

GPRC5D-BINDING MOIETIES, CHIMERIC ANTIGEN RECEPTORS AND USES
THEREOF

CROSS REFERENCE TO RELATED APPLICATION

5 This application claims priority benefit of International Application No. PCT/CN2023/131797 filed 15 November 2023, the contents of which is incorporated herein by reference in their entirety.

SEQUENCE STATEMENT

10 The content of the following submission on XML file is incorporated herein by reference in its entirety: a computer readable Sequence Listing (file name: IEC240497PCT_SEQUENCE LISTING.xml, date recorded: November 13, 2024, size: 359,094 bytes).

TECHNICAL FIELD

15 The present disclosure relates to GPRC5D-binding moieties, chimeric antigen receptors (CARs) having these GPRC5D-binding moieties and uses thereof. The present disclosure also relates to genetically modified immune cells having a chimeric antigen receptor for use in adoptive cell therapy for treating GPRC5D-expressing cancers or tumors in a subject in need thereof.

20

BACKGROUND

 G-protein-coupled receptor family C group 5 member D (GPRC5D) is a type-C 7-pass transmembrane receptor protein. It is an orphan receptor whose ligand and signaling mechanism are yet to be defined. The GPRC5D gene that is mapped on chromosome 12p13.3 comprises
25 three exons and spans about 9.6 kb. The large first exon encodes the seven-transmembrane domain. High messenger RNA (mRNA) expression of GPRC5D was observed in patients with multiple myeloma, whereas only low expression was detected in normal tissues. In addition, mRNA expression of GPRC5D showed a significant correlation with poor overall survival rates. Through immunohistochemical analyses, Eric L. Smith and colleagues demonstrated that
30 GPRC5D was expressed on malignant bone marrow plasma cells, whereas normal tissue expression was limited to the hair follicle. Overexpression in poor-risk myeloma, low expression in normal tissues and cell surface expression suggest GPRC5D is an attractive target for cancer immunotherapy. Current immunotherapies targeting GPRC5D have yet to become a successful therapy.

Thus, GPRC5D-targeting therapeutic options represent unmet needs. New generation of GPRC5D-targeting antibodies for the treatment of various cancers or other diseases were needed.

SUMMARY

5 Based on the shortcomings of the prior art, one of the main objects of the present disclosure is to provide anti-GPRC5D moieties. Thus, the present disclosure provides anti-GPRC5D moieties (e.g., V_HHs), chimeric antigen receptors (CARs) comprising these moieties, pharmaceutical compositions comprising these moieties, nucleic acids encoding these moieties, vectors, and host cells for making these moieties, methods of treating a subject using these
10 moieties, and the moieties of the present disclosure can be used for detection and/or treatment of a tumor.

In one aspect, the present disclosure provides an anti-GPRC5D V_HH, comprising:

- (1) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 4;
- 15 (2) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 8;
- (3) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 12;
- (4) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,
20 and CDR3, respectively, as set forth in SEQ ID NO: 16;
- (5) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 20;
- (6) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 24;
- 25 (7) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 28;
- (8) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 32;
- (9) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,
30 and CDR3, respectively, as set forth in SEQ ID NO: 36;
- (10) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 40;
- (11) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 44;
- 35 (12) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,

and CDR3, respectively, as set forth in SEQ ID NO: 48;

(13) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 52;

(14) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 56;

(15) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 60;

(16) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 64;

(17) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 68;

(18) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 72;

(19) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 76;

(20) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 80;

(21) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 84;

(22) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 88;

(23) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 92;

(24) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 96;

(25) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 100;

(26) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 104;

(27) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 108;

(28) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 112;

(29) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 115;

(30) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 119;

(31) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 123;

5 (32) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 127;

(33) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 131;

10 (34) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 135;

(35) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 139;

(36) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 143;

15 (37) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 147;

(38) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 151;

20 (39) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 155;

(40) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 159;

(41) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 163;

25 (42) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 167;

(43) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 171;

30 (44) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 175;

(45) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 179;

(46) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 183;

35 (47) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,

and CDR3, respectively, as set forth in SEQ ID NO: 187;

(48) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 190;

(49) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,
5 and CDR3, respectively, as set forth in SEQ ID NO: 193;

(50) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 197;

(51) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 201;

10 (52) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 205;

(53) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 209;

(54) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,
15 and CDR3, respectively, as set forth in SEQ ID NO: 213;

(55) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 216;

(56) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 220;

20 (57) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 224;

(58) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 228;

(59) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,
25 and CDR3, respectively, as set forth in SEQ ID NO: 232;

(60) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 236;

(61) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 240;

30 (62) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 244;

(63) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 248;

(64) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,
35 and CDR3, respectively, as set forth in SEQ ID NO: 252;

(65) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 256;

(66) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 260;

5 (67) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 264;

(68) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 266;

10 (69) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 270;

(70) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 274;

(71) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 278;

15 (72) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 282;

(73) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 286;

20 (74) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 290;

(75) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 294;

(76) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 298;

25 (77) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 302;

(78) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 306;

30 (79) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 310.

In certain embodiments, the CDR1, CDR2 or CDR3 are determined according to the AbM numbering scheme, the IMGT numbering scheme, the Kabat numbering scheme, the Chothia numbering scheme, the Contact numbering scheme, or any combination thereof.

35 In certain embodiments, the CDR1, CDR2 or CDR3 are determined according to the AbM numbering scheme.

In another aspect, the present disclosure provides an anti-GPRC5D V_HH comprising a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of:

- (1) SEQ ID NO: 5, 6 and 7; or (2) SEQ ID NO: 9, 10 and 11; or
(3) SEQ ID NO: 13, 14 and 15; or (4) SEQ ID NO: 17, 18 and 19; or
5 (5) SEQ ID NO: 21, 22 and 23; or (6) SEQ ID NO: 25, 26 and 27; or
(7) SEQ ID NO: 29, 30 and 31; or (8) SEQ ID NO: 33, 34 and 35; or
(9) SEQ ID NO: 37, 38 and 39; or (10) SEQ ID NO: 41, 42 and 43; or
(11) SEQ ID NO: 45, 46 and 47; or (12) SEQ ID NO: 49, 50 and 51; or
(13) SEQ ID NO: 53, 54 and 55; or (14) SEQ ID NO: 57, 58 and 59; or
10 (15) SEQ ID NO: 61, 62 and 63; or (16) SEQ ID NO: 65, 66 and 67; or
(17) SEQ ID NO: 69, 70 and 71; or (18) SEQ ID NO: 73, 74 and 75; or
(19) SEQ ID NO: 77, 78 and 79; or (20) SEQ ID NO: 81, 82 and 83; or
(21) SEQ ID NO: 85, 86 and 87; or (22) SEQ ID NO: 89, 90 and 91; or
(23) SEQ ID NO: 93, 94 and 95; or (24) SEQ ID NO: 97, 98 and 99; or
15 (25) SEQ ID NO: 101, 102 and 103; or (26) SEQ ID NO: 105, 106 and 107; or
(27) SEQ ID NO: 109, 110 and 111; or (28) SEQ ID NO: 113, 114 and 115; or
(29) SEQ ID NO: 116, 117 and 118; or (30) SEQ ID NO: 120, 121 and 122; or
(31) SEQ ID NO: 124, 125 and 126; or (32) SEQ ID NO: 128, 129 and 130; or
(33) SEQ ID NO: 132, 133 and 134; or (34) SEQ ID NO: 136, 137 and 138; or
20 (35) SEQ ID NO: 140, 141 and 142; or (36) SEQ ID NO: 144, 145 and 146; or
(37) SEQ ID NO: 148, 149 and 150; or (38) SEQ ID NO: 152, 153 and 154; or
(39) SEQ ID NO: 156, 157 and 158; or (40) SEQ ID NO: 160, 161 and 162; or
(41) SEQ ID NO: 164, 165 and 166; or (42) SEQ ID NO: 168, 169 and 170; or
(43) SEQ ID NO: 172, 173 and 174; or (44) SEQ ID NO: 176, 177 and 178; or
25 (45) SEQ ID NO: 180, 181 and 182; or (46) SEQ ID NO: 184, 185 and 186; or
(47) SEQ ID NO: 188, 189 and 190; or (48) SEQ ID NO: 191, 192 and 193; or
(49) SEQ ID NO: 194, 195 and 196; or (50) SEQ ID NO: 198, 199 and 200; or
(51) SEQ ID NO: 202, 203 and 204; or (52) SEQ ID NO: 206, 207 and 208; or
(53) SEQ ID NO: 210, 211 and 212; or (54) SEQ ID NO: 214, 215 and 216; or
30 (55) SEQ ID NO: 217, 218 and 219; or (56) SEQ ID NO: 221, 222 and 223; or
(57) SEQ ID NO: 225, 226 and 227; or (58) SEQ ID NO: 229, 230 and 231; or
(59) SEQ ID NO: 233, 234 and 235; or (60) SEQ ID NO: 237, 238 and 239; or
(61) SEQ ID NO: 241, 242 and 243; or (62) SEQ ID NO: 245, 246 and 247; or
(63) SEQ ID NO: 249, 250 and 251; or (64) SEQ ID NO: 253, 254 and 255; or
35 (65) SEQ ID NO: 257, 258 and 259; or (66) SEQ ID NO: 261, 262 and 263; or

(67) SEQ ID NO: 5, 6 and 265; or (68) SEQ ID NO: 267, 268 and 269; or
(69) SEQ ID NO: 271, 272 and 273; or (70) SEQ ID NO: 275, 276 and 277; or
(71) SEQ ID NO: 279, 280 and 281; or (72) SEQ ID NO: 283, 284 and 285; or
(73) SEQ ID NO: 287, 288 and 289; or (74) SEQ ID NO: 291, 292 and 293; or
5 (75) SEQ ID NO: 295, 296 and 297; or (76) SEQ ID NO: 299, 300 and 301; or
(77) SEQ ID NO: 303, 304 and 305; or (78) SEQ ID NO: 307, 308 and 309; or
(79) SEQ ID NO: 311, 312 and 313.

In certain embodiments, the V_HH comprising the amino acid sequence of SEQ ID NO: 4, 8,
12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108,
10 112, 115, 119, 123, 127, 131, 135, 139, 143, 147, 151, 155, 159, 163, 167, 171, 175, 179, 183,
187, 190, 193, 197, 201, 205, 209, 213, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256,
260, 264, 266, 270, 274, 278, 282, 286, 290, 294, 298, 302, 306 or 310, or an amino acid
sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%,
92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

15 In certain embodiments, the V_HH is camelid, chimeric or humanized.

In certain embodiments, the V_HH comprising the amino acid sequence of SEQ ID NO: 16,
24, 48, 143, 179, 187, 193, 220, 244, 274, 298, 302, 306 or 310, or an amino acid sequence
having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%,
94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

20 In certain embodiments, the V_HH comprising the amino acid sequence of any one of the
followings:

(1) SEQ ID NO: 328, 329, 330, 331, 332 or 333; (2) SEQ ID NO: 334, 335, 336 or 337;
(3) SEQ ID NO: 338, 339, 340, 341 or 342; (4) SEQ ID NO: 343, 344, 345 or 346;
(5) SEQ ID NO: 347, 348 or 349; (6) SEQ ID NO: 350, 351 or 352;
25 (7) SEQ ID NO: 353, 354, 355, 356, 357 or 358; (8) SEQ ID NO: 359, 360, 361, 362 or 363;
(9) SEQ ID NO: 364, 365, 366 or 367; (10) SEQ ID NO: 368, 369, 370 or 371;
(11) SEQ ID NO: 372, 373, 374, 375 or 376; (12) SEQ ID NO: 377, 378 or 379;
(13) SEQ ID NO: 380, 381, 382, 383 or 384; (14) SEQ ID NO: 385, 386, 387, 388, 389 or
390.

30 In another aspect, the present disclosure provides a polypeptide construct, comprising the
V_HH of the present disclosure.

In certain embodiments, the construct is a monospecific molecule, a bispecific molecule, a
multispecific molecule, an immunoconjugate, or a fusion protein.

In certain embodiments, the monospecific molecule is a sdAb, or antigen binding fragment
35 thereof.

In certain embodiments, the construct comprising an additional polypeptide.

In certain embodiments, the additional polypeptide is an immunoglobulin Fc region.

In certain embodiments, the immunoglobulin Fc region is an IgG Fc region, e.g., an IgG1, IgG2, IgG3, or IgG4 Fc region.

5 In certain embodiments, the additional polypeptide is an additional binding domain that binds to a second target other than GPRC5D.

In another aspect, the present disclosure provides a multispecific molecule comprising a GPRC5D-binding domain which comprises the V_HH of the present disclosure and an additional binding domain that binds to a second target other than GPRC5D.

10 In certain embodiments, the multispecific molecule is a bispecific antibody.

In certain embodiments, the additional binding domain is a monovalent antibody fragment, e.g., a Fab, an Fv, a scFv, or a V_HH.

In certain embodiments, the second target is selected from CD3, CD33, CD19, CD20, CD22, CD30, CD70, CLL-1, BCMA, DLL-3, Claudin 6, Claudin 18.2, GPC3, GPC2, CD229, 15 FcRH5, GUCY2C, mesothelin, HER2, PSMA, or PSCA.

In another aspect, the present disclosure provides a nucleic acid molecule, comprising a nucleotide sequence encoding the V_HH of the present disclosure, the polypeptide construct of the present disclosure, or the multispecific molecule of the present disclosure.

In another aspect, the present disclosure provides a vector, which comprises the nucleic acid 20 molecule as described above.

In another aspect, the present disclosure provides a host cell, which comprises the nucleic acid molecule or vector as described above.

In another aspect, the present disclosure provides a method for producing the V_HH of the present disclosure, or the polypeptide construct of the present disclosure, or the multispecific 25 molecule of the present disclosure, comprising: culturing a host cell comprising the nucleic acid molecule of the present disclosure or the vector of the present disclosure, or the cell of the present disclosure under a condition that allows protein expression, and recovering the V_HH, the polypeptide construct, or the multispecific molecule from a culture of the cultured cell.

In another aspect, the present disclosure provides an GPRC5D binding moiety, comprising 30 the V_HH of the present disclosure.

In certain embodiments, the binding moiety is an sdAb or antigen binding fragment thereof.

In another aspect, the present disclosure provides a chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises a 35 first binding moiety that specifically binds to a first antigen or epitope, wherein the first binding

moiety comprises the V_HH of the present disclosure, the polypeptide of the present disclosure, or the multispecific molecule of the present disclosure.

In certain embodiments, the extracellular antigen-binding domain further comprises a second binding moiety that specifically binds to a second antigen or epitope.

5 In certain embodiments, wherein the first antigen or epitope is the same as the second antigen or epitope. In certain embodiments, wherein the first antigen or epitope is different from the second antigen or epitope. In certain embodiments, wherein the first binding moiety and the second binding moiety are linked in tandem.

10 In certain embodiments, the second binding moiety is an sdAb, an scFv, or an extracellular domain of a receptor.

In certain embodiments, wherein the second binding moiety is an anti-tumor antigen sdAb or scFv, and the tumor antigen selected from CD33, CD19, CD20, CD22, CD30, CD70, CLL-1, BCMA, DLL3, Claudin 6, Claudin 18.2, GPC3, GPC2, GPRC5D, CD229, FcRH5, GUCY2C, mesothelin, HER2, PSMA, or PSCA.

15 In certain embodiments, wherein the second binding moiety is an anti-GPRC5D sdAb, and comprises the V_HH of the present disclosure, the polypeptide construct of the present disclosure, or the multispecific molecule of the present disclosure.

In certain embodiments, the CAR further comprising a spacer domain is selected from a hinge domain and/or CH2 and CH3 regions of an immunoglobulin (e.g., IgG1 or IgG4). In
20 certain embodiments, the hinge domain comprises a hinge region of CD8 α , IgG4, PD1, CD152 or CD154. In certain embodiments, the spacer domain comprises a hinge region of CD8 α (e.g., a sequence as set forth in SEQ ID NO: 316).

