

CLAIMS

- 1) A monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, said antibody being selected in the group consisting of:
- 5 a) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 3, 4 and 5 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 8;
 - b) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 9, 10 and 5 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 8;
 - 10 c) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 11, 12 and 13 and the three light-chain CDRs of sequences SEQ ID Nos. 14, 15 and 16;
 - d) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 17, 18 and 19 and the three light-chain CDRs of sequences SEQ ID Nos. 20, 21 and 22;
 - 15 e) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 23, 24 and 3 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 25;
 - f) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 26, 27 and 28 and the three light-chain CDRs of sequences SEQ ID Nos. 29, 30 and 31;
 - 20 g) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 32, 33 and 34 and the three light-chain CDRs of sequences SEQ ID Nos. 35, 36 and 16;
 - 25 h) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 37, 38 and 39 and the three light-chain CDRs of sequences SEQ ID Nos. 40, 41 and 42;
 - i) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 43, 44 and 45 and the three light-chain CDRs of sequences SEQ ID Nos. 46, 47 and 48;
 - 30 j) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 49, 50 and 51 and the three light-chain CDRs of sequences SEQ ID Nos. 52, 53 and 54;

- k) an antibody comprising the three heavy-chain CDRs of sequences SEQ ID Nos. 17, 18 and 55 and the three light-chain CDRs of sequences SEQ ID Nos. 56, 57 and 58.
- 2) The monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, of **claim 1**, wherein the antibody is selected among single chain antibodies, camelised antibodies, chimeric antibodies, humanised antibodies, and human antibodies.
- 3) The monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, of any one of **claims 1 or 2**, wherein the antibody is a human antibody.
- 4) The monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, of any one of **claims 1 to 3**, wherein the antibody is selected among IgA1 antibodies, IgA2 antibodies, IgD antibodies, IgE antibodies, IgG1 antibodies, IgG2 antibodies, IgG3 antibodies, IgG4 antibodies and IgM antibodies.
- 5) The monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, of any one of **claims 1 to 3**, wherein the antigen-binding fragment is selected in the group consisting of Fab, Fab', (Fab')₂, Fv, scFv (sc for single chain), Bis-scFv, scFv-Fc fragments, Fab2, Fab3, minibodies, diabodies, triabodies, tetrabodies, and nanobodies.
- 6) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 5**, wherein said antigen-binding fragment is an scFv.
- 7) The monoclonal anti-VSIG4 antibody, or an antigen-binding fragment thereof, of any one of **claims 1 to 6**, wherein the antibody is selected in the group consisting of:
- a) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 129 or any sequence exhibiting at least 80% identity with SEQ ID No. 129 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 8;
- b) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 131 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 131 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 8;
- c) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 133 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 133 and the three light-chain CDRs of sequences SEQ ID Nos. 14, 15 and 16;

- d) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 135 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 135 and the three light-chain CDRs of sequences SEQ ID Nos. 20, 21 and 22;
 - 5 e) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 137 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 137 and the three light-chain CDRs of sequences SEQ ID Nos. 6, 7 and 25;
 - 10 f) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 139 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 139 and the three light-chain CDRs of sequences SEQ ID Nos. 29, 30 and 31;
 - 15 g) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 141 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 141 and the three light-chain CDRs of sequences SEQ ID Nos. 35, 36 and 16;
 - 20 h) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 143 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 143 and the three light-chain CDRs of sequences SEQ ID Nos. 40, 41 and 42;
 - i) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 145 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 145 and the three light-chain CDRs of sequences SEQ ID Nos. 46, 47 and 48;
 - 25 j) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 147 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 147 and the three light-chain CDRs of sequences SEQ ID Nos. 52, 53 and 54;
 - 30 k) an antibody comprising, or consisting of, a heavy chain variable domain of sequence SEQ ID No. 149 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 149 and the three light-chain CDRs of sequences SEQ ID Nos. 56, 57 and 58.
- 8) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 6**, the antibody being selected in the group consisting of:

