

CLAIMS

1. An isolated antibody or an antigen binding fragment comprising a heavy chain complementarity determining region 1 (HCDR1), a HCDR2, and a HCDR3, and a light chain complementarity determining region 1 (LCDR1), a LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 comprise the amino acid sequences selected from the group consisting of:
 - a. RYGMH (SEQ ID NO: 4), LISYDGSNRYADSVKG (SEQ ID NO: 5) , ERESSGWFEQYFDY (SEQ ID NO: 6), GGNNIGSKSVH (SEQ ID NO: 7), DNSDRPS (SEQ ID NO: 8), and QVWDSSSDHV (SEQ ID NO: 9), respectively;
 - b. SYYWN (SEQ ID NO: 10), RIYSSGNTDYNPSLKS (SEQ ID NO: 11), GRGANVGLFDY (SEQ ID NO: 12), TGSNSNIGANYDVH (SEQ ID NO: 13), GNINRPL (SEQ ID NO: 14), and QSYDFSLSGSV (SEQ ID NO: 15), respectively;
 - c. GYGMH (SEQ ID NO: 16), VISYDGSNRYADSVKG (SEQ ID NO: 17), DGNWGSLLDYFDL (SEQ ID NO: 18), TGSSSNIGADYDVH (SEQ ID NO: 19), VNNNRPS (SEQ ID NO: 20), and QSYDNTLSGVV (SEQ ID NO: 21), respectively;
 - d. SYGMH (SEQ ID NO: 22), VISYDGSNKYYADSVKG (SEQ ID NO: 23), EHYDSSGYYHGYYGMDV (SEQ ID NO: 24), SGSSSNIGSNYVY (SEQ ID NO: 25), SNNQRPS (SEQ ID NO: 26), AARDDSLSGYV (SEQ ID NO: 27), respectively;
 - e. SYDMH (SEQ ID NO: 28), VISFDGSNKYYVDSVKG (SEQ ID NO: 29), TYYDILTGYSYHSGMDV (SEQ ID NO: 30), RASQGISNYLA (SEQ ID NO: 31), ATSTLQS (SEQ ID NO: 32), and QKYNSAPFT (SEQ ID NO: 33), respectively;
 - f. TYGMH (SEQ ID NO: 34), FISYDGSNKYYADSVKG (SEQ ID NO: 35), RDNLRFLEWFMDV (SEQ ID NO: 36), RASQSVRSNLA (SEQ ID NO: 37), GASTRAT (SEQ ID NO: 38), and HQYNDWPPYT (SEQ ID NO: 39), respectively;
 - g. IYSMN (SEQ ID NO: 40), SISSSSSYIFYADSVKG (SEQ ID NO: 41), SSYGADY (SEQ ID NO: 42), RASQDITNFLA (SEQ ID NO: 43), TASTLQS (SEQ ID NO: 44), and QKYNSAPLT (SEQ ID NO: 45), respectively;
 - h. SYSLN (SEQ ID NO: 46), SISSSSSYISYADAVKG (SEQ ID NO: 47), DRGFLEDYYYYYGMDV (SEQ ID NO: 48), RASQGISNWLA (SEQ ID NO: 49), VASSLQS (SEQ ID NO: 50), and QQAYSFPLT (SEQ ID NO: 51), respectively;