In certain embodiments, the transmembrane domain is selected from one or more transmembrane regions selected from the group consisting of: α , β or ζ chain of T cell receptor,
25 CD3 ϵ , CD3 ζ , CD4, CD5, CD8 α , CD28, CD137, CD152, CD154 and PD1. In certain embodiments, the transmembrane domain comprises a transmembrane region of CD8 α (e.g., a sequence as set forth in SEQ ID NO: 317).

In certain embodiments, the intracellular signaling domain comprises a primary signaling domain and/or a costimulatory signaling domain.

30 In certain embodiments, the intracellular signaling domain comprises a primary signaling domain and at least one costimulatory signaling domain.

In certain embodiments, the primary signaling domain comprises an intracellular signaling domain of a protein selected from the group consisting of: CD3 ζ , FcR γ , FcR β , CD3 γ , CD3 δ , CD3 ϵ , CD5, CD22, CD79a, CD79b and CD66d.

35 In certain embodiments, the costimulatory signaling domain comprises an intracellular

signaling domain of a protein selected from the group consisting of: CARD11, CD2, CD7, CD27, CD28, CD30, CD54 (ICAM), CD83, CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD152 (CTLA4), CD223 (LAGS), CD270 (HVEM), CD273 (PD-L2), CD274 (PD-L1), CD278 (ICOS), DAP10 and DAP12.

5 In certain embodiments, the intracellular signaling domain comprises a primary signaling domain and a costimulatory signaling domain, wherein the primary signaling domain comprises an intracellular signaling domain of CD3 ζ (e.g., a sequence as set forth in SEQ ID NO: 319), the costimulatory signaling domain comprises an intracellular signaling domain of CD137 (e.g., a sequence as set forth in SEQ ID NO: 318).

10 In certain embodiments, the chimeric antigen receptor further comprises a signal peptide and/or a tag.

In certain embodiments, the tag is selected from a myc-tag, a His-tag, a short linear peptide sequence from yeast transcription factor GCN4, a leucine zipper sequence or a short linear peptide sequence from a human nuclear protein.

15 In certain embodiments, the tag is a myc-tag, and the myc-tag comprises a sequence as set forth in SEQ ID NO: 315.

In certain embodiments, the signal peptide is derived from a molecule selected from the group consisting of CD8 α , GM-CSF receptor α , and IgG1 heavy chain.

In certain embodiments, the signal peptide comprises a sequence as set forth in SEQ ID NO: 314.

In certain embodiments, the chimeric antigen receptor comprises the following domains in sequence from the N-terminal to the C-terminal: the signal peptide, the tag, the antigen-binding domain, the spacer domain, the transmembrane domain and the intracellular signaling domain.

In another aspect, the present disclosure provides a dual-chimeric antigen receptor (CAR), comprising:

a first engineered receptor comprising the chimeric antigen receptor of the present disclosure; and

a second engineered receptor comprising: a second extracellular antigen-binding domain, a second transmembrane domain and a second intracellular domain.

30 In certain embodiments, wherein the second extracellular antigen-binding domain is an anti-tumor antigen sdAb or scFv, and the tumor antigen selected from BCMA, CD33, CD19, CD20, CD22, CD30, CD70, CLL-1, DLL3, Claudin 6, Claudin 18.2, GPC3, GPC2, GPRC5D, CD229, FcRH5, GUCY2C, mesothelin, HER2, PSMA, or PSCA.

In another aspect, the present disclosure provides a nucleic acid molecule comprising a nucleotide sequence encoding the chimeric antigen receptor or the dual-chimeric antigen

receptor of the present disclosure.

In certain embodiments, the CAR is expressed by introducing a nucleic acid encoding it into a cell *in vivo* (in vivo cell therapy) or *in vitro* (including autologous cell therapy and allogeneic cell therapy). In certain embodiments, the cell is an immune cell.

5 In another aspect, the present disclosure provides a vector comprising the nucleic acid molecule of the present disclosure.

In another aspect, the present disclosure provides a host cell, which comprises the nucleic acid molecule of the present disclosure or the vector of the present disclosure.

10 In certain embodiments, the host cell is selected from an immune cell (e.g., human immune cell).

In certain embodiments, the immune cell is selected from the group consisting of T lymphocyte, NK cell, monocyte, macrophage or dendritic cell, and any combination thereof.

In another aspect, the present disclosure provides an engineered immune cell, which expresses the chimeric antigen receptor or the dual-chimeric antigen receptor of the present disclosure.

15 In certain embodiments, the chimeric antigen receptor or the dual-chimeric antigen receptor is expressed on the surface of the engineered immune cell.

In certain embodiments, the engineered immune cell also expresses a chimeric antigen receptor that is not specific for GPRC5D.

20 In certain embodiments, the immune cell is selected from the group consisting of T lymphocyte, NK cell, monocyte, macrophage or dendritic cell and any combination thereof.

In certain embodiments, the immune cell is obtained from a patient or a healthy donor.

In another aspect, the present disclosure provides a pharmaceutical composition comprising the V_HH of the present disclosure, the polypeptide construct of the present disclosure, the multispecific molecule of the present disclosure, or the chimeric antigen receptor of the present disclosure, or the dual-chimeric antigen receptor of the present disclosure; and a pharmaceutically acceptable carrier and/or excipient.

25 In certain embodiments, the pharmaceutical composition of the present disclosure, which further comprises an additional therapeutic agent.

30 In certain embodiments, the additional therapeutic agent is an anti-tumor agent.

In certain embodiments, the additional therapeutic agent is a cytotoxic agent, such as an alkylating agent, an anti-mitotic agent, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, a tyrosine kinase inhibitor, or a radionuclide.

In another aspect, the present disclosure provides use of the V_HH of the present disclosure or the polypeptide construct of the present disclosure or the multispecific molecule of the present

disclosure or the nucleic acid molecule of the present disclosure or the vector of the present disclosure or the cell of the present disclosure or the chimeric antigen receptor of the present disclosure or the dual-chimeric antigen receptor of the present disclosure or engineered immune cell of the present disclosure or the pharmaceutical composition of the present disclosure in
5 manufacture of a medicament for use in preventing and/or treating a disease in a subject.

In certain embodiments, the disease is tumor or autoimmune disease.

In certain embodiments, the tumor expresses GPRC5D.

In certain embodiments, the tumor is a solid tumor, e.g., ovarian cancer, endometrial cancer, breast cancer, lung cancer (small cell or non-small cell), colon cancer, prostate cancer, cervical
10 cancer, pancreatic cancer, gastric cancer, esophageal cancer, hepatocellular carcinoma (liver cancer), renal cell carcinoma (kidney cancer), head-and-neck tumors, mesothelioma, melanoma, sarcomas, or brain tumors (e.g., gliomas, such as glioblastomas).

In certain embodiments, the tumor is a hematological malignancy, e.g., leukemia, lymphoma and myeloma, including acute myeloid leukemia, adult T-cell leukemia, T-cell large
15 granula lymphocyte leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute monocytic leukemia, Hodgkin's and Non-Hodgkin's lymphoma and multiple myeloma.

In certain embodiments, the subject is a mammal, such as a human.

In certain embodiments, the V_HH or the polypeptide construct or the multispecific molecule
20 or the chimeric antigen receptor or the dual-chimeric antigen receptor or engineered immune cell or the pharmaceutical composition is used in combination with an additional therapeutic agent or an additional therapy.

In certain embodiments, the additional therapeutic agent is an anti-tumor agent.

In certain embodiments, the additional therapeutic agent is an additional immune
25 checkpoint inhibitor, such as anti-PD-1 antibody, anti-PD-L1 antibody, anti-TIM-3 antibody, anti-LAG-3 antibody, or anti-CTLA-4 antibody.

In certain embodiments, the additional therapeutic agent is a cytotoxic agent, such as an alkylating agent, an anti-mitotic agent, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, a tyrosine kinase inhibitor, or a radionuclide.

30 In certain embodiments, the additional therapy is a standard cancer treatment, such as surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy, hormone therapy, gene therapy or palliative care.

In another aspect, the present disclosure provides the V_HH of the present disclosure or the polypeptide construct of the present disclosure or the multispecific molecule of the present
35 disclosure or the nucleic acid molecule of the present disclosure or the vector of the present

disclosure or the cell of the present disclosure or the chimeric antigen receptor of the present disclosure or the dual-chimeric antigen receptor of the present disclosure or engineered immune cell of the present disclosure or the pharmaceutical composition of the present disclosure, for use in preventing and/or treating a disease in a subject.

5 In certain embodiments, the disease is tumor or autoimmune disease.

In certain embodiments, the tumor expresses GPRC5D.

In certain embodiments, the tumor is a solid tumor, e.g., ovarian cancer, endometrial cancer, breast cancer, lung cancer (small cell or non-small cell), colon cancer, prostate cancer, cervical cancer, pancreatic cancer, gastric cancer, esophageal cancer, hepatocellular carcinoma (liver cancer), renal cell carcinoma (kidney cancer), head-and-neck tumors, mesothelioma, melanoma, sarcomas, or brain tumors (e.g., gliomas, such as glioblastomas).

In certain embodiments, the tumor is a hematological malignancy, e.g., leukemia, lymphoma and myeloma, including acute myeloid leukemia, adult T-cell leukemia, T-cell large granula lymphocyte leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, 15 chronic myelogenous leukemia, acute monocytic leukemia, Hodgkin's and Non-Hodgkin's lymphoma and multiple myeloma.

In certain embodiments, the subject is a mammal, such as a human.

In certain embodiments, the V_HH or the polypeptide construct or the multispecific molecule or the chimeric antigen receptor or the dual-chimeric antigen receptor or engineered immune cell 20 or the pharmaceutical composition is used in combination with an additional therapeutic agent or an additional therapy.

In certain embodiments, the additional therapeutic agent is an anti-tumor agent.

In certain embodiments, the additional therapeutic agent is an additional immune checkpoint inhibitor, such as anti-PD-1 antibody, anti-PD-L1 antibody, anti-TIM-3 antibody, 25 anti-LAG-3 antibody, or anti-CTLA-4 antibody.

In certain embodiments, the additional therapeutic agent is a cytotoxic agent, such as an alkylating agent, an anti-mitotic agent, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, a tyrosine kinase inhibitor, or a radionuclide.

In certain embodiments, the additional therapy is a standard cancer treatment, such as 30 surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy, hormone therapy, gene therapy or palliative care.

In another aspect, the present disclosure provides a method for preventing and/or treating a disease in a subject, the method comprising administering to a subject in need thereof an effective amount of the V_HH of the present disclosure or the polypeptide construct of the present disclosure or the multispecific molecule of the present disclosure or the nucleic acid molecule of 35

the present disclosure or the vector of the present disclosure or the cell of the present disclosure or the chimeric antigen receptor of the present disclosure or the dual-chimeric antigen receptor of the present disclosure or engineered immune cell of the present disclosure or the pharmaceutical composition according of the present disclosure.

5 In certain embodiments, the disease is tumor or autoimmune disease.

In certain embodiments, the tumor expresses GPRC5D.

In certain embodiments, the tumor is a solid tumor, e.g., ovarian cancer, endometrial cancer, breast cancer, lung cancer (small cell or non-small cell), colon cancer, prostate cancer, cervical cancer, pancreatic cancer, gastric cancer, esophageal cancer, hepatocellular carcinoma (liver cancer), renal cell carcinoma (kidney cancer), head-and-neck tumors, mesothelioma, melanoma, sarcomas, or brain tumors (e.g., gliomas, such as glioblastomas).

In certain embodiments, the tumor is a hematological malignancy, e.g., leukemia, lymphoma and myeloma, including acute myeloid leukemia, adult T-cell leukemia, T-cell large granula lymphocyte leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute monocytic leukemia, Hodgkin's and Non-Hodgkin's lymphoma and multiple myeloma.

In certain embodiments, the subject is a mammal, such as a human.

In certain embodiments, the V_HH or the polypeptide construct or the multispecific molecule or the chimeric antigen receptor or the dual-chimeric antigen receptor or engineered immune cell or the pharmaceutical composition is used in combination with an additional therapeutic agent or an additional therapy.

In certain embodiments, the additional therapeutic agent is an anti-tumor agent.

In certain embodiments, the additional therapeutic agent is an additional immune checkpoint inhibitor, such as anti-PD-1 antibody, anti-PD-L1 antibody, anti-TIM-3 antibody, anti-LAG-3 antibody, or anti-CTLA-4 antibody.

In certain embodiments, the additional therapeutic agent is a cytotoxic agent, such as an alkylating agent, an anti-mitotic agent, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, a tyrosine kinase inhibitor, or a radionuclide.

In certain embodiments, the additional therapy is a standard cancer treatment, such as surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy, hormone therapy, gene therapy or palliative care.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Binding of 20 anti-GPRC5D antibodies AS300399 (Fig. 1a), AS300413 (Fig. 1b), AS300442 (Fig. 1c), AS300452 (Fig. 1d), AS300533 (Fig. 1e), AS302376 (Fig. 1f), AS302399

(Fig. 1g), AS302509 (Fig. 1h), AS302553 (Fig. 1i), AS302558 (Fig. 1j), AS302643 (Fig. 1k), AS307587 (Fig. 1l), AS307685 (Fig. 1m), AS307858 (Fig. 1n), AS307879 (Fig. 1o), AS307946 (Fig. 1p), AS308386 (Fig. 1q), AS308506 (Fig. 1r), AS310012 (Fig. 1s) and AS310027 (Fig. 1t) to HEK293/human GPRC5D cells. 5E11 IgG, G109 scFv-Fc and isotype control antibody were used in every figure for comparison.

Figure 2. Binding of 20 anti-GPRC5D antibodies AS300399 (Fig. 2a), AS300413 (Fig. 2b), AS300442 (Fig. 2c), AS300452 (Fig. 2d), AS300533 (Fig. 2e), AS302376 (Fig. 2f), AS302399 (Fig. 2g), AS302509 (Fig. 2h), AS302553 (Fig. 2i), AS302558 (Fig. 2j), AS302643 (Fig. 2k), AS307587 (Fig. 2l), AS307685 (Fig. 2m), AS307858 (Fig. 2n), AS307879 (Fig. 2o), AS307946 (Fig. 2p), AS308386 (Fig. 2q), AS308506 (Fig. 2r), AS310012 (Fig. 2s) and AS310027 (Fig. 2t) to H929. 5E11 IgG and isotype control antibodies were used in every figure for comparison.

Figure 3. Schematic representation of chimeric GPRC5D proteins. Chimeric DB1 (Fig.3a), chimeric DA2 (Fig.3b), chimeric DA3 (Fig.3c) and chimeric DB4 (Fig.3d) were constructed by replacing extracellular region or loops with their counterparts from GPRC5A or GPRC5B.

Figure 4. Binding of 20 anti-GPRC5D antibodies AS300399, AS300413, AS300442, AS300452 (Fig. 4a), AS300533, AS302376, AS302399, AS302509 (Fig. 4b), AS302553, AS302558, AS302643, AS307587 (Fig. 4c), AS307685, AS307858, AS307879, AS307946 (Fig. 4d), AS308386, AS308506, AS310012 and AS310027 (Fig. 4e) to chimeric GPRC5Ds expressed on FreeStyle™ 293-F cells. 5E11 IgG, G109 scFv-Fc and isotype control antibody were used in every figure for comparison.

Figure 5A shows the *in vitro* long-term cytotoxicity of monospecific anti-GPRC5D V_HH CAR-T cells against GPRC5D positive cell line MM.1S, with benchmark 5E11bbz as a control.

Figure 5B shows the *in vitro* proliferation of monospecific anti-GPRC5D V_HH CAR-T cells against repeated stimulation of GPRC5D positive cell line MM.1S, with benchmark 5E11bbz as a control.

Figure 6 shows the *in vitro* IFN-γ production of monospecific anti-GPRC5D V_HH CAR-T cells following stimulation of GPRC5D positive cell line MM.1S, with benchmark 5E11bbz as a control.

