQ ID NO: 33; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 34, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 36; or

e) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 114, a HCDR2 comprising the sequence of SEQ ID NO: 115, and a HCDR3 comprising the sequence of SEQ ID NO: 116; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 117, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 118; or

f) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 119, a HCDR2 comprising the sequence of SEQ ID NO: 115, and a HCDR3 comprising the sequence of SEQ ID NO: 120; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 121, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 118; or

g) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 119, a HCDR2 comprising the sequence of SEQ ID NO: 115, and a HCDR3 comprising the sequence of SEQ ID NO: 120; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 122, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 118; or

h) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 123, a HCDR2 comprising the sequence of SEQ ID NO: 115, and a HCDR3 comprising the sequence of SEQ ID NO: 124; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 125, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 118; or

i) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 114, a HCDR2 comprising the sequence of SEQ ID NO: 115, and a HCDR3 comprising the sequence of SEQ ID NO: 116; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 117, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 118; or

j) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 119, a HCDR2 comprising the sequence of SEQ ID NO: 115, and a HCDR3 comprising the sequence of SEQ ID NO: 120; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 121, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 118; or

k) the heavy chain variable region comprises a HCDR1 comprising the sequence of SEQ ID NO: 119, a HCDR2 comprising the sequence of SEQ ID NO: 115, and a HCDR3 comprising the sequence of SEQ ID NO: 120; and the light chain variable region comprises a LCDR1 comprising the sequence of SEQ ID NO: 122, a LCDR2 comprising the sequence of SEQ ID NO: 35, and a LCDR3 comprising the sequence of SEQ ID NO: 118.

57. The antibody or an antigen-binding fragment thereof of any one of the preceding claims, wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 7, SEQ ID NO: 17, SEQ ID NO: 27, SEQ ID NO: 37, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 126, SEQ ID NO: 128, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, and SEQ ID NO: 134, and a homologous sequence thereof having at least 80% sequence identity yet retaining specific binding specificity or affinity to gremlin, and/or.

~~8. The antibody or an antigen-binding fragment thereof of any of the preceding claims,~~ wherein the light chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 18, SEQ ID NO: 28, SEQ ID NO: 38, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 127, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 135, SEQ ID NO: 136, and SEQ ID NO: 137, and a homologous sequence thereof having at least 80% sequence identity yet retaining specific binding specificity or affinity to gremlin.

69. The antibody or an antigen-binding fragment thereof of any one of the preceding claims, comprising:

a) a heavy chain variable region comprising the sequence of SEQ ID NO: 7 and a light chain variable region comprising the sequence of SEQ ID NO: 8; or

b) a heavy chain variable region comprising a sequence of SEQ ID NO: 17 and a light chain variable region comprising a sequence of SEQ ID NO: 18; or

c) a heavy chain variable region comprising a sequence of SEQ ID NO: 27 and a light chain variable region comprising a sequence of SEQ ID NO: 28; or

d) a heavy chain variable region comprising a sequence of SEQ ID NO: 37 and a light chain variable region comprising a sequence of SEQ ID NO: 38; or

e) a heavy chain variable region comprising a sequence of SEQ ID NO: 126 and a light chain variable region comprising a sequence of SEQ ID NO: 127; or

f) a heavy chain variable region comprising a sequence of SEQ ID NO: 128 and a light chain variable region comprising a sequence of SEQ ID NO: 129; or

g) a heavy chain variable region comprising a sequence of SEQ ID NO: 128 and a light chain variable region comprising a sequence of SEQ ID NO: 130; or

h) a heavy chain variable region comprising a sequence selected from the group consisting of SEQ ID NO: 41, SEQ ID NO: 43 and SEQ ID NO: 45, and a light chain variable region comprising a sequence selected from the group consisting of SEQ ID NO: 47 and SEQ ID NO: 49; or