- i. SYYWS (SEQ ID NO: 272), RIYSSGSTNYPNPSLKS (SEQ ID NO: 273), VGVWPGAFDI (SEQ ID NO: 274), SGSSSNIGSNTVN (SEQ ID NO: 275), SSNQRPS (SEQ ID NO: 276) and AAWDDSLNGVV (SEQ ID NO: 277), respectively;
- j. GFTLSRY (SEQ ID NO: 124), SYDGSN (SEQ ID NO:125), ERESSGWFEQYFDY (SEQ ID NO: 6), GGNNIGSKSVH (SEQ ID NO: 7), DNSDRPS (SEQ ID NO: 8) and QVWDSSSDHV (SEQ ID NO: 9), respectively;
- k. GGSISSY (SEQ ID NO: 130), YSSGN (SEQ ID NO: 131), GRGANVGLFDY (SEQ ID NO: 12), TGSNSNIGANYDVH (SEQ ID NO: 13), GNINRPL (SEQ ID NO:14), and QSYDFSLSGSV (SEQ ID NO:15), respectively;
- l. VRTFSGY (SEQ ID NO: 136), SYDGSN (SEQ ID NO:125), DGNWGSLLDYFDL (SEQ ID NO:18), TGSSSNIGADYDVH (SEQ ID NO:19), VNNNRPS (SEQ ID NO: 20), and QSYDNTLSGVV (SEQ ID NO: 21), respectively;
- m. GFTFTSY (SEQ ID NO: 142), SYDGSN (SEQ ID NO: 125), EHYDSSGYYHGYYGMDV (SEQ ID NO: 24), SGSSSNIGSNYVY (SEQ ID NO:25), SSNQRPS (SEQ ID NO: 26), and AARDDSLSGYV (SEQ ID NO:27), respectively;
- n. GFTFSSY (SEQ ID NO: 148), SFDGSN (SEQ ID NO:149), TYYDILTGYSHYSYGMV (SEQ ID NO: 30), RASQGISNYLA (SEQ ID NO: 31), ATSTLQS (SEQ ID NO: 32), and QKYNSAPFT (SEQ ID NO: 33), respectively;
- o. GFTFSTY (SEQ ID NO: 154), SYDGSN (SEQ ID NO: 125), RDNLRFLWFMDV (SEQ ID NO:36), RASQSVRSNLA (SEQ ID NO:37), GASTRAT (SEQ ID NO:38), and HQYNDWPPYT (SEQ ID NO:39), respectively;
- p. GFTLSIY (SEQ ID NO: 160), SSSSSY (SEQ ID NO:161), SSYGADY (SEQ ID NO:42), RASQDITNLA (SEQ ID NO:43), TASTLQS (SEQ ID NO:44), and QKYNSAPLT (SEQ ID NO:45), respectively;
- q. GFTFSSY (SEQ ID NO: 166), SSSSSY (SEQ ID NO: 167), DRGFLEDYYYYYGMDV (SEQ ID NO:48), RASQGISNLA (SEQ ID NO: 49), VASSLQS (SEQ ID NO:50), and QQAYSFPLT (SEQ ID NO: 51), respectively;
- r. GGSIIISY (SEQ ID NO: 290), YSSGS (SEQ ID NO:291), VGVWPGAFDI (SEQ ID NO: 274), SGSSSNIGSNTVN (SEQ ID NO:275), SSNQRPS (SEQ ID NO:276), and AAWDDSLNGVV (SEQ ID NO: 277), respectively;

s. GFTLSRYGMH (SEQ ID NO: 172), LISYDGSNRY (SEQ ID NO:173), ERESSGWFEgyFDY (SEQ ID NO:6), GGNNIGSKSVH (SEQ ID NO:7), DNSDRPS (SEQ ID NO: 8), and QVWDSSSDHV V (SEQ ID NO:9), respectively;

t. GGSISSYYWN (SEQ ID NO: 178), RIYSSGNTD (SEQ ID NO:179), GRGANVGLFDY (SEQ ID NO:12), TGSNSNIGANYDVH (SEQ ID NO:13), GNINRPL (SEQ ID NO:14), and QSYDFSLSGSV (SEQ ID NO:15), respectively;

u. VRTFSGYGMH (SEQ ID NO: 184), VISYDGSNRY (SEQ ID NO:185), DGNWGS LDLYFDL (SEQ ID NO: 18), TGSSSNIGADYDVH (SEQ ID NO:19), VNNNRPS (SEQ ID NO: 20), and QSYDNTLSGVV (SEQ ID NO:21), respectively;

v. GFTFTSYGMH (SEQ ID NO: 190), VISYDGSNKY (SEQ ID NO:191), EHYDSSGYHHGYGMDV (SEQ ID NO:24), SGSSSNIGSNYVY (SEQ ID NO:25), SNNQRPS (SEQ ID NO:26), and AARDDSLSGYV (SEQ ID NO:27), respectively;

w. GFTFSSYDMH (SEQ ID NO: 196), VISFDGSNKY (SEQ ID NO: 197), TYYDILTGYSHYSYGMDV (SEQ ID NO: 30), RASQGISNYLA (SEQ ID NO:31), ATSTLQS (SEQ ID NO:32), and QKYNSAPFT (SEQ ID NO:33), respectively;

x. GFTFSTYGMH (SEQ ID NO: 202), FISYDGSNKY (SEQ ID NO:203), RDNLRFLEWFMDV (SEQ ID NO: 36), RASQSVRSNLA (SEQ ID NO:37), GASTRAT (SEQ ID NO:38), and HQYNDWPPYT (SEQ ID NO: 39), respectively;

y. GFTLSIYSMN (SEQ ID NO: 208), SSSSSSYIF (SEQ ID NO:209), SSGADY (SEQ ID NO: 42), RASQDITNFLA, (SEQ ID NO: 43), TASTLQS (SEQ ID NO: 44), and QKYNSAPLT (SEQ ID NO:45), respectively;