Figure 7A shows the *in vitro* short-term cytotoxicity of monospecific anti-GPRC5D V_HH CAR-T cells against GPRC5D-high cell line Raji-luc, with benchmark 5E11bbz and UnT as a control.

Figure 7B shows the *in vitro* short-term cytotoxicity of monospecific anti-GPRC5D V_HH CAR-T cells against GPRC5D-medium cell line Raji-luc, with benchmark 5E11bbz and UnT as a control.

Figure 7C shows the *in vitro* short-term cytotoxicity of monospecific anti-GPRC5D V_HH

CAR-T cells against GPRC5D-low cell line Raji-luc, with benchmark 5E11bbz and UnT as a control.

Figure 8 shows the *in vitro* cytotoxicity of monospecific GPRC5D V_HH CAR-T cells against GPRC5D positive cell line MM.1S. All GPRC5D V_HH CAR-T cells show cytotoxicity against GPRC5D-positive cells effectively. UnT refers to T cells un-transduced with CAR and serve as control.

Figure 9 shows the results of an *in vitro* long-term cytotoxicity assay of monospecific GPRC5D V_HH CAR-T cells against GPRC5D low expression cell line (Hep3B2.1-7-5D). The result shows that monospecific GPRC5D V_HH CAR-T cells can eliminate tumor cells quickly.

DETAILED DESCRIPTION

Anti-GPRC5D V_HH

The terms “V_HH” or “V_HH domain” are used interchangeably herein to refer to the antigen-binding portion of a single-domain antibody, such as a camelid heavy-chain antibody or shark heavy-chain antibody. A V_HH typically comprises three CDRs and four framework regions, designated FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. In some cases, a V_HH may be truncated at the N-terminus or C-terminus such that it comprises only a partial FR1 and/or FR4, or lacks one or both of those framework regions, so long as the V_HH substantially maintains antigen binding and specificity.

In one aspect, the present disclosure provides an anti-GPRC5D V_HH, comprising:

(1) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 4;

(2) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 8;

(3) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 12;

(4) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 16;

(5) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 20;

(6) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 24;

(7) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 28;

(8) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,

and CDR3, respectively, as set forth in SEQ ID NO: 32;

(9) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 36;

(10) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 40;

(11) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 44;

(12) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 48;

(13) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 52;

(14) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 56;

(15) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 60;

(16) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 64;

(17) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 68;

(18) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 72;

(19) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 76;

(20) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 80;

(21) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 84;

(22) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 88;

(23) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 92;

(24) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 96;

(25) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 100;

(26) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 104;

(27) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 108;

5 (28) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 112;

(29) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 115;

10 (30) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 119;

(31) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 123;

(32) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 127;

15 (33) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 131;

(34) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 135;

20 (35) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 139;

(36) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 143;

(37) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 147;

25 (38) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 151;

(39) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 155;

30 (40) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 159;

(41) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 163;

(42) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 167;

35 (43) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,

and CDR3, respectively, as set forth in SEQ ID NO: 171;

(44) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 175;

(45) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 179;

(46) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 183;

(47) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 187;

(48) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 190;

(49) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 193;

(50) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 197;

(51) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 201;

(52) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 205;

(53) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 209;

(54) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 213;

(55) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 216;

(56) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 220;

(57) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 224;

(58) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 228;

(59) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 232;

(60) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 236;

(61) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 240;

(62) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 244;

5 (63) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 248;

(64) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 252;

10 (65) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 256;

(66) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 260;

(67) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 264;

15 (68) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 266;

(69) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 270;

20 (70) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 274;

(71) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 278;

(72) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 282;

25 (73) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 286;

(74) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 290;

30 (75) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 294;

(76) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 298;

(77) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 302;

35 (78) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,

and CDR3, respectively, as set forth in SEQ ID NO: 306;

(79) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 310.

The CDR1, CDR2 or CDR3 described above may be determined according to the AbM
5 numbering scheme, the IMGT numbering scheme, the Kabat numbering scheme, the Chothia numbering scheme, the Contact numbering scheme, or any combination thereof.

The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 5, 6 and 7. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NOs: SEQ ID NO: 9, 10
10 and 11. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NOs: SEQ ID NO: 13, 14 and 15. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NOs: SEQ ID NO: 17, 18 and 19. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NOs: SEQ ID NO: 21, 22 and 23. The V_HH
15 may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NOs: SEQ ID NO: 25, 26 and 27. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NOs: SEQ ID NO: 29, 30 and 31. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NOs: SEQ ID NO: 33, 34 and 35. The V_HH may comprise a
20 CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 37, 38 and 39. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 41, 42 and 43. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 45, 46 and 47. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 49, 50 and 51. The V_HH may comprise a CDR1, a CDR2,
25 and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 53, 54 and 55. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 57, 58 and 59. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 61, 62 and 63. The
30 V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 65, 66 and 67. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 69, 70 and 71. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 73, 74 and 75. The V_HH may comprise a CDR1, a CDR2, and a
35 CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 77, 78 and 79. The

V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 81, 82 and 83. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 85, 86 and 87. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 89, 90 and 91. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 93, 94 and 95. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 97, 98 and 99. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 101, 102 and 103. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 105, 106 and 107. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 109, 110 and 111. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 81, 113 and 114. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 116, 117 and 118. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 120, 121 and 122. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 124, 125 and 126. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 128, 129 and 130. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 132, 133 and 134. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 136, 137 and 138. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 140, 141 and 142. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 144, 145 and 146. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 148, 149 and 150. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 152, 153 and 154. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 156, 157 and 158. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 160, 161 and 162. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 164, 165 and 166. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 168, 169 and 170. The V_HH may comprise a CDR1, a CDR2, and a

CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 172, 173 and 174. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 176, 177 and 178. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 180, 181 and 182. The

5 V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 184, 185 and 186. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 136, 188 and 189. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 191, 192 and 138. The V_HH may comprise a CDR1, a CDR2, and a

10 CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 194, 195 and 196. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 198, 199 and 200. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 202, 203 and 204. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 206, 207 and 208. The V_HH may comprise a CDR1, a CDR2, and a

15 CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 210, 211 and 212. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 120, 214 and 215. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 217, 218 and 219. The

20 V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 221, 222 and 223. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 225, 226 and 227. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 229, 230 and 231. The V_HH may comprise a CDR1, a CDR2, and a

25 CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 233, 234 and 235. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 237, 238 and 239. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 241, 242 and 243. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 245, 246 and 247. The V_HH may comprise a CDR1, a CDR2, and a

30 CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 249, 250 and 251. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 253, 254 and 255. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 257, 258 and 259. The

35 V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid

sequences of SEQ ID NO: 261, 262 and 263. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 5, 6 and 265. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 267, 268 and 269. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 271, 272 and 273. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 275, 276 and 277. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 279, 280 and 281. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 283, 284 and 285. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 287, 288 and 289. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 291, 292 and 293. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 295, 296 and 297. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 299, 300 and 301. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 303, 304 and 305. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 307, 308 and 309. The V_HH may comprise a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of SEQ ID NO: 311, 312 and 313.

The V_HH disclosed herein may further comprise framework regions (FRs).

The V_HH may comprise framework regions (FRs) derived from a camelid heavy-chain antibody.

The V_HH may comprise the amino acid sequence of SEQ ID NO: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 115, 119, 123, 127, 131, 135, 139, 143, 147, 151, 155, 159, 163, 167, 171, 175, 179, 183, 187, 190, 193, 197, 201, 205, 209, 213, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 266, 270, 274, 278, 282, 286, 290, 294, 298, 302, 306 or 310, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

The V_HH may be camelid, chimeric or humanized.

The V_HH may be a humanized V_HH, in which one or more framework regions have been substantially replaced with human framework regions. The V_HH may comprise framework regions (FRs) derived from a human immunoglobulin heavy chain variable region, in which one or several framework residues can be mutated back to their camelid counterparts (i.e.,

backmutation).

The V_HH may comprise the amino acid sequence of SEQ ID NO: 16, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may
5 comprise the amino acid sequence of SEQ ID NO: 328, 329, 330, 331, 332 or 333.

The V_HH may comprise the amino acid sequence of SEQ ID NO: 24, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may comprise the amino acid sequence of SEQ ID NO: 334, 335, 336 or 337.

10 The V_HH may comprise the amino acid sequence of SEQ ID NO: 48, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may comprise the amino acid sequence of SEQ ID NO: 338, 339, 340, 341 or 342.

The V_HH may comprise the amino acid sequence of SEQ ID NO: 143, or an amino acid
15 sequence having at least 80%, 81%, 82%, 83%, 84%, %, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may comprise the amino acid sequence of SEQ ID NO: 343, 344, 345 or 346.

The V_HH may comprise the amino acid sequence of SEQ ID NO: 179, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%,
20 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may comprise the amino acid sequence of SEQ ID NO: 347, 348 or 349.

The V_HH may comprise the amino acid sequence of SEQ ID NO: 187, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may
25 comprise the amino acid sequence of SEQ ID NO: 350, 351 or 352.

The V_HH may comprise the amino acid sequence of SEQ ID NO: 193, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may comprise the amino acid sequence of SEQ ID NO: 353, 354, 355, 356, 357 or 358.

30 The V_HH may comprise the amino acid sequence of SEQ ID NO: 220, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may comprise the amino acid sequence of SEQ ID NO: 359, 360, 361, 362 or 363.

The V_HH may comprise the amino acid sequence of SEQ ID NO: 244, or an amino acid
35 sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%,

92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may comprise the amino acid sequence of SEQ ID NO: 364, 365, 366 or 367.

The V_HH may comprise the amino acid sequence of SEQ ID NO: 274, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may comprise the amino acid sequence of SEQ ID NO: 368, 369, 370 or 371.

The V_HH may comprise the amino acid sequence of SEQ ID NO: 298, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may comprise the amino acid sequence of SEQ ID NO: 372, 373, 374, 375 or 376.

The V_HH may comprise the amino acid sequence of SEQ ID NO: 302, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may comprise the amino acid sequence of SEQ ID NO: 377, 378 or 379.

The V_HH may comprise the amino acid sequence of SEQ ID NO: 306, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may comprise the amino acid sequence of SEQ ID NO: 380, 381, 382, 383 or 384.

The V_HH may comprise the amino acid sequence of SEQ ID NO: 310, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. The V_HH may comprise the amino acid sequence of SEQ ID NO: 385, 386, 387, 388, 389 or 390.

Polypeptide construct

In another aspect, the present disclosure provides a polypeptide construct, comprising the V_HH of the present disclosure.

The construct may be a monospecific molecule, a bispecific molecule, a multispecific molecule, an immunoconjugate, or a fusion protein. The monospecific molecule may be a sdAb, or antigen binding fragment thereof. The construct may comprise an additional polypeptide. The additional polypeptide may be an immunoglobulin Fc region. The immunoglobulin Fc region may be an IgG Fc region, e.g., an IgG1, IgG2, IgG3, or IgG4 Fc region. The additional polypeptide may be an additional binding domain that binds to a second target other than GPRC5D.

In another aspect, the present disclosure provides a polypeptide construct, comprising the V_HH of the present disclosure and an immunoglobulin Fc region.

The immunoglobulin Fc region may be an IgG Fc region, e.g., an IgG1, IgG2, IgG3, or IgG4 Fc region. The immunoglobulin Fc region may further be a human IgG Fc region, e.g., a human IgG1, IgG2, IgG3, or IgG4 Fc region.

5 The immunoglobulin Fc region may be a native sequence Fc region comprising an amino acid sequence identical to the amino acid sequence of an Fc region found in nature.

Alternatively, the immunoglobulin Fc region may be a variant Fc region comprising an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid mutation. Mutation(s) (e.g., one or more amino acid substitutions) can be introduced into the Fc region of constant region to alter (increase, reduce or eliminate) the effector function(s) of the antibody, such as ADCC, CDC or ADCCP compared with the same antibody without the mutation(s). The immunoglobulin Fc region may possess reduced or eliminated effector function(s).

The V_HH may be fused (e.g., at its C-terminus) to the N-terminus of the immunoglobulin Fc region without a linker.

15 Alternatively, the V_HH may be fused (e.g., at its C-terminus) to the N-terminus of the immunoglobulin Fc region with a linker. The linker may be selected from a cleavable linker, a non-cleavable linker, a peptide linker, a flexible linker, a rigid linker, a helical linker, and a non-helical linker. The linker may be a peptide linker. The linker may comprise the sequence of (GmS)_n, wherein m is selected from integer of 1-6, e.g., 1, 2, 3, or 4, n is selected from integer of 1-6, e.g., 1, 2, or 3.

Multispecific molecules

In another aspect, the present disclosure provides a multispecific molecule comprising a GPRC5D-binding domain which comprises the V_HH of the present disclosure and an additional binding domain that binds to a second target other than GPRC5D.

The multispecific molecule may be a bispecific antibody.

The additional binding domain may be a monovalent antibody fragment, e.g., a Fab, an Fv, a scFv, or a V_HH.

30 The second target may be selected from CD3, CD33, CD19, CD20, CD22, CD30, CD70, CLL-1, BCMA, DLL-3, Claudin 6, Claudin 18.2, GPC3, GPC2, CD229, FcRH5, GUCY2C, mesothelin, HER2, PSMA, or PSCA.

The multispecific molecule as described herein may further comprise an immunoglobulin Fc domain. Exemplary Fc domains can be chosen from the heavy chain constant regions of IgG (e.g., IgG1, IgG2, IgG3 or IgG4); more particularly, the heavy chain constant region of human IgG (e.g., IgG1, IgG2, IgG3 or IgG4).

The Fc domain may be composed of a first and a second subunit. The GPRC5D-binding domain and the additional binding domain may be each fused to the first and second Fc subunits. The first and second Fc subunits may be engineered for heterodimerization.

5 V_HH Production

In a further aspect, nucleic acid molecules, vectors and host cells for producing the V_HHs, polypeptide constructs, or multispecific molecules disclosed herein, are provided.

In another aspect, the present disclosure provides a nucleic acid molecule, comprising a nucleotide sequence encoding the V_HH of the present disclosure, the polypeptide construct of the present disclosure, or the multispecific molecule of the present disclosure.

In another aspect, the present disclosure provides a vector, which comprises the nucleic acid molecule as described above.

The vector disclosed herein may be, for example, a plasmid, a cosmid, a phage.

The vector may comprise a nucleotide sequence encoding the V_HH disclosed herein.

15 The vector may comprise a nucleotide sequence encoding the polypeptide construct disclosed herein.

The vector may comprise different nucleotide sequences encoding different polypeptide chains of the multispecific molecule respectively. The different nucleotide sequences can be located on same or different vectors.

20 In another aspect, the present disclosure provides a host cell, which comprises the nucleic acid molecule or vector as described above. Such host cells include, but are not limited to, prokaryotic cell such as *E. coli* cell, and eukaryotic cell such as yeast cell, insect cell, plant cell and animal cell (e.g., mammalian cell, such as mouse cell and human cell).

Also provided is a method for producing the V_HH of the present disclosure, or the polypeptide construct of the present disclosure, or the multispecific molecule of the present disclosure, comprising: culturing a host cell comprising the nucleic acid molecule of the present disclosure or the vector of the present disclosure, or the cell of the present disclosure under a condition that allows protein expression, and recovering the V_HH, the polypeptide construct, or the multispecific molecule from a culture of the cultured cell.

30

Chimeric antigen receptor

In another aspect, the present disclosure provides a chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises a first binding moiety that specifically binds to a first antigen or epitope, wherein the first binding

moiety comprises the V_HH of the present disclosure, the polypeptide of the present disclosure, or the multispecific molecule of the present disclosure.

5 The “binding moiety” refers to a molecule that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of binding moieties include but are not limited to F_v, Fab, Fab’, F(ab’)₂; diabodies; linear antibodies; heavy chain variable (VH) regions, single-chain antibody molecules such as scFvs and single-domain antibodies comprising only the VH region.

The extracellular antigen-binding domain may further comprise a second binding moiety that specifically binds to a second antigen or epitope.