i) a pair of heavy chain variable region and light chain variable region sequences selected from the group consisting of: SEQ ID NOs: 41/47, 41/49, 43/47, 43/49, 45/47, and 45/49; or

j) a heavy chain variable region comprising a sequence selected from the group consisting of SEQ ID NO: 51, SEQ ID NO: 53, SEQ ID NO: 55 and SEQ ID NO: 57, and a light chain variable region comprising a sequence selected from the group consisting of SEQ ID NO: 59 and SEQ ID NO: 61; or

k) a pair of heavy chain variable region and light chain variable region sequences selected from the group consisting of: SEQ ID NOs: 51/59, 51/61, 53/59, 53/61, 55/59, 55/61, 57/59, and 57/61; or

l) a heavy chain variable region comprising a sequence selected from the group consisting of SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133 and SEQ ID NO: 134, and a light chain variable region comprising a sequence selected from the group consisting of SEQ ID NO: 135, SEQ ID NO: 136 and SEQ ID NO: 137; or

m) a pair of heavy chain variable region and light chain variable region sequences selected from the group consisting of: SEQ ID NOs: 131/135, 131/136, 131/137, 132/135, 132/136, 132/137, 133/135, 133/136, 133/137, 134/135, 134/136, and 134/137.

7~~10~~. The antibody or antigen-binding fragment thereof of any one of the preceding claims, further comprising one or more amino acid residue substitutions or modifications yet retains specific binding specificity or affinity to hGREM1, optionally wherein at least one of the substitutions or modifications is in one or more of the CDR sequences, and/or in one or more of the non-CDR regions of the VH or VL sequences.

~~11. The antibody or antigen-binding fragment thereof of claim 10, wherein at least one of the substitutions or modifications is in one or more of the CDR sequences, and/or in one or more of the non-CDR regions of the VH or VL sequences.~~

8~~12~~. The antibody or antigen-binding fragment thereof of any one of the preceding claims, further comprising an immunoglobulin constant region, optionally a constant region of~~–~~ human IgG, optionally wherein the constant region comprises a constant region of human IgG1, IgG2, IgG3, or IgG4, and optionally the constant region comprises a heavy chain constant region comprising a sequence of SEQ ID NO: 138 and/or a light chain constant region comprising a sequence of SEQ ID NO:139.

~~13. The antibody or antigen-binding fragment thereof of claim 12, wherein the constant region comprises a constant region of human IgG1, IgG2, IgG3, or IgG4, and optionally the constant region comprises a heavy chain constant region comprising a sequence of SEQ ID NO: 138 and/or a light chain constant region comprising a sequence of SEQ ID NO:139.~~

9~~14~~. The antibody or an antigen-binding fragment thereof of any one of the preceding claims, which is humanized or chimeric.

10~~15~~. The antibody or antigen-binding fragment thereof of any one of the preceding claims, which is a diabody, a Fab, a Fab', a $F(ab')_2$, a Fd, an Fv fragment, a disulfide stabilized Fv fragment (dsFv), a $(dsFv)_2$, a bispecific dsFv (dsFv-dsFv'), a disulfide stabilized diabody (ds diabody), a single-chain antibody molecule (scFv), an scFv dimer (bivalent diabody), a multispecific antibody, a camelized single domain antibody, a nanobody, a domain antibody, and a bivalent domain antibody.