z. GFTFSSYSLN (SEQ ID NO: 214), SSSSSSYIS (SEQ ID NO:215), DRGFLEDYYYYYGMDV (SEQ ID NO:48), RASQGISNWL (SEQ ID NO:49), VASSLQS (SEQ ID NO:50), and QQAYSF (SEQ ID NO:51), respectively;

aa. GGSIISSYYWS (SEQ ID NO: 296), RIYSSGSTN (SEQ ID NO: 297), VGVWPGAFDI (SEQ ID NO:274), SGSSSNIGSNTVN (SEQ ID NO:275), SSNQRPS (SEQ ID NO:276), and AAWDDSLNGVV (SEQ ID NO:277), respectively;

bb. GFTLSRYG (SEQ ID NO: 220), ISYDGSNR (SEQ ID NO:221), ARERESSGWFEgyFDY (SEQ ID NO: 222), NIGSKS (SEQ ID NO:223), DNS, and QVWDSSSDHV V (SEQ ID NO:9), respectively;

cc. GGSISSYY (SEQ ID NO: 226), IYSSGNT (SEQ ID NO: 227), ARGRGANVGLFDY (SEQ ID NO:228), NSNIGANYD (SEQ ID NO:229), GNI, and QSYDFSLSGSV (SEQ ID NO:15), respectively;

dd. VRTFSGYG (SEQ ID NO: 232), ISYDGSNR (SEQ ID NO:233), ARDGNWGSLDLYFDL (SEQ ID NO:234), SSNIGADYD (SEQ ID NO:235), VNN, and QSYDNTLSGVV (SEQ ID NO:21), respectively;

ee. GFTFTSYG (SEQ ID NO: 238), ISYDGSNK (SEQ ID NO:239), AREHYDSSGYYHGYYGMDV (SEQ ID NO: 240), SSNIGSNY (SEQ ID NO:241), SNN, and AARDDSLSGYV (SEQ ID NO:27), respectively;

ff. GFTFSSYD (SEQ ID NO: 244), ISFDGSNK (SEQ ID NO:245), ARTYYDILTGYSYHYSYGMDV (SEQ ID NO: 246), QGISNY (SEQ ID NO:247), ATS, and QKYNSAPFT (SEQ ID NO:33), respectively;

gg. GFTFSTYG (SEQ ID NO: 250), ISYDGSNK (SEQ ID NO:251), AGRDNLRFLEWFMDV (SEQ ID NO:252), QSVRSN (SEQ ID NO: 253), GAS, and HQYNDWPPYT (SEQ ID NO:39), respectively;

hh. GFTLSIYS (SEQ ID NO: 256), ISSSSSYI (SEQ ID NO:257), ARSSYGADY (SEQ ID NO:258), QDITNF (SEQ ID NO: 259), TAS, and QKYNSAPLT (SEQ ID NO:45), respectively;

ii. GFTFSSYS (SEQ ID NO: 262), ISSSSSYI (SEQ ID NO:263), ARDRGFLEDYYYYYGMDV (SEQ ID NO:264), QGISNW (SEQ ID NO:265), VAS, and QQAYSFPLT (SEQ ID NO:51), respectively; and

jj. GGSIISSYY (SEQ ID NO: 302), IYSSGST (SEQ ID NO:303), AKVGVWPGAFDI (SEQ ID NO:304), SSNIGSNT (SEQ ID NO:305), SSN, and AAWDDSLNGVV (SEQ ID NO: 277), respectively.

2. The isolated antibody or antigen binding fragment of claim 1, comprising a heavy chain variable region (VH) and a light chain variable region (VL) selected from:

- a. SEQ ID NOs: 52 and 53 respectively;
- b. SEQ ID NOs: 54 and 55 respectively;
- c. SEQ ID NOs: 56 and 57 respectively;
- d. SEQ ID NOs: 58 and 59 respectively;

- e. SEQ ID NOs: 60 and 61 respectively;
- f. SEQ ID NOs: 62 and 63 respectively;
- g. SEQ ID NOs: 64 and 65 respectively;
- h. SEQ ID NOs: 66 and 67 respectively; and
- i. SEQ ID NOs: 278 and 279 respectively.

3. The isolated antibody or antigen binding fragment of claim 1, comprising a heavy chain amino acid sequence selected from SEQ ID NOs. 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 268, 282, 284, and 288;

and a light chain amino acid sequence selected from SEQ ID NOs. 85, 89, 93, 95, 97, 99, 101, 103, and 269.