10 The first antigen or epitope may be the same as the second antigen or epitope. The first antigen or epitope may be different from the second antigen or epitope. The first binding moiety and the second binding moiety may be linked in tandem.

The second binding moiety may be an sdAb, an scFv, or an extracellular domain of a receptor.

15 The second binding moiety may be an anti-tumor antigen sdAb or scFv, and the tumor antigen selected from CD33, CD19, CD20, CD22, CD30, CD70, CLL-1, BCMA, DLL3, Claudin 6, Claudin 18.2, GPC3, GPC2, GPRC5D, CD229, FcRH5, GUCY2C, mesothelin, HER2, PSMA, or PSCA.

20 The second binding moiety may be an anti-GPRC5D sdAb, and comprises the V_HH of the present disclosure, the polypeptide construct of the present disclosure, or the multispecific molecule of the present disclosure.

25 The CAR may further comprise a spacer domain is selected from a hinge domain and/or CH2 and CH3 regions of an immunoglobulin (e.g., IgG1 or IgG4). In general, the spacer is a sequence of amino acids located between, such that connects, the extracellular antigen-binding domain and the transmembrane domain of the CAR.

30 Among such spacers are portions of human immunoglobulins or modified forms thereof, including those that have a length of greater than 125 amino acids in lengths, such as greater than 150 amino acids, greater than 180 amino acids, greater than 200 amino acids or greater than 200 amino acids in length. The hinge domain may comprise a hinge region of CD8 α , IgG4, PD1, CD152 or CD154. The spacer domain may comprise a hinge region of CD8 α . The spacer domain may comprise a sequence as set forth in SEQ ID NO: 316.

35 The transmembrane domain of the CAR may comprise a hydrophobic alpha helix that spans at least a portion of the membrane. Different transmembrane domains result in different receptor stability. After antigen recognition, receptors cluster and a signal are transmitted to the cell. In accordance with the presently disclosed subject matter, the transmembrane domain may be

selected from one or more transmembrane regions selected from the group consisting of: α , β or ζ chain of T cell receptor, CD3 ϵ , CD3 ζ , CD4, CD5, CD8 α , CD28, CD137, CD152, CD154 and PD1.

The transmembrane domain may comprise a transmembrane region of CD8 α . The
5 transmembrane domain may comprise a sequence as set forth in SEQ ID NO: 317.

The intracellular signaling domain may comprise a primary signaling domain and/or a costimulatory signaling domain. The intracellular signaling domain may comprise a primary signaling domain and at least one costimulatory signaling domain.

The primary signaling domain may comprise an intracellular signaling domain of a protein
10 selected from the group consisting of: CD3 ζ , FcR γ , FcR β , CD3 γ , CD3 δ , CD3 ϵ , CD5, CD22, CD79a, CD79b and CD66d.

The costimulatory signaling domain may comprise an intracellular signaling domain of a protein selected from the group consisting of: CARD11, CD2, CD7, CD27, CD28, CD30, CD54 (ICAM), CD83, CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD152 (CTLA4), CD223
15 (LAGS), CD270 (HVEM), CD273 (PD-L2), CD274 (PD-L1), CD278 (ICOS), DAP10 and DAP12.

The intracellular signaling domain may comprise a primary signaling domain and a costimulatory signaling domain, wherein the primary signaling domain comprises an intracellular signaling domain of CD3 ζ , the costimulatory signaling domain comprises an
20 intracellular signaling domain of CD137. The primary signaling domain may comprise a sequence as set forth in SEQ ID NO: 319. The costimulatory signaling domain may comprise a sequence as set forth in SEQ ID NO: 318.

The chimeric antigen receptor may further comprise a signal peptide.

The chimeric antigen receptor may further comprise a tag.

The tag may be selected from a myc-tag, a His-tag, a short linear peptide sequence from yeast transcription factor GCN4, a leucine zipper sequence or a short linear peptide sequence from a human nuclear protein. The tag may be a myc-tag, and the myc-tag may comprise a
25 sequence as set forth in SEQ ID NO: 315.

The signal peptide may be derived from a molecule selected from the group consisting of
30 CD8 α , GM-CSF receptor α , and IgG1 heavy chain. The signal peptide may comprise a sequence as set forth in SEQ ID NO: 314.

The chimeric antigen receptor may comprise the following domains in sequence from the N-terminal to the C-terminal: the signal peptide, the tag, the antigen-binding domain, the spacer domain, the transmembrane domain and the intracellular signaling domain.

35 In some cases, simultaneously targeting both antigens may improve the depth and durability

of responses across patients, in addition to minimizing relapse due to antigen escape. A mechanism of resistance to CAR T-cell therapies, as evidenced by data from CAR T-cell trials in B-cell malignancies, may be the loss or downregulation (“escape”) of the target antigen. (Robbie G. Majzner and Crystal L. Mackall, Cancer Discov Aug. 22, 2018; DOI 10.1158/2159-8290.CD-18-0442). Such a combination or dual targeting strategy may achieve synergistic or improved tumor responses based on targeting two antigens compared to monotherapy approaches involving only single antigen targeting.

Thus, the present disclosure provides a dual-chimeric antigen receptor (CAR), comprising:

a first engineered receptor comprising the chimeric antigen receptor of the present disclosure; and

a second engineered receptor comprising: a second extracellular antigen-binding domain, a second transmembrane domain and a second intracellular domain.

The second extracellular antigen-binding domain may be an anti-tumor antigen sdAb or scFv, and the tumor antigen selected from BCMA, CD33, CD19, CD20, CD22, CD30, CD70, CLL-1, DLL3, Claudin 6, Claudin 18.2, GPC3, GPC2, GPRC5D, CD229, FcRH5, GUCY2C, mesothelin, HER2, PSMA, or PSCA.

In some cases, the CAR is expressed by introducing a nucleic acid encoding it into a cell *in vivo* (in vivo cell therapy) or *in vitro* (including autologous cell therapy and allogeneic cell therapy). In some cases, the cell is an immune cell.

Also provided are nucleic acid molecules, vectors and host cells for expressing the chimeric antigen receptors or the dual-chimeric antigen receptors, and for producing the engineered immune cells expressing such chimeric antigen receptors or the dual-chimeric antigen receptors. The genetic engineering generally involves introduction of a nucleic acid encoding the chimeric antigen receptors or the dual-chimeric antigen receptors into the cell, such as by lentiviral transduction, retroviral transduction, transfection, or transformation.

Thus, the present disclosure provides a nucleic acid molecule comprising a nucleotide sequence encoding the chimeric antigen receptor or the dual-chimeric antigen receptor of the present disclosure.

In another aspect, the present disclosure provides a vector comprising the nucleic acid molecule of the present disclosure.

In another aspect, the present disclosure provides a host cell, which comprises the nucleic acid molecule of the present disclosure or the vector of the present disclosure.

The host cell may be selected from an immune cell (e.g., human immune cell).

The immune cell may be selected from the group consisting of T lymphocyte, NK cell, monocyte, macrophage or dendritic cell, and any combination thereof.

In another aspect, the present disclosure provides an engineered immune cell, which expresses the chimeric antigen receptor or the dual-chimeric antigen receptor of the present disclosure.

Optionally, the chimeric antigen receptor or the dual-chimeric antigen receptor is expressed
5 on the surface of the engineered immune cell.

Optionally, the engineered immune cell also expresses a chimeric antigen receptor or the dual-chimeric antigen receptor that is not specific for GPRC5D.

The immune cell may be selected from the group consisting of T lymphocyte, NK cell, monocyte, macrophage or dendritic cell and any combination thereof.

10 The immune cell may be obtained from a patient or a healthy donor.

Pharmaceutical Composition

In a further aspect, the present disclosure provides a pharmaceutical composition comprising the V_HH of the present disclosure, the polypeptide construct of the present disclosure,
15 the multispecific molecule of the present disclosure, or the chimeric antigen receptor of the present disclosure, or the dual-chimeric antigen receptor of the present disclosure; and a pharmaceutically acceptable carrier and/or excipient.

The pharmaceutical composition may comprise an effective amount of the V_HH. The V_HH may be the only active ingredient included in the pharmaceutical composition.

20 The pharmaceutical composition may comprise an effective amount of the polypeptide construct. The polypeptide construct may be the only active ingredient included in the pharmaceutical composition.

The pharmaceutical composition may comprise an effective amount of the multispecific molecule. The multispecific molecule may be the only active ingredient included in the
25 pharmaceutical composition.

The pharmaceutical composition may comprise an effective amount of the chimeric antigen receptor. The chimeric antigen receptor may be the only active ingredient included in the pharmaceutical composition.

The pharmaceutical composition may comprise an effective amount of the dual-chimeric
30 antigen receptor. The dual-chimeric antigen receptor may be the only active ingredient included in the pharmaceutical composition.

The pharmaceutical composition disclosed herein may further comprise an additional therapeutic agent. The additional therapeutic agent may be an anti-tumor agent. The additional therapeutic agent may be a cytotoxic agent, such as an alkylating agent, an anti-mitotic agent, an
35 antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, a tyrosine kinase inhibitor, or a

radionuclide.

The V_{HH} , the polypeptide construct, the multispecific molecule, the chimeric antigen receptor, the dual-chimeric antigen receptor, and the additional therapeutic agent may be provided as separate components or as components of a single composition. The V_{HH} , the polypeptide construct, the multispecific molecule, the chimeric antigen receptor, the dual-chimeric antigen receptor herein may be used in combination with the other agents simultaneously, separately, or successively.

The pharmaceutical composition can be provided in unit dosage form (i.e., the dosage for a single administration).

The pharmaceutical composition can be formulated using one or more pharmaceutically acceptable carriers and/or excipients. The formulation depends on the route of administration chosen. For parenteral administration, the pharmaceutical composition is preferably sterile and substantially isotonic and manufactured under GMP conditions. By way of example, the V_{HH} , the heavy chain antibody, the polypeptide construct, the multispecific molecule, the chimeric antigen receptor, or the dual-chimeric antigen receptor disclosed herein can be formulated in aqueous solutions for injection, preferably in physiologically compatible buffers, such as water for injection (WFI), bacteriostatic water for injection (BWFI), sodium chloride solution (e.g., 0.9% (w/v) NaCl), glucose solution (e.g., 5% glucose), surfactant-containing solution (e.g., 0.01% polysorbate 20), pH buffered solution (e.g., phosphate buffered solution), Ringer's solution. The solution can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the V_{HH} , the polypeptide construct, the multispecific molecule, the chimeric antigen receptor, or the dual-chimeric antigen receptor disclosed herein can be in lyophilized form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

Pharmaceutical compositions described herein can be useful in treating a disease, such as tumor.

Methods or uses of treating diseases/tumors

In a further aspect, methods or uses of treating diseases/tumors using the V_{HH} , or the polypeptide construct, or the multispecific molecule, or the nucleic acid molecule, or the vector, or the cell, or the chimeric antigen receptor, or the dual-chimeric antigen receptor, or engineered immune cell, or the pharmaceutical composition as described herein are provided.

In one aspect, the present disclosure provides use of the V_{HH} of the present disclosure or the polypeptide construct of the present disclosure or the multispecific molecule of the present disclosure or the nucleic acid molecule of the present disclosure or the vector of the present disclosure or the cell of the present disclosure or the chimeric antigen receptor of the present

disclosure or the dual-chimeric antigen receptor of the present disclosure or engineered immune cell of the present disclosure or the pharmaceutical composition of the present disclosure in manufacture of a medicament for use in preventing and/or treating a tumor in a subject.

5 In another aspect, the present disclosure provides the V_HH of the present disclosure or the polypeptide construct of the present disclosure or the multispecific molecule of the present disclosure or the nucleic acid molecule of the present disclosure or the vector of the present disclosure or the cell of the present disclosure or the chimeric antigen receptor of the present disclosure or the dual-chimeric antigen receptor of the present disclosure or engineered immune cell of the present disclosure or the pharmaceutical composition of the present disclosure, for use
10 in preventing and/or treating a tumor in a subject.

In another aspect, the present disclosure provides a method for preventing and/or treating a tumor in a subject, the method comprising administering to a subject in need thereof an effective amount of the V_HH of the present disclosure or the polypeptide construct of the present disclosure or the multispecific molecule of the present disclosure or the nucleic acid molecule of
15 the present disclosure or the vector of the present disclosure or the cell of the present disclosure or the chimeric antigen receptor of the present disclosure or the dual-chimeric antigen receptor of the present disclosure or engineered immune cell of the present disclosure or the pharmaceutical composition according of the present disclosure.

The tumor may express GPRC5D.

20 The tumor may be a solid tumor, e.g., ovarian cancer, endometrial cancer, breast cancer, lung cancer (small cell or non-small cell), colon cancer, prostate cancer, cervical cancer, pancreatic cancer, gastric cancer, esophageal cancer, hepatocellular carcinoma (liver cancer), renal cell carcinoma (kidney cancer), head-and-neck tumors, mesothelioma, melanoma, sarcomas, or brain tumors (e.g., gliomas, such as glioblastomas).

25 The tumor may be a hematological malignancy, e.g., leukemia, lymphoma and myeloma, including acute myeloid leukemia, adult T-cell leukemia, T-cell large granula lymphocyte leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute monocytic leukemia, Hodgkin's and Non-Hodgkin's lymphoma and multiple myeloma.

30 The subject may be a mammal, such as a human.

The V_HH or the polypeptide construct or the multispecific molecule or the chimeric antigen receptor or engineered immune cell or the pharmaceutical composition may be used in combination with an additional therapeutic agent or an additional therapy.

The additional therapeutic agent may be an anti-tumor agent.

35 The additional therapeutic agent may be an additional immune checkpoint inhibitor, such as

anti-PD-1 antibody, anti-PD-L1 antibody, anti-TIM-3 antibody, anti-LAG-3 antibody, or anti-CTLA-4 antibody.

The additional therapeutic agent may be a cytotoxic agent, such as an alkylating agent, an anti-mitotic agent, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, a
5 tyrosine kinase inhibitor, or a radionuclide.

The additional therapy may be a standard cancer treatment, such as surgery, chemotherapy, radiation therapy, targeted therapy, immunotherapy, hormone therapy, gene therapy or palliative care.

10 DEFINITIONS

In the present disclosure, the scientific and technical terms used herein have the meanings commonly understood by those skilled in the art, unless otherwise stated. For better understanding of the present disclosure, definitions and explanations of terms are provided below.

As used herein, the term "antibody" refers to an immunoglobulin molecule capable of
15 specific binding to a target through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. Unless otherwise indicated or clear from the context, the term "antibody" as used to herein may include whole antibodies and any antigen binding fragments (i.e., "antigen-binding portions") or single chains thereof. The term "antibody" may refer to conventional antibodies typically comprising at least one heavy chain and at least one
20 light chain. Antibody light chains can be classified as κ and λ light chains. Heavy chains can be classified as μ , δ , γ , α , or ϵ , and the isotypes of antibody are defined as IgM, IgD, IgG, IgA, and IgE, respectively. Within the light and heavy chains, variable region and constant region are joined by a "J" region of about 12 or more amino acids, and the heavy chain further comprises a
25 "D" region of about 3 or more amino acids. Each heavy chain consists of a heavy chain variable region (V_H) and a heavy chain constant region (C_H). The heavy chain constant region consists of three domains (C_{H1} , C_{H2} and C_{H3}). Each light chain consists of a light chain variable region (V_L) and a light chain constant region (C_L). The light chain constant region consists of one domain C_L . The V_H and V_L regions can also be subdivided into hypervariable regions (referred to as complementarity determining regions (CDRs)) interspaced with relatively conservative regions
30 called framework regions (FR). Each of V_H and V_L consists of three CDRs and four FRs arranged in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4 from the amino terminus to the carboxy terminus. The variable regions (V_H and V_L) of each heavy/light chain pair form an antibody binding site, respectively. The term "antibody" is not limited by any particular method for producing the antibody.