11~~16~~. The antibody or antigen-binding fragment thereof of any one of the preceding claims, which is bispecific, capable of specifically binding to a first and a second epitope of gremlin, or capable of specifically binding to both hGREM1 and a second antigen, optionally wherein the second antigen is selected from the group consisting of: PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, LAG3, A2AR, CD160, 2B4, TGF β, VISTA, BTLA, TIGIT, LAIR1, OX40, CD2, CD27, CD28, CD30, CD40, CD47, CD122, ICAM-1, IDO, NKG2C, SLAMF7, SIGLEC7, NKp80, CD160, B7-H3, LFA-1, 1COS, 4-1BB, GITR, BAFFR, HVEM, CD7, LIGHT, IL-2, IL-7, IL-15, IL-21, CD3, CD16 CD83, prostate specific antigen (PSA), CA-125, gangliosides G(D2), G(M2) and G(D3), CD20, CD52, CD33, Ep-CAM, CEA, bombesin-like peptides, HER2/neu, epidermal growth factor receptor (EGFR), erbB2, erbB3/HER3, erbB4, CD44v6, Ki-67, cancer-associated mucin, VEGF, VEGFRs (e.g., VEGFR-1, VEGFR-2, VEGFR-3), estrogen receptors, Lewis-Y antigen, TGFβ1, IGF-1 receptor, EGFα, c-Kit receptor, transferrin receptor, Claudin 18.2, GPC-3, Nectin-4, ROR1, methothelin, PCMA, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, pl5, BCR-ABL, E2APRL, H4-RET, IGH-IGK, MYL-RAR, IL-2R, CO17-1A, TROP2, or LIV-1.

~~17. The antibody or antigen-binding fragment thereof of claim 16, capable of specifically binding to a first and a second epitope of gremlin, or capable of specifically binding to both hGREM1 and a second antigen.~~

~~18. The antibody or antigen-binding fragment thereof of claim 17, wherein the second~~

~~antigen comprises an immune related target.~~

~~19. The antibody or antigen-binding fragment thereof of claim 18, wherein the second antigen comprises PD-1, PD-L1, PD-L2, CTLA-4, TIM-3, LAG3, A2AR, CD160, 2B4, TGF β, VISTA, BTLA, TIGIT, LAIR1, OX40, CD2, CD27, CD28, CD30, CD40, CD47, CD122, ICAM-1, IDO, NKG2C, SLAMF7, SIGLEC7, NKp80, CD160, B7-H3, LFA-1, 1COS, 4-1BB, GITR, BAFFR, HVEM, CD7, LIGHT, IL-2, IL-7, IL-15, IL-21, CD3, CD16 or CD83.~~

~~20. The antibody or antigen-binding fragment thereof of claim 17, wherein the second antigen comprises a tumor antigen.~~

~~21. The antibody or antigen-binding fragment thereof of claim 20, wherein the tumor antigen comprises a tumor specific antigen or a tumor associated antigen.~~

~~22. The antibody or antigen-binding fragment thereof of claim 20, wherein the tumor antigen comprises prostate specific antigen (PSA), CA-125, gangliosides G(D2), G(M2) and G(D3), CD20, CD52, CD33, Ep-CAM, CEA, bombesin-like peptides, HER2/neu, epidermal growth factor receptor (EGFR), erbB2, erbB3/HER3, erbB4, CD44v6, Ki-67, cancer-associated mucin, VEGF, VEGFRs (e.g., VEGFR-1, VEGFR-2, VEGFR-3), estrogen receptors, Lewis-Y antigen, TGFβ1, IGF-1 receptor, EGFα, c-Kit receptor, transferrin receptor, Claudin-18.2, GPC-3, Nectin-4, ROR1, methothelin, PCMA, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, pl5, BCR-ABL, E2APRL, H4-RET, IGH-IGK, MYL-RAR, IL-2R, CO17-1A, TROP2, or LIV-1.~~

12~~23~~. The antibody or an antigen-binding fragment thereof of any one of the preceding claims, which is not cross-reactive to mouse gremlin1 or cross-reactive to mouse gremlin1.

~~24. The antibody or an antigen-binding fragment thereof of any of claims 1-22, which is cross-reactive to mouse gremlin1.~~

13~~25~~. The antibody or antigen-binding fragment thereof of any one of the preceding claims linked to one or more conjugate moieties, optionally wherein the conjugate

moiety comprises a clearance-modifying agent, a chemotherapeutic agent, a toxin, a radioactive isotope, a lanthanide, a luminescent label, a fluorescent label, an enzyme-substrate label, a DNA-alkylator, a topoisomerase inhibitor, a tubulin-binders, or other anticancer drugs such as androgen receptor inhibitor.