- a) an antibody comprising a light chain variable domain of sequence SEQ ID No. 130 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 130 and the three heavy-chain CDRs of sequences SEQ ID Nos. 3, 4, and 5;
- 5 b) an antibody comprising a light chain variable domain of sequence SEQ ID No. 132 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 132 and the three heavy-chain CDRs of sequences SEQ ID Nos. 9, 10, and 5;
- 10 c) an antibody comprising a light chain variable domain of sequence SEQ ID No. 134 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 134 and the three heavy-chain CDRs of sequences SEQ ID Nos. 11, 12, and 13;
- 15 d) an antibody comprising a light chain variable domain of sequence SEQ ID No. 136 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 136 and the three heavy-chain CDRs of sequences SEQ ID Nos. 17, 18, and 19;
- 20 e) an antibody comprising a light chain variable domain of sequence SEQ ID No. 138 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 138 and the three heavy-chain CDRs of sequences SEQ ID Nos. 23, 24 and 3;
- f) an antibody comprising a light chain variable domain of sequence SEQ ID No. 140 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 140 and the three heavy-chain CDRs of sequences SEQ ID Nos. 26, 27 and 28;
- 25 g) an antibody comprising a light chain variable domain of sequence SEQ ID No. 142 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 142 and the three heavy-chain CDRs of sequences SEQ ID Nos. 32, 33 and 34;
- 30 h) an antibody comprising a light chain variable domain of sequence SEQ ID No. 144 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 144 and the three heavy-chain CDRs of sequences SEQ ID Nos. 37, 38 and 39;
- i) an antibody comprising a light chain variable domain of sequence SEQ ID No. 146 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with

- SEQ ID No. 146 and the three heavy-chain CDRs of sequences SEQ ID Nos. 43, 44 and 45;
- 5 j) an antibody comprising a light chain variable domain of sequence SEQ ID No. 148 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 148 and the three heavy-chain CDRs of sequences SEQ ID Nos. 49, 50 and 51; and
- 10 k) an antibody comprising a light chain variable domain of sequence SEQ ID No. 150 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 150 and the three heavy-chain CDRs of sequences SEQ ID Nos. 17, 18 and 55.
- 9) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 8**, the antibody being selected in the group consisting of:
- 15 a) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 129 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 129 and a light chain variable domain of sequence SEQ ID No. 130 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 130;
- 20 b) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 131 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 131 and a light chain variable domain of sequence SEQ ID No. 132 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID NO. 132;
- 25 c) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 133 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 133 and a light chain variable domain of sequence SEQ ID No. 134 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 134;
- 30 d) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 135 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 135 and a light chain variable domain of sequence SEQ ID No. 136 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 136;
- e) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 137 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98%

- identity with SEQ ID No. 137 and a light chain variable domain of sequence SEQ ID No. 138 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 138;
- 5 f) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 139 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 139 and a light chain variable domain of sequence SEQ ID No. 140 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 140;
- 10 g) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 141 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 141 and a light chain variable domain of sequence SEQ ID No. 142 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID NO. 142;
- 15 h) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 143 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 143 and a light chain variable domain of sequence SEQ ID No. 144 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 144;
- 20 i) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 145 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 145 and a light chain variable domain of sequence SEQ ID No. 146 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 146;
- 25 j) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 147 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 147 and a light chain variable domain of sequence SEQ ID No. 148 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 148; and
- 30 k) an antibody comprising a heavy chain variable domain of sequence SEQ ID No. 149 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 149 and a light chain variable domain of sequence SEQ ID No. 150 or any sequence exhibiting at least 80%, 85%, 90%, 95% or 98% identity with SEQ ID No. 150.

- 10) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 9**, the antibody being an internalising antibody.
- 11) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 10**, the antibody being an antibody which binds to at least one amino acid in one or more epitope, the epitope being selected in the group consisting of:
- a) an epitope M1 comprising residues E24, V25, E27, V29, and/or T30 of the sequence set forth in SEQ ID No. 2;
 - b) an epitope M2 comprising residues D36, N38, L39, and/or T42 of the sequence set forth in SEQ ID No. 2;
 - c) an epitope M3 comprising residues Q59, G61, S62, D63, and/or V65 of the sequence set forth in SEQ ID No. 2;
 - d) an epitope M4 comprising residues I77, A80, Y82, and/or Q83 of the sequence set forth in SEQ ID No. 2;
 - e) an epitope M5 comprising residues H87, H90, K91, and/or V92 of the sequence set forth in SEQ ID No. 2;
 - f) an epitope M6 comprising residues S97, Q99, S101, and/or T102 of the sequence set forth in SEQ ID No. 2;
 - g) an epitope M7 comprising residues R108, S109, H110, T112, and/or E114 of the sequence set forth in SEQ ID No. 2;
 - h) an epitope M8 comprising residues T119, P120, D121, N123, Q124, and/or V125 of the sequence set forth in SEQ ID No. 2.
- 12) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of **claim 11**, wherein said antibody binds:
- a) at least one of the amino acids in M1;
 - b) at least one of the amino acids in M4, and optionally at least one of the residues of M3;
 - c) at least one of the amino acids in M7;
 - d) at least one of the amino acids in M8;
 - e) at least one of the amino acids in M7 and at least one of the amino acids in M8; or
 - f) at least one of the amino acids in M3, at least one of the amino acids in M7, and at least one of the amino acids in M8, and optionally at least one of the residues of M2 and/or at least one of the residues of M4.