35 As used herein, the term " V_{HH} " or " V_{HH} domain" refers to the antigen-binding portion of a

single-domain antibody, such as a camelid heavy-chain antibody or shark heavy-chain antibody. A V_HH may comprise three CDRs and four framework regions, designated FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. A V_HH may be truncated at the N-terminus or C-terminus such that it comprises only a partial FR1 and/or FR4, or lacks one or both of those framework regions, so long as the V_HH substantially maintains antigen binding and specificity. A "humanized V_HH" as used herein refers to a V_HH in which one or more framework regions have been substantially replaced with human framework regions. In some instances, certain framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized V_HH can comprise residues that are found neither in the original V_HH nor in the human framework sequences, but are included to further refine and optimize the performance of V_HH. As will be appreciated, a humanized sequence can be identified by its primary sequence and does not necessarily denote the process by which the antibody was created.

As used herein, the term "complementarity determining region" or "CDR" refers to the amino acid residues in the variable region of an antibody that are responsible for antigen binding. The precise boundaries of these amino acid residues can be defined according to various numbering systems known in the art, for example, according to the definitions in the Kabat numbering system (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991), Chothia numbering system (Chothia & Lesk (1987) J. Mol. Biol. 196: 901-917; Chothia et al. (1989) Nature 342: 878-883), AbM numbering system (Martin, in Antibody Engineering, Vol. 2, Chapter 3, Springer Verlag) or IMGT numbering system (Lefranc et al., Dev. Comparat. Immunol. 27: 55-77, 2003). For a given antibody, those skilled in the art can easily identify the CDRs defined by each numbering system. Moreover, the correspondence between different numbering systems is well known to those skilled in the art (e.g., see Lefranc et al., Dev. Comparat. Immunol. 27: 55-77, 2003). The CDRs of the antibodies of the disclosure may be defined according to Kabat, AbM, IMGT, or Chothia numbering system, or any combination thereof. Unless otherwise indicated or clear from the context, the CDRs of the antibodies of the disclosure are preferably defined according to AbM numbering system.

As used herein, the term "framework region" or "FR" residues refers to those amino acid residues other than the CDR residues as defined above in the variable regions of antibody.

As used herein, the term "antigen-binding fragment" of an antibody refers to a polypeptide comprising a fragment of a full-length antibody, which retains the ability to specifically bind to the same antigen to which the full-length antibody binds, and/or competes with the full-length antibody to specifically bind to the antigen, and which is also referred to as an "antigen-binding portion". An antigen-binding fragment of an antibody can be produced by recombinant DNA

techniques or by enzymatic or chemical cleavage of the intact antibody. The antigen-binding fragment may comprise Fab, Fab', F(ab')₂, Fd, Fv, dAb and fragments of complementarity determining regions (CDRs), single chain antibodies (e.g., scFv), chimeric antibodies, diabodies, and polypeptides comprising at least a portion of the antibody that is sufficient to confer the specific antigen binding ability to the polypeptide.

As used herein, the term "heavy chain-only antibody" or "HCAb" refers to a functional antibody, which comprises heavy chains, but lacks the light chains usually found in 4-chain antibodies. Camelid animals (such as camels, llamas, or alpacas) are known to produce HCAbs. The HCAb may comprise a sdAb that is fused with a Fc region. The HCAb may comprise a sdAb that is fused with a human IgG1 hinge and Fc region.

As used herein, the term "Fd fragment" refers to an antibody fragment consisting of V_H and C_{H1} domains; the term "dAb fragment" refers to an antibody fragment consisting of V_H domain; the term "Fab fragment" refers to an antibody fragment consisting of V_L, V_H, C_L and C_{H1} domains; the term "F(ab')₂ fragment" refers to an antibody fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region.

As used herein, the term "Fv fragment" refers to an antibody fragment consisting of V_L and V_H domains of a single arm of an antibody. An Fv fragment is generally considered to be the smallest antibody fragment that can form a complete antigen binding site. It is believed that six CDRs confer the antigen binding specificity to the antibody. However, even one variable region (e.g., an Fd fragment, which contains only three CDRs specific for an antigen) is able to recognize and bind an antigen, albeit with less affinity than that of the entire binding site.

As used herein, the term "scFv" refers to a single polypeptide chain comprising V_L and V_H domains, having a general structure of NH₂-V_L-linker-V_H-COOH or NH₂-V_H-linker-V_L-COOH. A suitable linker of prior art consists of a repeated G4S amino acid sequence or variants thereof. In some cases, there may also be a disulfide bond between the V_H and V_L of scFv.

As used herein, the term "diabody" refers to a dimer of scFv which consists of V_H and V_L domains connected by a short peptide linker. The linker is too short to form intrachain pairing of V_H and V_L domains. Instead, two such scFv fragments are co-expressed to form multimers by inter-chain pairing (cross-over pairing) of V_H and V_L domains.

Each of the antigen-binding fragments maintains the ability to specifically bind to the same antigen to which the full-length antibody binds, and/or compete with the full-length antibody for specific binding to the antigen. An antigen-binding fragment can be obtained from a given antibody (e.g., an intact antibody provided herein) using conventional techniques known to those skilled in the art (e.g., recombinant DNA techniques or enzymatic or chemical cleavage methods), and can be screened for specificity in the same manner by which intact antibodies are

screened.

As used herein, the term “Fc region” refers to a portion of a heavy chain constant region comprising CH2 and CH3. An Fc region may comprise a hinge, CH2, and CH3. An Fc region may be of any antibody heavy chain constant region isotype discussed herein. An Fc region may be an IgG1, IgG2, IgG3, or IgG4.

As used herein, the term “chimeric antibody” refers to such an antibody wherein a part of its light chain and/or heavy chain is derived from an antibody (which may be originated from a specific species or belongs to a specific antibody type or subtype), and the other part of its light chain and/or heavy chain is derived from another antibody (which may be originated from an identical or different species or belongs to an identical or different antibody type or subtype), provided that the antibody still retains the activity of binding to the antigen of interest. For example, the term “chimeric antibody” may include such an antibody (e.g., a human-camelid chimeric antibody), wherein the heavy chain and light chain variable region of the antibody are from a first antibody (e.g., a camelid antibody), while the heavy chain and light chain constant region of the antibody are from a second antibody (e.g., a human antibody).

As used herein, the term “humanized antibody” refers to a genetically engineered non-human antibody of which the amino acid sequence has been modified to increase its homology to the sequence of a human antibody. Generally, all or part of the CDR regions of a humanized antibody are derived from a non-human antibody (donor antibody), and all or part of the non-CDR regions (e.g., variable region FR and/or constant region) are derived from a human immunoglobulin (receptor antibody). The humanized antibody typically retains the expected properties of the donor antibody, including, but not limited to, the ability of specifically binding to GPRC5D.

As used herein, the term “specifically bind” or “specifically binding” refers to the binding of two molecules in a non-random manner, such as the reaction between an antibody and the antigen it directs to. An antibody that specifically binds to an antigen (or an antibody specific for an antigen) may refer to an antibody that binds to the antigen with an affinity (K_D) of less than about 10^{-5} M, e.g., less than about 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, or 10^{-10} M or less.

As used herein, the term “ K_D ” refers to a dissociation constant of a specific antibody-antigen interaction, which is used to describe the binding affinity of an antibody to an antigen. The smaller the dissociation constant, the more tightly bound the antibody is, and the higher the affinity between antibody and antigen. Generally, an antibody (e.g., the antibody of the disclosure) binds to an antigen (e.g., GPRC5D) with a K_D of less than about 10^{-5} M, e.g., less than about 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, or 10^{-10} M or less, determined by, for example, surface plasmon resonance (SPR) in BIACORE device.

As used herein, the term “vector” refers to a nucleic acid vehicle which can have a polynucleotide inserted therein. When the vector allows for the expression of the protein encoded by the polynucleotide inserted therein, the vector is called an expression vector. The vector can have the carried genetic material elements expressed in a host cell by transformation, transduction, or transfection into the host cell. Vectors are well known by a person skilled in the art, including, but not limited to plasmids, phages, cosmids, artificial chromosome such as yeast artificial chromosome (YAC), bacterial artificial chromosome (BAC) or P1-derived artificial chromosome (PAC); phage such as λ phage or M13 phage and animal virus. The animal viruses that can be used as vectors, include, but are not limited to, retrovirus (including lentivirus), adenovirus, adeno-associated virus, herpes virus (such as herpes simplex virus), pox virus, baculovirus, papillomavirus, papova virus (such as SV40). A vector may comprise multiple elements for controlling expression, including, but not limited to, a promoter sequence, a transcription initiation sequence, an enhancer sequence, a selection element, and a reporter gene. In addition, a vector may comprise origin of replication.

As used herein, the term “host cell” refers to a cell into which a vector can be introduced or transformed, including, but not limited to, prokaryotic cells such as *E. coli* or *Bacillus subtilis*, and eukaryotic cells such as mammal cells (e.g., mouse cell or human cell), insect cells or yeast cells. Suitable eukaryotic cells include, but not limited to, NS0 cells, Vero cells, Hela cells, COS cells, CHO cells, HEK293 cells, BHK cells or MDCKII cells.

As used herein, the term “identity” refers to the match degree between two polypeptides or between two nucleic acids. When two sequences for comparison have the same monomer sub-unit of base or amino acid at a certain site (e.g., each of two DNA molecules has an adenine at a certain site, or each of two polypeptides has a lysine at a certain site), the two molecules are identical at the site. The percent identity between two sequences is a function of the number of identical sites shared by the two sequences over the total number of sites for comparison $\times 100$. For example, if 6 of 10 sites of two sequences are matched, these two sequences have an identity of 60%. For example, DNA sequences: CTGACT and CAGGTT share an identity of 50% (3 of 6 sites are matched). Generally, the comparison of two sequences is conducted in a manner to produce maximum identity. Such alignment can be conducted by using a computer program such as Align program (DNASTar, Inc.) which is based on the method of Needleman, et al. (J. Mol. Biol. 48:443-453, 1970). The percent identity between two amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (Comput. Appl. Biosci., 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percentage of identity between two amino acid sequences can be determined by the algorithm of

Needleman and Wunsch (J. Mol. Biol. 48:444-453 (1970)) which has been incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

5 As used herein, the term "pharmaceutically acceptable carrier and/or excipient" refers to a carrier and/or excipient that is pharmacologically and/or physiologically compatible with a subject and an active ingredient, which includes, but is not limited to: pH adjusting agents, surfactants, adjuvants, ionic strength enhancers, diluents, agents to maintain osmotic pressure, agents to delay absorption, preservatives. For example, pH adjusting agents include, but are not
10 limited to, phosphate buffered saline. Surfactants include, but are not limited to, cationic, anionic or non-ionic surfactants, such as Tween-80. Ionic strength enhancers include, but are not limited to, sodium chloride. Preservatives include, but are not limited to, various antibacterial and antifungal agents, such as parabens, trichloro-t-butanol, phenol, sorbic acid, and the like. Agents to maintain osmotic pressure include, but are not limited to, sugar, NaCl, and the like. Agents to
15 delay absorption include, but are not limited to, monostearate and gelatin. Diluents include, but are not limited to, water, aqueous buffers (e.g., buffered saline), alcohols and polyols (e.g., glycerol), and the like. Stabilizers have the meaning commonly understood by those skilled in the art, which can stabilize the desired activity of active ingredient in drug, including but not limited to sodium glutamate, gelatin, SPGA, saccharides (e.g., sorbitol, mannitol, starch, sucrose,
20 lactose, dextran, or glucose), amino acids (e.g., glutamic acid, glycine), proteins (e.g., dried whey, albumin, or casein) or degradation products thereof (e.g., lactalbumin hydrolysate), etc. The pharmaceutically acceptable carrier or excipient may include a sterile injectable liquid (e.g., an aqueous or non-aqueous suspension or solution). Such sterile injectable liquid may be selected from the group consisting of water for injection (WFI), bacteriostatic water for injection (BWFI),
25 sodium chloride solution (e.g., 0.9% (w/v) NaCl), glucose solution (e.g., 5% glucose), surfactant-containing solution (e.g., 0.01% polysorbate 20), pH buffer solution (e.g., phosphate buffer solution), Ringer's solution, and any combination thereof.

As used herein, the term "treatment/treating" refers to a method that is carried out in order to obtain a beneficial or desired clinical outcome. For the purpose of the disclosure, the
30 beneficial or desired clinical outcome includes, but is not limited to, easing symptom, narrowing the scope of disease, stabilizing (i.e., not aggravating) the state of disease, delaying or slowing the progress of disease, and alleviating symptoms (either partially or completely), no matter detectable or not detectable. In addition, "treatment" also refers to a prolonged survival period compared to the expected survival period (if no treatment is accepted). The beneficial or desired
35 clinical outcome described herein may include, but not limited to, slowing of tumor progression,

cancer regression, enhancement of anti-tumor immune response, a reduction in tumor growth or size, necrosis of the tumor, a decrease in severity of at least one disease symptom, an increase in frequency and duration of disease symptom-free periods, a prevention of impairment or disability due to the disease affliction, or otherwise amelioration of disease symptoms in the patient.

As used herein, the term “subject” refers to any human or non-human animal that receives treatment. The term “non-human animal” includes all vertebrates, e.g., mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, reptiles, etc.

As used herein, the term “an effective amount” refers to an amount that is sufficient to achieve or at least partially achieve the expected effect. For example, an effective amount for treating a disease refers to an amount effective for curing or at least partially blocking a disease and its complication in a patient having the disease. The determination of such an effective amount is within the ability of a person skilled in the art. For example, an amount effective for a therapeutic use depends on severity of a disease to be treated, general state of the immune system in a patient, general conditions of a patient, such as age, weight and gender, administration routes of drugs, additional therapies used simultaneously, and the like.

As used herein, the term “immune cell” includes cells that have a hematopoietic origin and play a role in immune response, for example, lymphocytes, such as B cells and T cells; natural killer (NK) cells; myeloid cells, such as monocytes, macrophages, eosinophils, mast cells, basophils and granulocytes.

As used herein, the term “effector function” refers to those biological activities attributable to the Fc region of an antibody (Fc region of a natural sequence or an amino acid sequence variant), which varies as the isotype of an antibody. Examples of antibody effector functions include, but are not limited to, Fc receptor binding affinity, antibody-dependent cell-mediated cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), downregulation of cell surface receptors (e.g., B cell receptors), B cell activation, cytokine secretion, half-life/clearance of antibodies and antigen-antibody complexes, and the like. Methods for altering the effector function of an antibody are known in the art, for example by introducing a mutation in the Fc region.

As used herein, the term “chimeric antigen receptor” or “CAR” as used herein refers to genetically engineered receptors, which can be used to graft one or more antigen specificity onto immune effector cells, such as T cells. Some CARs are also known as “artificial T-cell receptors,” “chimeric T cell receptors,” or “chimeric immune receptors.” A CAR may comprise an extracellular ligand binding domain or an extracellular antigen binding domain specific for one or more ligands or antigens (such as tumor antigens), a transmembrane domain, and an

intracellular signaling domain. "CAR-T cell" refers to a T cell that expresses a CAR.

As used herein, the terms "cancer" and "tumor" are used interchangeably and refer to a large group of diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division may lead to the formation of malignant tumors or cells that invade adjacent tissues, and may metastasize to distant parts of the body through the lymphatic system or bloodstream. Cancers include benign and malignant cancers as well as dormant tumors or micrometastasis. Cancers also include hematological malignancies.

EXAMPLES

The examples provided below are for purposes of illustration only and are not intended to be limiting unless otherwise specified. Thus, the disclosure should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

EXAMPLE 1 Anti-GPRC5D Antibody Generation

Two camels and two llamas were successively immunized with human GPRC5D antigens in different forms under all current animal welfare regulations. For protein immunization, human GPRC5D protein-VLP (Q9NZD1-1, SEQ ID No: 1, Kactus, Cat. # GPR-HM05P) was formulated as an emulsion with Alhydrogel® adjuvant 2% (InvivoGen, Cat. # vac-alu-250). The antigen emulsion was administered by double-spot subcutaneous injection at the neck. For cell immunization, HEK293/GPRC5D cells (ACRO, Cat. # CHEK-STP042) were administered intramuscularly by double-spot injections at the neck. The animals received 4 emulsion injections containing 100-400 µg of human GPRC5D protein-VLP at 2-week intervals and subsequently 3 injections of 2×10^7 HEK293/GPRC5D cells at weekly intervals. Three days after the terminal immunization, 150 mL blood sample was collected from the immunized animals. About 3×10^8 peripheral blood lymphocytes (PBLs), as the genetic source of heavy chain antibodies, were isolated from the blood.

