CLAIMS

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

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.

2. The antibody or an antigen-binding fragment thereof of claim 1, wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 7, SEQ ID NO: 41, SEQ ID NO: 43, and SEQ ID NO: 45, and wherein the light chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 47, and SEQ ID NO: 49.

3. 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: 41 and a light chain variable region comprising a sequence of SEQ ID NO: 47; or
c) a heavy chain variable region comprising a sequence of SEQ ID NO: 41 and a light chain variable region comprising a sequence of SEQ ID NO: 49; or
d) a heavy chain variable region comprising a sequence of SEQ ID NO: 43 and a light chain variable region comprising a sequence of SEQ ID NO: 47; or
e) a heavy chain variable region comprising a sequence of SEQ ID NO: 43 and a light chain variable region comprising a sequence of SEQ ID NO: 49; or
f) a heavy chain variable region comprising a sequence of SEQ ID NO: 45 and a

light chain variable region comprising a sequence of SEQ ID NO: 47; or

g) a heavy chain variable region comprising a sequence of SEQ ID NO: 45 and a light chain variable region comprising a sequence of SEQ ID NO: 49.

4. 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 non-CDR regions of the VH or VL sequences.

5. 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.

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

7. 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), or a multispecific antibody.

8. 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.

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

10. 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.

11. 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.

12. The pharmaceutical composition or kit of claim 11, further comprising a second therapeutic agent.

13. An isolated polynucleotide encoding the antibody or an antigen-binding fragment thereof of any one of claims 1-10.

14. A vector comprising the isolated polynucleotide of claim 13.

15. A host cell comprising the vector of claim 14.

16. A method of expressing the antibody or antigen-binding fragment thereof of any one of claims 1-10, comprising culturing the host cell of claim 15 under the condition at which the vector of claim 14 is expressed.

17. Use of an antibody or antigen-binding fragment thereof of any one of claims 1-10, or a pharmaceutical composition of claims 11 or 12, in the manufacture of a medicament for treating a GREM1-related disease or condition in a subject (e.g., human), or for inhibiting FGFR1 activation in a subject (e.g., human) in need thereof, or for treating a disease or a condition associated with FGFR1 activation mediated by GREM1.

18. The use of claim 17, 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)).

19. The use of claim 18, 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).

20. The use of any one of claims 17-19, wherein a therapeutically effective amount of a 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, one or more anti-emetics, 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).

21. Use of an antibody or antigen-binding fragment thereof of any one of claims 1-10 in the manufacture of a diagnostic reagent in detecting presence or amount of gremlin in a sample.

22. Use of an antibody or antigen-binding fragment thereof of any one of claims 1-10, or a pharmaceutical composition of claims 11 or 12 in the manufacture of a medicament for treating a disease that can benefit from increasing BMP7 activity or reducing gremlin-mediated inhibition on BMP7 activity, wherein the disease is a fibrotic disease, kidney disease, 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.