~~26. The antibody or antigen-binding fragment thereof of claim 25, wherein the conjugate moiety comprises a clearance-modifying agent, a chemotherapeutic agent, a toxin, a radioactive isotope, a lanthanide, a luminescent label, a fluorescent label, an enzyme-substrate label, a DNA-alkylator, a topoisomerase inhibitor, a tubulin-binders, or other anticancer drugs such as androgen receptor inhibitor.~~

14~~27~~. An antibody or an antigen-binding fragment thereof, which competes for binding to hGREM1 with the antibody or antigen-binding fragment thereof of any one of the preceding claims.

15~~28~~. A pharmaceutical composition or kit comprising the antibody or antigen-binding fragment thereof of any one of the preceding claims, and optionally a pharmaceutically acceptable carrier.

16~~29~~. The pharmaceutical composition or kit of claim 15~~28~~, further comprising a second therapeutic agent.

17~~30~~. An isolated polynucleotide encoding the antibody or an antigen-binding fragment thereof of any one of the preceding claims.

18~~31~~. A vector comprising the isolated polynucleotide of claim 17~~30~~.

19~~32~~. A host cell comprising the vector of claim 18~~31~~.

20~~33~~. A method of expressing the antibody or antigen-binding fragment thereof of any one of claims 1-14~~27~~, comprising culturing the host cell of claim 19~~32~~ under the condition at which the vector of claim 18~~31~~ is expressed.

21~~34~~. Use of an antibody or antigen-binding fragment thereof of any one of claims 1-14, or a pharmaceutical composition of claims 15 or-16, in the manufacture of a medicament for ~~A method of~~ treating a GREM1-related disease or condition in a subject

(e.g., human), or fora ~~method of~~ inhibiting FGFR1 activation in a subject (e.g., human) in need thereof, or fora ~~method of~~ treating a disease or a condition associated with FGFR1 activation mediated by GREM1~~, comprising administering to the subject a therapeutically effective amount of the antibody or antigen-binding fragment thereof of any of claims 1-27, or the pharmaceutical composition of any of claims 28-29~~.

2235. The use~~method~~ of claim 2134, wherein the GREM1-related disease or condition is selected from the group consisting of cancer, fibrotic disease (e.g., a fibrotic disease in lungs, liver, kidney, eyes, skin, heart, gut or muscle), angiogenesis, glaucoma or retinal disease, kidney disease, pulmonary arterial hypertension, or osteoarthritis (OA), or the GREM1-related disease or condition is associated with increased level of GREM1 selected from the group consisting of scleroderma, idiopathic lung fibrosis, diabetic nephropathy, IgAN, lupus nephritis, Alport syndrome, glioma, head and neck cancer, prostate cancer, lung cancer, gastric cancer, pancreatic cancer, esopahgeal cancer, bladder cancer, breast cancer and colorectal cancer, optionally wherein the cancer is a GREM1-expressing cancer, optionally is PD-L1-expressing or is not a PD-L1-expressing cancer, and further optionally is resistant or refractory to the treatment with a PD-1/PD-L1 axis inhibitor, optionally wherein the subject is identified as having a GREM1-expressing cancer cell, or having GREM1 expression in cancer microenvironment, optionally wherein the cancer is a solid tumor or a hematological cancer, optionally wherein the cancer is prostate cancer, gastric-esophageal cancer, lung cancer (e.g., non-small cell lung cancer), liver cancer, pancreatic cancer, breast cancer (e.g., triple negative breast cancer), bronchial cancer, bone cancer, liver and bile duct cancer, ovarian cancer, testicle cancer, kidney cancer, bladder cancer, head and neck cancer, spine cancer, brain cancer, cervix cancer, uterine cancer, endometrial cancer, colon cancer, colorectal cancer, rectal cancer, anal cancer, gastrointestinal cancer, skin cancer, pituitary cancer, stomach cancer, vagina cancer, thyroid cancer, glioblastoma, astrocytoma, melanoma, myelodysplastic syndrome, sarcoma, teratoma, glioma, adenocarcinoma, leukemia (such as Acute lymphocytic leukemia (ALL), Acute myeloid leukemia (AML), Chronic lymphocytic leukemia (CLL), Chronic myeloid