Total RNA was extracted from lymphocytes of the immunized camel or llama using TRIZOL® Reagent (Invitrogen™, Cat. # 15596026). cDNA was synthesized based on RNA template using PRIMESCRIPT™ 1st Strand cDNA Synthesis Kit with an oligo(dT)20 primer (Takara, Cat. # 6110A). DNAs encoding V_HHs (variable region of heavy chain-only antibody, also known as single domain antibody, sdAb) were amplified from camel or llama cDNA, purified and ligated in an *in house* phagemid vector (see Patent No. US20170089914A1 Fig. 1). The ligation product was used to transform SS320 electrocompetent cells. The sdAb phagemid libraries were supplemented with 20% glycerol and stored at -80°C.

The sdAb phagmid libraries were rescued and the resulting phage libraries were stored after filter sterilization at 4°C for further use. Binders were isolated from phage libraries using protein-based panning as well as cell-based panning. One round of panning was carried out for both protein- and cell-based panning approaches. Percentage of GPRC5D positive clones identified by ELISA reached at least 50% and the sequence diversity of GPRC5D-specific clones was high for all output phages. These outputs were used for subsequent high-throughput screening.

Thousands of colonies from the output phages were picked individually and grown in 96-deep-well plates containing 1.4 mL 2YT medium. The phages displaying sdAb were analyzed for their ability to bind human GPRC5D protein-VLP, mouse GPRC5D protein-VLP (Kactus, Cat. # GPR-MM05P) and human envelop VLP control (ctrl VLP, Kactus, Cat. # VLP-HM00C) by ELISA. The human GPRC5D binders with unique sequences were selected for further characterization. To assess the cross-species reactivity and the specificity of the selected clones, flow cytometry was performed on human MM cell line H929 (American Type Culture Collection (ATCC)[®], Cat. # CRL-3580[™]), HEK293/human GPRC5D stable cells and FreeStyle[™] 293-F cells (Thermo Fisher, Cat. # R79007) with and without transiently expressed cynomolgus GPRC5D (A0A2K5W6I7, SEQ ID NO: 2) and mouse GPRC5D (Q9JIL6-2, SEQ ID NO: 3). The binding activity of selected clones were summarized in Table 1. The IDs of full-length sdAb and CDR sequences were listed in Table 2. The CDRs were defined according to AbM numbering system.

Table 1. Anti-GPRC5D antibodies binding to target proteins and cells

Clone ID	Protein binding by ELISA			Cell binding by flow cytometry				
	human GPRC5D	mouse GPRC5D	ctrl VLP	H929	human GPRC5D	cynomolgus GPRC5D	mouse GPRC5D	FreeStyle [™] 293-F cells
AS300395	+	-	-	N.T.	+	+	-	-
AS300396	+	+	-	N.T.	+	+	+	-
AS300398	+	+	-	N.T.	+	+	+	-
AS300399	+	-	-	N.T.	+	+	+	-
AS300409	+	-	-	N.T.	+	+	-	-
AS300413	+	+	-	N.T.	+	+	+	-
AS300424	+	+	-	N.T.	+	+	+	-
AS300435	+	+	-	N.T.	+	+	+	-
AS300441	+	+	-	N.T.	+	+	+	-
AS300442	+	+	-	N.T.	+	+	+	-
AS300447	+	+	-	N.T.	+	+	+	-
AS300452	+	+	-	N.T.	+	+	+	-
AS300461	+	+	-	N.T.	+	+	+	-
AS300463	+	+	-	N.T.	+	+	+	-
AS300469	+	+	-	N.T.	+	+	+	-
AS300477	+	+	-	N.T.	+	+	+	-

AS300488	+	+	-	N.T.	+	+	+	-
AS300494	+	+	-	N.T.	+	+	+	-
AS300506	+	+	-	N.T.	+	+	+	-
AS300513	+	+	-	N.T.	+	+	+	-
AS300524	+	+	-	N.T.	+	+	+	-
AS300527	+	+	-	N.T.	+	+	+	-
AS300529	+	+	-	N.T.	+	+	+	-
AS300533	+	-	-	N.T.	+	+	+	-
AS300535	+	+	-	N.T.	+	+	+	-
AS300573	+	+	-	N.T.	+	+	+	-
AS300579	+	+	-	N.T.	+	+	+	-
AS300614	+	+	-	N.T.	+	+	+	-
AS300629	+	+	-	N.T.	+	+	+	-
AS300637	+	+	-	N.T.	+	+	+	-
AS302369	+	-	-	+	+	+	-	-
AS302372	+	+	-	+	+	+	+	-
AS302376	+	+	-	+	+	+	+	-
AS302382	+	+	-	+	+	+	+	-
AS302396	+	-	-	+	+	+	+	-
AS302399	+	+	-	+	+	+	+	-
AS302400	+	+	-	+	+	+	+	-
AS302433	+	-	-	+	+	+	+	-
AS302434	+	+	-	+	+	+	+	-
AS302447	+	+	-	+	+	+	+	-
AS302468	+	+	-	+	+	+	+	-
AS302480	+	+	-	+	+	+	+	-
AS302493	+	+	-	+	+	+	+	-
AS302504	+	+	-	+	+	+	+	-
AS302509	+	-	-	+	+	+	+	-
AS302516	+	+	-	+	+	+	+	-
AS302553	+	+	-	+	+	+	+	-
AS302554	+	-	-	+	+	+	-	-
AS302558	+	+	-	+	+	+	+	-
AS302560	+	+	-	+	+	+	+	-
AS302564	+	+	-	+	+	+	+	-
AS302571	+	+	-	+	+	+	+	-
AS302575	+	+	-	+	+	+	+	-
AS302597	+	-	-	+	+	+	-	-
AS302599	+	+	-	+	+	+	+	-
AS302643	+	+	-	+	+	+	+	-
AS302654	+	+	-	+	+	+	+	-
AS302656	+	+	-	+	+	+	+	-
AS302721	+	+	-	+	+	+	+	-
AS302735	+	+	-	+	+	+	+	-
AS307553	+	+	-	+	+	+	+	-
AS307587	+	+	-	+	+	+	+	-
AS307626	+	-	-	+	+	+	+	-
AS307672	+	+	-	+	+	+	+	-
AS307685	+	+	-	+	+	+	+	-
AS307703	+	+	-	+	+	+	+	-

AS307775	+	+	-	+	+	+	+	-
AS307816	+	-	-	+	+	+	+	-
AS307854	+	+	-	+	+	+	+	-
AS307858	+	+	-	+	+	+	+	-
AS307879	+	+	-	+	+	+	+	-
AS307926	+	+	-	+	+	+	+	-
AS307927	+	+	-	+	+	+	+	-
AS307946	+	+	-	+	+	+	+	-
AS307971	+	+	-	+	+	+	+	-
AS308386	+	+	-	+	+	+	+	-
AS308506	+	+	-	+	+	+	+	-
AS310012	+	N.T.	-	+	+	-	+	-
AS310027	+	N.T.	-	+	+	+	-	-
N.T., not tested.								

Table 2. Camelid anti-GPRC5D antibody sequences

Clone ID	Antibody Fragment	Full length	HCDR1	HCDR2	HCDR3	Clone ID	Antibody Fragment	Full length	HCDR1	HCDR2	HCDR3
AS300395	V _H H	4	5	6	7	AS302468	V _H H	163	164	165	166
AS300396	V _H H	8	9	10	11	AS302480	V _H H	167	168	169	170
AS300398	V _H H	12	13	14	15	AS302493	V _H H	171	172	173	174
AS300399	V _H H	16	17	18	19	AS302504	V _H H	175	176	177	178
AS300409	V _H H	20	21	22	23	AS302509	V _H H	179	180	181	182
AS300413	V _H H	24	25	26	27	AS302516	V _H H	183	184	185	186
AS300424	V _H H	28	29	30	31	AS302553	V _H H	187	136	188	189
AS300435	V _H H	32	33	34	35	AS302554	V _H H	190	191	192	138
AS300441	V _H H	36	37	38	39	AS302558	V _H H	193	194	195	196
AS300442	V _H H	40	41	42	43	AS302560	V _H H	197	198	199	200
AS300447	V _H H	44	45	46	47	AS302564	V _H H	201	202	203	204
AS300452	V _H H	48	49	50	51	AS302571	V _H H	205	206	207	208
AS300461	V _H H	52	53	54	55	AS302575	V _H H	209	210	211	212
AS300463	V _H H	56	57	58	59	AS302597	V _H H	213	120	214	215
AS300469	V _H H	60	61	62	63	AS302599	V _H H	216	217	218	219
AS300477	V _H H	64	65	66	67	AS302643	V _H H	220	221	222	223
AS300488	V _H H	68	69	70	71	AS302654	V _H H	224	225	226	227
AS300494	V _H H	72	73	74	75	AS302656	V _H H	228	229	230	231
AS300506	V _H H	76	77	78	79	AS302721	V _H H	232	233	234	235
AS300513	V _H H	80	81	82	83	AS302735	V _H H	236	237	238	239
AS300524	V _H H	84	85	86	87	AS307553	V _H H	240	241	242	243
AS300527	V _H H	88	89	90	91	AS307587	V _H H	244	245	246	247
AS300529	V _H H	92	93	94	95	AS307626	V _H H	248	249	250	251
AS300533	V _H H	96	97	98	99	AS307672	V _H H	252	253	254	255
AS300535	V _H H	100	101	102	103	AS307685	V _H H	256	257	258	259
AS300573	V _H H	104	105	106	107	AS307703	V _H H	260	261	262	263
AS300579	V _H H	108	109	110	111	AS307775	V _H H	264	5	6	265
AS300614	V _H H	112	81	113	114	AS307816	V _H H	266	267	268	269
AS300629	V _H H	115	116	117	118	AS307854	V _H H	270	271	272	273
AS300637	V _H H	119	120	121	122	AS307858	V _H H	274	275	276	277
AS302369	V _H H	123	124	125	126	AS307879	V _H H	278	279	280	281
AS302372	V _H H	127	128	129	130	AS307926	V _H H	282	283	284	285
AS302376	V _H H	131	132	133	134	AS307927	V _H H	286	287	288	289

AS302382	V _H H	135	136	137	138	AS307946	V _H H	290	291	292	293
AS302396	V _H H	139	140	141	142	AS307971	V _H H	294	295	296	297
AS302399	V _H H	143	144	145	146	AS308386	V _H H	298	299	300	301
AS302400	V _H H	147	148	149	150	AS308506	V _H H	302	303	304	305
AS302433	V _H H	151	152	153	154	AS310012	V _H H	306	307	308	309
AS302434	V _H H	155	156	157	158	AS310027	V _H H	310	311	312	313
AS302447	V _H H	159	160	161	162						

EXAMPLE 2 *In Vitro* Efficacy of Anti-GPRC5D Camelid CAR Constructs

Seventy-nine anti-GPRC5D sdAbs identified in Example 1 were used as GPRC5D-binding moieties to construct CARs. The G109 scFv (from patent No. WO2016090312, VH SEQ ID NO: 37, VL SEQ ID NO: 38) used as the GPRC5D-binding moiety to construct a positive control CAR. The sequences of these CARs are, from the N-terminus to the C-terminus, leader sequence (SEQ ID No: 314), myc tag (SEQ ID NO: 315), target binding moiety (*e.g.* anti-GPRC5D sdAb/scFv), CD8 α hinge (SEQ ID NO: 316), CD8 α transmembrane (TM) region (SEQ ID NO: 317), the cytoplasmic portion of the 4-1BB (CD137) molecule (SEQ ID No: 318) and the cytoplasmic portion of the CD3 ζ molecule (SEQ ID NO: 319). These constructs were designated “[GPRC5D-binding moiety]bbz”. The CAR construct using G109 scFv as the target binding moiety was designated G109bbz (SEQ ID NO: 320).

For high-throughput retroviral production, the HEK 293-based packaging cell line, 293Vec-BaEV, that produces retroviral vectors pseudotyped by the baboon envelope protein, was seeded in 24-well plates. 293Vec-BaEV cells were transfected with myc-tagged sinCMV CAR-encoding plasmids designed *in house* and produced by GenScript (Piscataway, NJ), using Lipofectamine 3000 (Thermo Fisher, Cat. # L3000075) in 250 μ L OptiMEM (Gibco, Cat. # 31985-070) (at a DNA: Lipofectamine 3000 ratio of 2:1). Culture medium was changed after 6 hours, and 293Vec-BaEV cells were incubated for 3 days before retroviral supernatant collection. Retrovirus was collected on the day of T cell transduction, by spinning down the packaging cell line plate and collecting the supernatants. Then the retrovirus was applied directly to the pre-activated T cells.

Peripheral blood mononuclear cells (PBMCs, Hemacare) were recovered for one day from frozen vials in TexMACS (Miltenyi, Cat. # 130-097-196) supplemented with 200 IU/mL rhIL-2 (Miltenyi, Cat. # 170-076-147). Human T cells were purified from PBMCs using human CD4 and human CD8 microbeads (Miltenyi, Cat. # 130-045-101, 130-045-201, respectively) on an LS magnetic column (Miltenyi, Cat. # 130-042-401). The purified T cells were subsequently pre-activated for 24 hours with human T Cell TransAct (Miltenyi, Cat. # 130-111-160) in the presence of 200 IU/mL rhIL-2. Then 2.5×10^5 pre-activated T cells (in 250 μ L TexMACS supplemented with 200 IU/mL rhIL-2) were transferred into retronectin-coated 24-well plates

(20 µg/mL) (RetroNectin® GMP grade, Takara, Cat. # T202) and transduced with the 250 µL retroviral supernatant harvested off the 293Vec-BaEV packaging cells. Plates were spun at 1200 x g for 1 hour at 32°C in the presence of 10 µL of 1 M HEPES (Gibco, Cat. # 15630-080). T cells were then cultured for 10 days at 37°C, and medium was refreshed every 2 days with fresh
 5 TexMACS supplemented with 200 IU/mL rhIL-2, keeping T cell concentration around $1-2 \times 10^6$ cells/mL density.

Ten days after transduction, CAR expression on transduced T cells was assessed by flow cytometry following staining with anti-myc antibody (Cell Signaling Technology, Cat. # 2233S). Eleven days after transduction, CAR T cells were co-incubated with H929 cells, a multiple
 10 myeloma cell line with high expression of BCMA and around 70% population expressing GPRC5D, at E:T ratio of 2:1 (*i.e.* 10,000 CAR T cells + 5,000 H929 cells) or E:T ratio 1:1 (*i.e.* 5,000 CAR T cells + 5,000 H929 cells) in 200 µL of 1:1 mixed media (TexMACS + RPMI 1640 (Gibco, Cat. # 11875-093)) supplemented with 10% FBS (Gibco, Cat. # 16140-071) in 96-well plates. Twenty-four hours after co-incubation, supernatants were collected for LDH release
 15 cytotoxicity assays (LDH-Glo™ Cytotoxicity Assay, Promega, Cat. # J2381).

According to the results of target cell specific lysis (*i.e.* cytotoxicity) in Table 3, most of CAR constructs exhibited greater killing efficiency than the benchmark G109bbz CAR T cells (positive control CAR T cells). Those constructs are: AS300398bbz, AS300399bbz, AS300409bbz, AS300413bbz, AS300424bbz, AS300435bbz, AS300442bbz, AS300452bbz,
 20 AS300463bbz, AS300469bbz, AS300477bbz, AS300488bbz, AS300494bbz, AS300506bbz, AS300513bbz, AS300524bbz, AS300527bbz, AS300529bbz, AS300535bbz, AS300573bbz, AS300579bbz, AS300614bbz, AS300629bbz and AS300637bbz.