4. The isolated antibody or antigen binding fragment of claim 1, wherein the antibody or the antigen binding fragment is an IgG1, an IgG2, an IgG3 or an IgG4 isotype.

5. The isolated antibody or antigen binding fragment of claim 4, wherein the antibody or antigen binding fragment is an IgG1 isotype.

6. The isolated antibody or antigen binding fragment of claim 1, further comprising an Ig constant region, wherein the Ig constant region comprises at least one mutation that results in reduced binding of the antibody or antigen binding fragment thereof to a Fc γ receptor (Fc γ R).

7. The isolated antibody or antigen binding fragment of claim 6, wherein the at least one mutation that results in reduced binding of the protein to the Fc γ R is selected from the group consisting of F234A/L235A, L234A/L235A, L234A/L235A/D265S, V234A/G237A/P238S/H268A/V309L/A330S/P331S, F234A/L235A, S228P/F234A/L235A, N297A, V234A/G237A, K214T/E233P/L234V/L235A/G236-deleted/A327G/P331A/D365E/L358M, H268Q/V309L/A330S/P331S, S267E/L328F, L234F/L235E/D265A, L234A/L235A/G237A/P238S/H268A/A330S/P331S, S228P/F234A/L235A/G237A/P238S and S228P/F234A/L235A/G236-deleted/G237A/P238S, wherein residue numbering is according to the EU index.

8. The isolated antibody or antigen binding fragment of claim 7, wherein the mutations that results in reduced binding of the antibody or antigen binding fragment to the FcγR are L234A, L235A, and D265S.
9. The isolated antibody or antigen binding fragment of claim 1, further comprising an Ig constant region, wherein the IgG constant region comprises at least one mutation that modulates a half-life of the antibody.
10. The isolated antibody or antigen binding fragment of claim 9, wherein at least one mutation that modulates the half-life of the antibody is selected from the group consisting of H435A, P257I/N434H, D376V/N434H, M252Y/S254T/T256E, M252Y/S254T/T256E/H433K/N434F, T308P/N434A and H435R, wherein residue numbering is according to the EU index.
11. The isolated antibody or antigen binding fragment of claim 9, wherein the mutations that modulates the half-life of the antibody or antigen binding fragment thereof are M252Y, S254T, and T256E mutations.
12. A polynucleotide encoding an isolated antibody or antigen binding fragment of claim 1.
13. The polynucleotide of claim 12, wherein the polynucleotide sequence is selected from SEQ ID NOs: 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 104, 105, 106, 108, 109, 110, 112, 113, 114, 115, 116, 116, 118, 119, 120, 121, 122, 123, 134, 135, 270, 271, 280, 281, 283, 286 or 289.
14. A vector comprising the polynucleotide sequence of claim 12 or 13.
15. A host cell comprising the vector of claim 14.

16. An antibody drug conjugate comprising an antibody or antigen binding fragment of claim 1.

17. The antibody drug conjugate of claim 16, wherein the antibody or antigen binding fragment comprises:

a. a heavy chain variable region (VH) comprising a VH CDR1 having an amino acid sequence of SEQ ID NO:4, a VH CDR2 having an amino acid sequence of and SEQ ID NO:5 and a VH CDR3 having an amino acid sequence of SEQ ID NO:6; and a light chain variable region (VL) comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:7, a VL CDR2 having an amino acid sequence of and SEQ ID NO:8 and a VL CDR3 having an amino acid sequence of SEQ ID NO:9; or

b. a heavy chain variable region (VH) comprising a VH CDR1 having an amino acid sequence of SEQ ID NO:10, a VH CDR2 having an amino acid sequence of and SEQ ID NO:11 and a VH CDR3 having an amino acid sequence of SEQ ID NO:12; and a light chain variable region (VL) comprising a VL CDR1 having an amino acid sequence of SEQ ID NO:13, a VL CDR2 having an amino acid sequence of and SEQ ID NO:14 and a VL CDR3 having an amino acid sequence of SEQ ID NO:15.

18. A pharmaceutical composition comprising the isolated antibody or antigen binding fragment of claim 1, and a pharmaceutically acceptable carrier.

19. Use of the antibody drug conjugate of claim 16 in the manufacture of a medicament for treating a PSMA expressing cancer in a subject in need thereof, wherein a therapeutically effective amount of the antibody drug conjugate is to be administered to the subject in need thereof.

20. The use of claim 19, wherein the PSMA expressing cancer is prostate cancer.

21. The use of claim 20, wherein the prostate cancer is a metastatic castration-resistant cancer (mCRPC).

22. A kit comprising the isolated antibody or antigen binding fragment of claim 1.

23. The antibody drug conjugate of claim 16 for use in therapy.