leukemia (CML)), lymphoma (such as Hodgkin's lymphoma, or Non-Hodgkin's lymphoma (e.g. Waldenstrom macroglobulinemia (WM))), or myeloma (such as multiple myeloma (MM)).

~~36. The method of claim 35, wherein the cancer is a GREM1-expressing cancer, optionally is PD-L1-expressing or is not a PD-L1-expressing cancer, and further optionally is resistant or refractory to the treatment with a PD-1/PD-L1 axis inhibitor.~~

~~37. The method of claim 34, wherein the subject is identified as having a GREM1-expressing cancer cell, or having GREM1 expression in cancer microenvironment.~~

~~38. The method of any of claims 34-37, wherein the cancer is a solid tumor or a hematological cancer.~~

~~39. The method of claim 38, wherein the cancer is prostate cancer, gastric-esophageal cancer, lung cancer (e.g., non-small cell lung cancer), liver cancer, pancreatic cancer, breast cancer, bronchial cancer, bone cancer, liver and bile duct cancer, ovarian cancer, testicle cancer, kidney cancer, bladder cancer, head and neck cancer, spine cancer, brain cancer, cervix cancer, uterine cancer, endometrial cancer, colon cancer, colorectal cancer, rectal cancer, anal cancer, gastrointestinal cancer, skin cancer, pituitary cancer, stomach cancer, vagina cancer, thyroid cancer, glioblastoma, astrocytoma, melanoma, myelodysplastic syndrome, sarcoma, teratoma, glioma, adenocarcinoma, leukemia (such as Acute lymphocytic leukemia (ALL), Acute myeloid leukemia (AML), Chronic lymphocytic leukemia (CLL), Chronic myeloid leukemia (CML)), lymphoma (such as Hodgkin's lymphoma, or Non-Hodgkin's lymphoma (e.g. Waldenstrom macroglobulinemia (WM))), or myeloma (such as multiple myeloma (MM)).~~

~~40. The method of claim 39, wherein the cancer is selected from the group consisting of prostate cancer, gastric cancer, esophageal cancer, gastric-esophageal junction cancer, lung cancer (e.g., non-small cell lung cancer), liver cancer, colon cancer, colorectal cancer, glioma, pancreatic cancer, bladder cancer, breast cancer, and multiple myeloma.~~

~~41. The method of claim 40, wherein the cancer is prostate cancer, breast cancer or liver cancer.~~

~~42. The method of claim 40, wherein the breast cancer is triple negative breast cancer.~~

2343. The use~~method~~ of claim 2240, wherein the cancer is esophageal cancer, optionally is resistant or refractory to the treatment with a PD-1/PD-L1 axis inhibitor, and further optionally is resistant or refractory to the treatment with an anti-PD-1 antibody (e.g. nivolumab).

~~44. The method of claim 35, wherein the fibrotic disease is a fibrotic disease in lungs, liver, kidney, eyes, skin, heart, gut or muscle.~~

~~45. The method of claim 34, wherein the subject is human.~~

~~46. The method of claim 34, wherein the administration is via oral, nasal, intravenous, subcutaneous, sublingual, or intramuscular administration.~~

~~47. The method of any of claims 34-46, further comprising administering a therapeutically effective amount of a second therapeutic agent.~~