Table 3. Cytotoxicity of CAR T cells after 24 hours co-culture with H929 tumor cells

Batch 1			Batch 2		
CAR constructs	% Cytotoxicity		CAR constructs	% Cytotoxicity	
	E:T ratio 2:1	E:T ratio 1:1		E:T ratio 2:1	E:T ratio 1:1
AS300395bbz	45.5	16.2	AS300494bbz	55.6	16.8
AS300396bbz	42.9	16.5	AS300506bbz	49.9	31.4
AS300398bbz	49.0	29.2	AS300513bbz	65.0	14.8
AS300399bbz	48.9	37.6	AS300524bbz	71.6	46.1
AS300409bbz	30.8	29.1	AS300527bbz	65.3	49.3
AS300413bbz	39.6	23.2	AS300529bbz	64.7	35.8
AS300424bbz	38.9	22.9	AS300535bbz	68.3	43.7
AS300435bbz	45.8	36.0	AS300573bbz	67.2	43.9
AS300441bbz	43.3	19.8	AS300579bbz	45.8	13.3
AS300442bbz	50.5	22.4	AS300614bbz	51.5	15.8
AS300447bbz	35.0	19.8	AS300629bbz	65.5	45.4
AS300452bbz	39.8	24.2	AS300637bbz	58.5	36.0

AS300461bbz	48.2	16.5	/	/	/
AS300463bbz	43.5	24.1	/	/	/
AS300469bbz	50.3	23.6	/	/	/
AS300477bbz	55.5	38.5	/	/	/
AS300488bbz	60.7	40.8	/	/	/
G109bbz	50.3	20.9	G109bbz	43.3	19.3
Untransduced (UnT)	4.3	0.8	Untransduced (UnT)	-1.1	-3.7

A second group of anti-GPRC5D CAR constructs was tested as described above. CAR T cells were co-cultured with H929 target cells at E:T ratio 2:1 for 24 hours. Then those CAR T cells were rechallenged every 2 days with irradiated H929 target cells until most CAR constructs could no longer kill targets cells. According to the results of target cell specific lysis (i.e. cytotoxicity) in Tables 4, all CAR constructs exhibited greater killing efficiency than the benchmark G109bbz CAR T cells (positive control CAR T cells).

Table 4. Cytotoxicity of CAR T cells after co-culture with H929 tumor cells at E:T ratio 2:1

CAR constructs	Batch 1			
	Cytotoxicity			
	24 hrs	Rechallenge #1	Rechallenge #2	Rechallenge #3
AS302369bbz	38.6	74.6	63.7	31.5
AS302372bbz	69.5	67.7	61.6	29.7
AS302376bbz	50	73.7	53.8	26.1
AS302382bbz	49.7	72.3	61	33.5
AS302396bbz	56	71.8	59.7	26.7
AS302399bbz	52.7	80	66.9	24.4
AS302400bbz	32.5	79.9	69.6	25.1
AS302433bbz	68.6	80.1	59.2	21.5
AS302434bbz	54.2	88.5	60.4	17.1
AS302447bbz	47.7	88.2	66.4	26.1
AS302468bbz	49.2	82.7	62.2	21
AS302480bbz	52.4	93.8	52.9	15.6
AS302493bbz	59	90.9	58.7	21.9
AS302504bbz	49.5	100.9	52.6	15.4
AS302509bbz	97.8	81.3	67.3	19.5
AS302516bbz	71.4	73.5	72	26.8
AS302553bbz	66.5	76.3	63.2	23.6
AS302554bbz	59	85.3	66.8	21.6
AS302558bbz	61.2	80.3	68.7	25.1
AS302560bbz	81.7	75.2	48.8	7.5
AS302564bbz	58.9	85.4	59.5	18.7
AS302571bbz	80.2	83.1	61.8	25.8
AS302575bbz	71.6	84.1	58.4	18.7
AS302597bbz	44.9	88.8	74.9	27.7
AS302599bbz	46.7	92.6	57.8	20.3
AS302643bbz	78.1	112.4	67.5	23.9
AS302654bbz	47.3	103.1	68.6	24.2
AS302656bbz	59.7	108.3	56	20.6

AS302721bbz	81.1	110.7	54.4	17.2
AS302735bbz	45.1	88	64.6	23.8
G109bbz	37.2	38.1	53.1	-1.6
Untransduced (UnT)	-40.1	-22.5	12.7	-18.2
Batch 2				
AS300533bbz	73.9	/	/	/
G109bbz	56.1	/	/	/
Untransduced (UnT)	4.1	/	/	/

A third group of anti-GPRC5D CAR constructs was tested as described above. CAR T cells were co-cultured with H929 target cells at E:T ratio 2:1 for 24 hours. Based on the data in Table 5, 7 constructs (AS307858bbz, AS308386bbz, AS310027bbz, AS307587bbz, AS307685bbz, AS307879bbz and AS307946bbz) showed cytotoxicity comparable to or better than the benchmark G109bbz CAR T cells (positive control CAR T cells) in the first round of tumor cell killing. Those CAR T cells were re-challenged with 5,000 irradiated H929 cells and their cytotoxicity was assessed 24 hours later. All 7 constructs were comparable to or better than G109bbz after one round of rechallenge.

Table 5. Cytotoxicity of CAR T cells after co-culture with H929 tumor cells at E:T ratio 2:1

CAR constructs	Experiment batch	% Cytotoxicity	
		24 hrs	Rechallenge # 1
AS307553bbz	Batch 1	66.4	N.D.
AS307672bbz		68	N.D.
AS307703bbz		68.5	N.D.
AS307775bbz		66.1	N.D.
AS307854bbz		65.3	N.D.
AS307858bbz		76.3	43.9
AS307926bbz		55.7	N.D.
AS307927bbz		63.3	N.D.
AS307971bbz		62.3	N.D.
AS308386bbz		69	41.7
AS308506bbz		46.5	N.D.
AS310012bbz		45.7	N.D.
AS310027bbz		77.5	39.6
G109bbz		75.5	35.9
Untransduced (UnT)		6.4	6.9
AS307587bbz	Batch 2	62.8	16
AS307626bbz		44.7	N.D.
AS307685bbz		74.6	29
AS307816bbz		45.3	N.D.
AS307879bbz		71.6	21.8
AS307946bbz		65.7	17.9
G109bbz		66.7	14.2
Untransduced (UnT)		0.9	0.9

N.D., Not Determined

The 5E11 scFv (VH-(GGGGS)₃-VL, VH SEQ ID NO: 321, VL SEQ ID NO: 322 of the current disclosure, from patent No. WO2019154890A1, VH SEQ ID NO: 19, amino acid 1-117, VL SEQ ID NO: 17, amino acid 1-110) were used as the GPRC5D-binding moiety to construct a positive control CAR as described above. CAR constructs with comparable or better killing activity than G109bbz were further evaluated and compared with Benchmark 5E11.

CAR-T cells were co-cultured with MM.1S (ATCC, Cat. # CRL-2974) cells, a multiple myeloma cell line (which express endogenous GPRC5D), at a 1:1 effector-to-target (E:T) ratio. Cell counting was performed every 2-3 days, and the T cell numbers and CAR-T positive rate in the system were detected using FACS. T cells were re-challenged with MM.1S cells at a 1:1 E:T ratio if T cell frequency was greater than or equal to 80% until the end of experiment. The results (Figure 5A-B) showed that the proliferation and efficacy of all test groups were superior to those of Benchmark 5E11.

CAR-T cells were mixed with MM.1S tumor cells at a 1:2 E:T ratio, and the co-culture supernatant was collected 72 hours after the initial co-culture. IFN- γ production was detected using HTRF Human IFN- γ Detection Kit (Revvity, Cat. # 62HIFNGPEH). The results (Figure 6) showed that the IFN- γ production levels in all test groups were significantly lower than benchmark 5E11, indicating potential safer clinical profiles.

Using the Cell Line Nucleofector™ Kit V (LONZA, Cat. # VCA-1003), high, medium and low levels of GPRC5D mRNA were overexpressed in Raji-luc cells to construct Raji-luc^{GPRC5D (High)}, Raji-luc^{GPRC5D (Medium)}, and Raji-luc^{GPRC5D (Low)}. The GPRC5D logshift is 0.63 in Raji-luc^{GPRC5D (High)} (Figure 7A), 0.38 in Raji-luc^{GPRC5D (Medium)} (Figure 7B), and 0.17 in Raji-luc^{GPRC5D (Low)} (Figure 7C). CAR-T cells were mixed with Raji-luc^{GPRC5D (High)}, Raji-luc^{GPRC5D (Medium)}, and Raji-luc^{GPRC5D (Low)} at E:T ratios of 3:1, 1.5:1 and 0.75:1 for 24 hours. Viability of tumor cells was assessed using the ONE-Glo™ Luciferase Assay System (PROMEGA, Cat. # B6110). The results (Figure 7A-C) indicated that CAR-T cells in the test groups showed stronger efficacy against the Raji-luc cells with varying GPRC5D expression levels at different ratios compared to Benchmark 5E11, indicating a superior sensitivity profile.

EXAMPLE 3 Anti-GPRC5D Antibody Characterization and Epitope Mapping

Of all anti-GPRC5D antibodies, 20 camelid sdAb sequences were fused with human IgG1 hinge and Fc fragment to construct heavy chain only antibodies (HCAbs). VH and VL sequences (VH SEQ ID NO: 321, VL SEQ ID NO: 322 of the current disclosure, from patent No. WO2019154890A1, VH SEQ ID NO: 19, amino acid 1-117, VL SEQ ID NO: 17, amino acid 1-

110) derived from 5E11 were used to construct conventional IgG heavy and light chains. The scFv sequence (SEQ ID NO: 323 of the current disclosure, from patent No. WO2016090312, SEQ ID NO: 109) derived from G109 was fused with human IgG1 hinge and Fc fragment.

Heavy chain, light chain and scFv-Fc plasmids were prepared and used for HCAb, IgG and scFv-Fc production by FreeStyle™ 293-F cells. Antibodies were purified using Protein A Agarose column (Genscript, Cat. # L00464), followed by size-exclusion chromatography (Citiva, Cat. # GE28-9893-35). Two different formats of anti-GPRC5D antibodies 5E11 and G109 were used as positive controls in the following assays.

The binding affinity of selected molecules to human GPRC5D protein (ACRO, Cat. # GPD-H52D3) was determined by surface plasmon resonance (SPR) on a BIAcore T200 instrument (GE Healthcare). The experiment was carried out as follows: Antibodies were captured onto the sensorchip pre-coated with goat-anti-human pAb (Jackson ImmunoResearch, Cat. # 109-005-098) through the interaction between polyclonal antibody and human Fc. Increasing concentrations (ranging from 10 nM to 640 nM) of human GPRC5D were injected over the sensorchip surface, and were allowed to bind the captured antibody for 100 s followed by injection of the running buffer to allow dissociation of the complex for 300 s. After each cycle the surfaces were regenerated by an injection of 10 mM glycine-HCl buffer, pH2.0. Langmuir model, which describes a simple 1:1 interaction where one ligand molecule interacts with one analyte, was used to fit the experimental data to obtain the kinetic values of the on-rate (k_a) and off-rate (k_d), which were used to calculate the equilibrium dissociation constant (K_D). According to the result summarized in Table 6, the antibodies bind human GPRC5D with affinity (K_D) ranging from 220 nM to 23 nM.

Table 6. Binding affinity of purified antibodies to human GPRC5D protein

Antibody ID	Antibody format	k_a (1/Ms)	k_d (1/s)	K_D (M)
AS300399	HCAb	2.6E+04	1.5E-03	5.6E-08
AS300413	HCAb	2.1E+04	1.3E-03	6.2E-08
AS300442	HCAb	2.3E+04	8.8E-04	3.8E-08
AS300452	HCAb	3.7E+04	5.4E-03	1.5E-07
AS300533	HCAb	8.9E+04	1.9E-02	2.2E-07
AS302376	HCAb	3.2E+04	3.6E-03	1.1E-07
AS302399	HCAb	2.8E+04	3.8E-03	1.4E-07
AS302509	HCAb	3.9E+04	4.9E-03	1.2E-07
AS302553	HCAb	3.8E+04	2.7E-03	7.1E-08
AS302558	HCAb	2.4E+04	1.2E-03	5.1E-08
AS302643	HCAb	4.6E+04	3.4E-03	7.5E-08
AS307587	HCAb	1.6E+04	3.3E-03	2.0E-07
AS307685	HCAb	3.0E+04	7.0E-04	2.3E-08
AS307858	HCAb	2.7E+04	1.6E-03	6.1E-08
AS307879	HCAb	2.2E+04	6.1E-04	2.7E-08
AS307946	HCAb	1.9E+04	1.7E-03	9.2E-08

AS308386	HCAb	1.7E+04	2.1E-03	1.2E-07
AS308506	HCAb	5.4E+04	2.7E-03	4.9E-08
AS310012	HCAb	3.5E+04	3.0E-03	8.3E-08
AS310027	HCAb	1.9E+04	3.6E-03	1.9E-07
5E11	IgG	2.1E+04	3.1E-04	1.5E-08
G109	scFv-Fc	Data were not available due to low binding and poor fitting.		

To determine the binding activity of selected molecules to human GPRC5D-expressing cells, HEK293/GPRC5D and H929 cells were incubated with gradient concentrations of 20 HCABs, followed by incubation with an Alexa Fluor 647-fluorescently-labeled goat anti-human IgG secondary antibody (Jackson ImmunoResearch, Cat. # 109-605-098) at 37° C for 30 minutes.

- 5 Samples were analyzed with flow cytometry. Binding activity of anti-GPRC5D antibodies were shown in Figure 1, Figure 2 and Table 7. Most of the selected antibodies have better or comparable binding activities than 5E11 and G109 antibodies, which are reflected by lower EC50 values and higher maximal binding signals (mean fluorescence intensity, MFI) especially on H929 cells.

10 Table 7. Binding activities of purified antibodies to human GPRC5D-expressing cells

Antibody ID	Antibody format	HEK293/human GPRC5D		H929	
		EC50 (nM)	Fitted Maximal MFI	EC50 (nM)	Fitted Maximal MFI
AS300399	HCAb	9.95	746314	0.88	1785
AS300413	HCAb	11.30	677121	6.13	1665
AS300442	HCAb	6.87	504118	0.65	1117
AS300452	HCAb	6.67	292605	0.26	1699
AS300533	HCAb	3.49	212146	1.19	2497
AS302376	HCAb	10.74	578539	0.89	1010
AS302399	HCAb	6.28	588953	0.40	1747
AS302509	HCAb	8.53	557898	0.97	1768
AS302553	HCAb	13.95	682105	0.17	1340
AS302558	HCAb	11.25	541674	2.26	2252
AS302643	HCAb	16.75	693524	1.00	1599
AS307587	HCAb	14.85	399576	95.26	812.6
AS307685	HCAb	7.86	570554	0.59	2400
AS307858	HCAb	10.41	545432	0.75	1219
AS307879	HCAb	13.66	702586	6.23	2139
AS307946	HCAb	13.87	600650	23.19	3560
AS308386	HCAb	7.03	418233	1.31	1107
AS308506	HCAb	7.99	518135	16.19	1328
AS310012	HCAb	8.60	176117	17.52	157.2
AS310027	HCAb	4.97	244783	1.01	757.9
5E11	IgG	8.37	239195	76.46	1201
G109	scFv-Fc	15.79	122379	NA	NA
Isotype ctrl	IgG	NA	44.09	NA	NA
NA, not available due to poor fitting.					