- 13) An immunoconjugate comprising the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**, wherein said antibody is conjugated to a cytotoxic agent.
- 14) A polynucleotide encoding a variable region of a light chain (VL) for the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**.
- 15) A polynucleotide encoding a variable region of a heavy chain (VH) for the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**.
- 16) A polynucleotide encoding a VL for the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12** and a VH for the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**.
- 17) An expression vector comprising:
- a polynucleotide according to **claim 14**;
 - a polynucleotide according to **claim 15**;
 - a polynucleotide according to **claim 14** and a polynucleotide according to **claim 15**; or
 - a polynucleotide according to **claim 16**.
- 18) A host cell transformed with the expression vector of **claim 17**.
- 19) A method of producing the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12** comprising:
- a) culturing the host cell of **claim 18** under suitable conditions and
 - b) recovering the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, from the culture medium or from the cultured cells.
- 20) A pharmaceutical composition comprising the monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**, or the immunoconjugate of **claim 13**, and a pharmaceutical acceptable carrier and/or an excipient.

- 21) The pharmaceutical composition of **claim 20**, further comprising an immune checkpoint inhibitor.
- 22) The pharmaceutical composition of **claim 21**, wherein said immune checkpoint inhibitor is an inhibitor of any one of CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD 160, CGEN-15049, CHK 1 and CHK2 kinases, IDO1, A2aR and any of the various B-7 family ligands.
- 23) The pharmaceutical composition of any one of **claims 20 or 21**, wherein said immune checkpoint inhibitor is selected in the group consisting of ipilimumab, pembrolizumab, nivolumab, cemiplimab, pidilizumab, atezolizumab, avelumab, durvalumab, BMS 936559, JNJ 61610588, urelumab, 9B12, PF-04518600, BMS-986016, TSR-022, MBG453, MEDI6469, MEDI6383, and epacadostat.
- 24) The pharmaceutical composition of any one of **claims 20 or 21**, for simultaneous, separate or sequential use.
- 25) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**, or the immunoconjugate of **claim 13**, or the pharmaceutical composition of any one of **claims 20 to 24**, for use in the treatment of a cancer in a patient.
- 26) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**, or the immunoconjugate of **claim 13**, or the pharmaceutical composition of any one of **claims 20 to 24**, for use in inducing an immune response in a cancer patient.
- 27) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**, or the immunoconjugate of **claim 13**, or the pharmaceutical composition of any one of **claims 20 to 24**, for the use of **claim 25**, wherein the immune response includes induction of pro-inflammatory cytokines release by macrophages, induction of CD4⁺ T cell proliferation, induction of CD8⁺ T cell proliferation, induction of CD4⁺ T cell cytokine production, and induction of CD8⁺ T cell cytokine production.
- 28) The monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of **claims 1 to 12**, or the immunoconjugate of **claim 13**, or the pharmaceutical composition of any one of **claims 20 to 24**, for the use of any one of **claims 25 to**

- 27, wherein the cancer is selected from bladder cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, oesophageal cancer, fallopian tube cancer, gall bladder cancer, gastrointestinal cancer, head-and-neck cancer, haematological cancer (e.g., leukaemia, lymphoma, or myeloma), laryngeal cancer, liver cancer, lung cancer, lymphoma, melanoma, mesothelioma, ovarian cancer, primary peritoneal cancer, salivary gland cancer, sarcoma, stomach cancer, thyroid cancer, pancreatic cancer, renal cell carcinoma, glioblastoma, and prostate cancer.
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- 29) An *in vitro* method for detecting a VSIG4-expressing cancer in a subject, said method comprising the steps of:
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- a) contacting a biological sample of said subject with a monoclonal anti-VSIG4 antibody, or antigen-binding fragment thereof, of any one of claims 1 to 12; and
 - b) detecting the binding of said reagent with said biological sample,
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- wherein the binding of VSIG4 indicates the presence of a VSIG4-expressing cancer.
- 30) The method of claim 29, wherein the monoclonal anti- VSIG4 antibody, or antigen-binding fragment thereof, is labelled with a detectable label.