2448. The use~~method~~ of any one of claims 21-2447, wherein a therapeutically effective amount of a~~the~~ second therapeutic agent is to be administered to a subject in need thereof, optionally wherein the second therapeutic agent comprises an anti-cancer therapy, optionally the anti-cancer therapy is selected from an anti-prostate cancer drug, a chemotherapeutic agent (e.g. cisplatin), radiation therapy, an immunotherapy agent (e.g. an immune checkpoint modulator, for example, a PD-1/PD-L1 axis inhibitor, TGF-beta inhibitor), anti-angiogenesis agent (e.g. antagonist of a VEGFR such as VEGFR-1, VEGFR-2, and VEGFR-3), a targeted therapy agent, a cellular therapy agent, a gene therapy agent, a hormonal therapy agent, cytokines, ~~palliative care, surgery for the treatment of cancer (e.g., tumorectomy),~~ one or more anti-emetics, ~~treatments for complications arising from chemotherapy,~~ a diet supplement for cancer patients (e.g. indole-3-carbinol), an agent that modulates tumor microenvironment (e.g. a bifunctional molecule comprising PD-L1 binding moiety and extracellular domain of TGF-beta receptor) or anti-fibrotic therapy (e.g., BMP7 treatment, ACE inhibitor (or ARB), anti-MASP2 antibody, endothelin receptor antagonist, NRF2 inhibitor steroid, CTLA4-IgG or TNF inhibitor), optionally wherein the anti-prostate cancer drug

comprises an androgen axis inhibitor; an androgen synthesis inhibitor; a PARP inhibitor; or a combination thereof, optionally wherein the androgen axis inhibitor is selected from the group consisting of Luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists and androgen receptor antagonist, optionally wherein the androgen axis inhibitor is degarelix, bicalutamide, flutamide, nilutamide, apalutamide, darolutamide, enzalutamide, or abiraterone, optionally wherein the anti-prostate cancer drug is selected from the group consisting of Abiraterone Acetate, Apalutamide, Bicalutamide, Cabazitaxel, Casodex (Bicalutamide), Darolutamide, Degarelix, Docetaxel, Eligard (Leuprolide Acetate), Enzalutamide, Erleada (Apalutamide), Firmagon (Degarelix), Flutamide, Goserelin Acetate, Jevtana (Cabazitaxel), Leuprolide Acetate, Lupron (Leuprolide Acetate), Lupron Depot (Leuprolide Acetate), Lynparza (Olaparib), Mitoxantrone Hydrochloride, Nilandron (Nilutamide), Nilutamide, Nubeqa (Darolutamide), Olaparib, Provenge (Sipuleucel-T), Radium 223 Dichloride, Rubraca (Rucaparib Camsylate), Rucaparib Camsylate, Sipuleucel-T, Taxotere (Docetaxel), Xofigo (Radium 223 Dichloride), Xtandi (Enzalutamide), Zoladex (Goserelin Acetate) and Zytiga (Abiraterone Acetate).

~~49. The method of claim 48, wherein the anti-cancer therapy comprises an anti-prostate cancer drug.~~

~~50. The method of claim 49, wherein the anti-prostate cancer drug comprises an androgen axis inhibitor; an androgen synthesis inhibitor; a PARP inhibitor; or a combination thereof.~~

~~51. The method of claim 50, the androgen axis inhibitor is selected from the group consisting of Luteinizing hormone-releasing hormone (LHRH) agonists, LHRH antagonists and androgen receptor antagonist.~~

~~52. The method of claim 50, wherein the androgen axis inhibitor is degarelix, bicalutamide, flutamide, nilutamide, apalutamide, darolutamide, enzalutamide, or abiraterone.~~

~~53. The method of claim50, wherein the anti-prostate cancer drug is selected from the~~

~~group consisting of Abiraterone Acetate, Apalutamide, Bicalutamide, Cabazitaxel, Casodex (Bicalutamide), Darolutamide, Degarelix, Docetaxel, Eligard (Leuprolide Acetate), Enzalutamide, Erleada (Apalutamide), Firmagon (Degarelix), Flutamide, Goserelin Acetate, Jevtana (Cabazitaxel), Leuprolide Acetate, Lupron (Leuprolide Acetate), Lupron Depot (Leuprolide Acetate), Lynparza (Olaparib), Mitoxantrone Hydrochloride, Nilandron (Nilutamide), Nilutamide, Nubeqa (Darolutamide), Olaparib, Provenge (Sipuleucel-T), Radium 223 Dichloride, Rubraca (Rucaparib Camsylate), Rucaparib Camsylate, Sipuleucel-T, Taxotere (Docetaxel), Xofigo (Radium 223 Dichloride), Xtandi (Enzalutamide), Zoladex (Goserelin Acetate) and Zytiga (Abiraterone Acetate).~~

~~54. A kit comprising an antibody or an antigen-binding fragment thereof of any of claims 1-27.~~

25~~55~~. Use of an antibody or antigen-binding fragment thereof of any one of claims 1-14 in the manufacture of a diagnostic reagent in ~~A method of~~ detecting presence or amount of gremlin in a sample~~, comprising contacting the sample with the antibody or antigen-binding fragment thereof of any of claims 1-27, and determining the presence or the amount of gremlin in the sample~~.

~~56. Use of the antibody or antigen-binding fragment thereof of any of claims 1-27 in the manufacture of a medicament for treating a GREM1-related disease or condition in a subject.~~

~~57. The use of claim 56, wherein the GREM1-related disease or condition is cancer.~~

~~58. The use of claim 56, wherein the GREM1-related disease or condition is fibrotic disease, angiogenesis, glaucoma, retinal disease, kidney disease, pulmonary arterial hypertension, or osteoarthritis (OA).~~

26~~59~~. Use of an antibody or antigen-binding fragment thereof of any one of claims 1-14, or a pharmaceutical composition of claims 15 or 16 in the manufacture of a medicament for~~A method of~~ treating a disease that can benefit from increasing BMP7 activity or reducing gremlin-mediated inhibition on BMP7 activity, optionally wherein

the disease is a fibrotic disease and/or kidney disease, optionally wherein the disease is selected from the group consisting of ischemia-reperfusion injury, ischemic acute renal failure, Immunoglobulin A Nephropathy, lupus nephritis, alport syndrome, diabetic nephropathy and hypertensive nephrosclerosis, renal fibrosis, chronic kidney disease, acute kidney disease, and hypertensive nephrosclerosis.~~comprising administering to the subject a therapeutically effective amount of the antibody or antigen-binding fragment thereof of any of claims 1-27, or the pharmaceutical composition of any of claims 28-29.~~

~~60. The method of claim 59, wherein the disease is a fibrotic disease and/or kidney disease.~~

~~61. The method of claim 59, wherein the disease is selected from the group consisting of ischemia-reperfusion injury, ischemic acute renal failure, Immunoglobulin A Nephropathy, lupus nephritis, alport syndrome, diabetic nephropathy and hypertensive nephrosclerosis, renal fibrosis, chronic kidney disease, acute kidney disease, and hypertensive nephrosclerosis.~~

27~~62~~. Use of an antibody or antigen-binding fragment thereof of any one of claims 1-14, or a pharmaceutical composition of claims 15 or 16 in the manufacture of a medicament for~~A method of~~ increasing efficacy of BMP7 treatment in a subject in need thereof, optionally wherein the subject is diagnosed with a fibrotic disease and/or kidney disease and is being subjected to for BMP7 treatment ~~comprising administering to the subject a therapeutically effective amount of the antibody or antigen-binding fragment thereof of any of claims 1-27, or the pharmaceutical composition of any of claims 28-29~~.

~~63. The method of claim 62, wherein the subject is diagnosed with a fibrotic disease and/or kidney disease and is being subject to for BMP7 treatment.~~