To find the antigen regions/loops that were crucial for antigen-antibody interaction, 4

plasmids encoding chimeric GPRC5D proteins were constructed by replacing each extracellular region/loop of human GPRC5D with their counterparts from GPRC5A or GPRC5B (Figure 3). The plasmids were used to transfect FreeStyle™ 293-F cells. The transfected cells transiently expressed those chimeric GPRC5D proteins (chimeric DB1, chimeric DA2, chimeric DA3, 5 chimeric DB4), and were subsequently subjected to binding of the aforementioned 20 HCABs and control antibodies. Flow cytometry was carried out to determine whether these antibodies bound the wild-type and chimeric antigen-expressing cells. For example, the fact that AS300399 bound both wild-type human GPRC5D and chimeric DB4 cells with high binding signals, but chimeric DA2 and DA3 cells with low or no binding signals, suggests that the epitope of AS300399 is located at the second and third extracellular loops. As shown in Figure 4 and Table 10 8, the epitopes of selected antibodies are largely diversified.

Table 8. Epitope grouping of selected antibodies

Antibody ID	Antibody format	Binding signals with wild-type and chimeric GPRC5D antigen-expressing cells (log shift)						Extracellular region/loop involved in antibody-antigen interaction
		wild-type	chimeric DB1	chimeric DA2	chimeric DA3	chimeric DB4	untransfected cells	
AS300399	HCAb	3.24	2.82	0.20	0.01	2.75	0.07	2, 3
AS300413	HCAb	3.20	2.54	0.04	-0.05	0.04	0.01	2,3,4
AS300442	HCAb	3.38	3.03	1.18	0.00	0.03	0.01	3,4
AS300452	HCAb	3.17	0.14	2.68	0.46	1.99	-0.04	1,3
AS300533	HCAb	3.30	-0.02	2.83	1.77	1.93	0.02	1
AS302376	HCAb	3.38	3.00	1.67	-0.02	3.01	0.00	3
AS302399	HCAb	3.28	2.85	2.31	0.18	0.04	-0.02	3,4
AS302509	HCAb	3.32	2.88	1.69	-0.02	0.00	-0.03	3,4
AS302553	HCAb	3.22	2.96	2.21	0.09	0.15	0.03	3,4
AS302558	HCAb	3.20	2.80	2.56	0.00	0.46	0.01	3,4
AS302643	HCAb	3.21	2.87	2.52	0.54	1.29	-0.01	3
AS307587	HCAb	3.19	1.99	0.05	-0.01	0.06	0.05	2,3,4
AS307685	HCAb	3.39	3.08	1.18	-0.02	2.81	0.07	3
AS307858	HCAb	3.41	2.99	1.24	-0.07	0.24	0.02	3,4
AS307879	HCAb	3.41	2.90	1.21	-0.03	1.43	0.03	3
AS307946	HCAb	3.24	2.76	0.80	-0.03	2.01	0.03	3
AS308386	HCAb	3.33	2.15	0.90	-0.06	0.01	-0.01	3,4
AS308506	HCAb	3.18	0.07	2.26	1.79	1.44	0.00	1
AS310012	HCAb	3.05	0.05	2.38	2.03	2.46	0.02	1
AS310027	HCAb	3.41	0.16	2.48	0.19	0.13	0.03	1,3,4
5E11	IgG	2.82	0.01	2.02	1.85	2.30	0.02	1
G109	scFv-Fc	2.38	0.01	1.36	0.87	1.36	0.04	1
Isotype ctrl	IgG	0.03	0.04	0.03	0.02	0.11	0.06	NA
NA, Not Applicable								

EXAMPLE 4 Humanization of Anti-GPRC5D antibody fragments

Fourteen camelid sdAbs were humanized using CDR grafting technology. The camelid sdAb sequences were BLASTed in NCBI human germline V gene database so the human VH germline sequences with the highest identity to camelid sdAbs were identified. The most appropriate human frameworks on which to build the CDR grafted VH (henceforth called human acceptor) were listed in Table 9.

Table 9. Human acceptors selected for camelid sdAbs

sdAb clone	Human acceptor GenBank accession #
AS300399	AEX29643
AS300413	AEX29643
AS300452	AEX29643
AS302399	ABF83223
AS302509	ABF83223
AS302553	AEX29643
AS302558	AXA20241
AS302643	AEX29643
AS307587	AEX29643
AS307858	AXA20241
AS308386	AXA20241
AS308506	AEX29643
AS310012	AXA20241
AS310027	AEX29643

In CDR grafting approach, CDRs of the human acceptor were replaced by those of the parental sdAb, which made the straight-graft sequence. Straight-graft antibody usually loses binding activity, which can be restored by gradually replacing the framework residues that are critical for the activity of the antibody with camelid residues (*i.e.* back mutation), resulting in humanized sdAbs with varying degrees of humanness (SEQ ID NOs: 328-390).

The camelid and humanized sdAb sequences were fused with human IgG1 hinge and Fc fragment. The DNAs encoding these fusion proteins were synthesized and inserted into pcDNA3.1 vector. Fusion protein expression plasmids were used to transfect HEK293 cells. Crude fusion proteins secreted to the medium were subjected to H929 cell binding assessment by flow cytometry and expression level assessment by SPR.

To evaluate the binding activity of parental and humanized sdAbs, 25-fold, 125-fold and 625-fold dilutions of aforementioned culture medium containing crude fusion proteins were incubated with GPRC5D-expressing H929 cells at 4°C for 30 minutes. Cells were washed 3 times followed by incubation with an Alexa Fluor 647-fluorescently-labeled goat anti-human IgG secondary antibody (Jackson ImmunoResearch, Cat. # 109-605-098) at 4°C for 30 minutes. Cells were washed 3 times and resuspended in DPBS (Servicebio, Cat. # G4200-500ML). Samples were acquired on BD FACSCelesta flow cytometer (BD Biosciences) to determine the

geometric mean fluorescent intensity (MFI) at each antibody concentration. The resulting experimental raw data were analyzed using FlowJo software.

The expression levels of fusion proteins in supernatants were assessed by SPR. Briefly, capturing antibody anti-human Fc pAb (Jackson ImmunoResearch, Cat. # 109-605-098) was immobilized on a Biacore™ CM5 chip to approximately 6,000 RU using EDC-activated amine coupling chemistry. The recombinant fusion proteins were captured for 15 seconds onto the sensorchip surface through the interaction between polyclonal antibody and human Fc. The expression levels of parental and humanized antibodies were reflected by the capture levels of corresponding supernatants. The binding activity and expression level of humanized variants were compared with those of camelid sdAbs (Table 10). Humanized clones retained H929 binding abilities were selected for CAR construction and further characterization.

Table 10. Expression level and H929 cell binding activity of camelid and humanized sdAbs

sdAb clone	SEQ ID NO:	Expression level	H929 cell binding		
		Capture level (RU)	with serial 5-fold dilutions (log shift)		
			25-fold dilution	125-fold dilution	625-fold dilution
AS300399	16	825.80	2.00	1.98	1.63
AS300399VH4	328	877.20	1.63	1.46	0.98
AS300399VH5	329	925.90	1.62	1.39	1.16
AS300399VH6	330	852.30	1.87	1.78	1.37
AS300399VH7	331	796.00	1.89	1.81	1.44
AS300399VH8	332	944.90	1.91	1.90	1.52
AS300399VH9	333	768.00	1.96	1.85	1.49
AS300413	24	457.00	1.08	0.70	0.32
AS300413VH4	334	618.40	1.29	1.02	0.55
AS300413VH5	335	632.20	1.26	0.97	0.53
AS300413VH6	336	633.40	1.26	0.96	0.56
AS300413VH7	337	555.40	1.28	1.01	0.57
AS300452	48	1255.70	2.20	2.33	1.98
AS300452VH4	338	36.40	2.20	2.08	1.44
AS300452VH5	339	66.80	2.11	1.84	1.17
AS300452VH6	340	27.80	2.15	1.99	1.32
AS300452VH7	341	1102.50	2.13	2.01	1.40
AS300452VH8	342	1148.40	2.14	2.04	1.40
AS302399	143	1193.90	1.65	1.62	1.47
AS302399VH4	343	301.40	1.57	1.23	0.55
AS302399VH5	344	219.60	1.53	1.16	0.50
AS302399VH6	345	400.40	1.55	1.20	0.58
AS302399VH7	346	1057.80	1.60	1.52	1.30
AS302509	179	731.30	1.57	1.39	0.89
AS302509VH4	347	497.10	1.50	1.20	0.53
AS302509VH5	348	422.00	1.51	1.13	0.44

AS302509VH6	349	283.00	1.42	0.98	0.31
AS302553	187	1340.90	1.68	1.65	1.58
AS302553VH4	350	1049.20	1.48	1.39	0.91
AS302553VH5	351	975.60	1.51	1.39	0.85
AS302553VH6	352	1014.50	1.52	1.43	1.17
AS302558	193	1077.40	1.57	1.51	1.19
AS302558VH4	353	786.20	0.80	0.63	0.07
AS302558VH5	354	749.60	0.80	0.56	-0.01
AS302558VH6	355	821.20	0.85	0.74	0.24
AS302558VH7	356	737.10	0.74	0.56	0.04
AS302558VH8	357	693.10	0.73	0.50	-0.10
AS302558VH9	358	741.70	0.81	0.68	0.09
AS302643	220	1341.10	2.28	2.34	2.02
AS302643VH8	359	1196.00	1.80	1.69	1.22
AS302643VH9	360	1192.50	1.78	1.60	1.08
AS302643VH10	361	1208.70	1.77	1.65	1.20
AS302643VH11	362	1111.90	1.79	1.52	0.97
AS302643VH12	363	1335.20	1.74	1.59	1.19
AS307587	244	1110.00	1.83	1.35	0.62
AS307587VH4	364	1283.60	1.75	1.27	0.65
AS307587VH5	365	1094.40	1.92	1.30	0.49
AS307587VH6	366	1050.90	2.01	1.58	0.70
AS307587VH7	367	1007.50	1.89	1.37	0.60
AS307858	274	449.30	2.06	1.66	1.02
AS307858VH4	368	554.80	2.04	1.78	1.18
AS307858VH5	369	535.50	2.09	1.74	1.09
AS307858VH6	370	504.90	2.06	1.71	1.11
AS307858VH7	371	480.10	2.01	1.68	1.08
AS308386	298	830.20	1.86	1.89	1.54
AS308386VH4	372	780.40	0.80	0.53	0.22
AS308386VH5	373	805.90	1.23	0.94	0.39
AS308386VH6	374	707.50	1.25	0.90	0.42
AS308386VH7	375	719.00	1.21	0.94	0.46
AS308386VH8	376	819.00	1.81	1.69	1.32
AS308506	302	963.70	1.80	1.61	1.00
AS308506VH4	377	1168.40	1.79	1.66	1.09
AS308506VH5	378	1029.20	1.76	1.49	0.84
AS308506VH6	379	893.70	1.70	1.42	0.77
AS310012	306	1185.00	0.77	1.04	0.17
AS310012VH4	380	1398.10	0.94	0.55	0.12
AS310012VH5	381	1355.30	1.05	0.57	0.16
AS310012VH6	382	1271.80	1.05	0.63	0.18
AS310012VH7	383	1254.40	1.05	0.61	0.19
AS310012VH8	384	1152.90	0.65	0.37	0.10
AS310027	310	409.40	2.00	1.61	0.90
AS310027VH4	385	550.40	1.82	1.51	1.06
AS310027VH5	386	607.90	1.82	1.48	0.90
AS310027VH6	387	526.80	1.77	1.41	0.83
AS310027VH7	388	493.70	1.83	1.41	0.84

AS310027VH8	389	532.70	1.96	1.80	1.15
AS310027VH9	390	459.60	2.05	1.77	1.04
Bold , camelid sdAb					

EXAMPLE 5 *In Vitro* Cytotoxicity of Humanized Anti-GPRC5D CAR Constructs

CAR constructs using humanized variants as the target binding moiety were synthesized and inserted into *in house* lentiviral transfer plasmid. The CAR-encoding transfer plasmid was mixed with lentivirus packaging plasmids including pMDLg/PRE, PRSV-REV, psPAX2 and pMD2.G (Addgene, Cat. # 12259) at approximately equal molar ratio. The plasmid mixture was then mixed with polyethylenimine (PEI) at plasmids: PEI ratio of 1:3. HEK293 cells were transfected with the mixture and were cultured for 48 hours. The culture supernatant was collected and centrifuged to remove cell debris. The supernatant was concentrated with Polyethylene Glycol (PEG)-6K. The viral particles were resuspended, then aliquoted and stored at -80°C immediately. The virus titer was determined by measuring CHO cell line transduction efficiency by a flow cytometric assay.

T lymphocytes were activated for 24 hours and then transduced with aforementioned lentiviral vectors. Seven days after transduction, CAR T cells were harvested and used for *in vitro* function evaluation.

CAR T cells were mixed at 4 different E:T ratios of 10:1, 5:1, 2.5:1 and 1:1 with H929-Luc (with luciferase marker) cells and incubated in Corning® 96-well solid white plate overnight. ONE-Glo™ Luciferase Assay System (PROMEGA, Cat. # B6110) was used to measure luciferase activity. Fifty µL ONE-Glo™ Reagent was added to each well of the 96-well plate, incubated, then placed onto Spark™ 10M multimode microplate reader (TECAN) for fluorescence measurements, which reflected the cytotoxicity of different CAR constructs on target cells.

The cytotoxicity of CAR T cells using camelid sdAbs as GPRC5D binding moieties (Table 11, bold) and their humanized counterparts were compared. All constructs appeared to have at least one humanized variant with similar or better functional activity (Table 11, *Italic*), suggesting that the humanization was successfully carried out.

Table 11. Cytotoxicity of CAR T cells after co-culture with H929-Luc at different E:T ratios

CAR construct	% Cytotoxicity			
	E:T = 10:1	E:T = 5:1	E:T = 2.5:1	E:T = 1:1
AS300399bbz	88±2.8	63.1±6.6	24.6±4.6	N.D.
<i>AS300399VH7bbz</i>	72.2±1.3	N.D.	N.D.	71.4±3.9
AS300413bbz	87.3±1.6	62±1.6	23.1±3.1	N.D.
<i>AS300413VH4bbz</i>	88.8±2.1	66.2±1.8	17.6±2.9	N.D.
<i>AS300413VH5bbz</i>	87.8±1.7	64.9±2.4	27.9±5.3	N.D.
<i>AS300413VH6bbz</i>	81.7±2.9	58.2±0.6	23.3±0.8	N.D.

<i>AS300413VH7bbz</i>	90±1	70.9±5.1	32.7±6.3	N.D.
AS300452bbz	47.5±9.9	N.D.	N.D.	N.D.
<i>AS300452VH4bbz</i>	61.5±2.0	N.D.	N.D.	N.D.
<i>AS300452VH5bbz</i>	57.0±3.0	N.D.	N.D.	N.D.
<i>AS300452VH6bbz</i>	45.3±3.0	N.D.	N.D.	N.D.
<i>AS300452VH7bbz</i>	31.6±2.2	N.D.	N.D.	N.D.
<i>AS300452VH8bbz</i>	34.1±2.5	N.D.	N.D.	N.D.
AS302399bbz	86.4±1	82.3±3.6	83±9.5	N.D.
<i>AS302399VH4bbz</i>	89.8±0.7	86.5±0.4	83.7±4.3	83.9±2.4
<i>AS302399VH5bbz</i>	91.2±1.8	85.3±3.9	81.3±4.9	N.D.
<i>AS302399VH6bbz</i>	92.2±5.5	84.9±0.6	76.9±3.9	N.D.
<i>AS302399VH7bbz</i>	86.2±1	74.2±0.9	68.8±5.2	N.D.
AS302509bbz	61.6±2	46.8±14	39.6±17.9	N.D.
<i>AS302509VH4bbz</i>	74.2±3.3	53.4±4.7	41.1±5.8	N.D.
<i>AS302509VH5bbz</i>	75.3±6.1	56.2±6.7	30.2±24.2	N.D.
<i>AS302509VH6bbz</i>	77.8±7.1	43.7±8.3	41.2±14.1	N.D.
AS302553bbz	77.8±5.6	56.2±14.8	22±16.5	N.D.
<i>AS302553VH4bbz</i>	43.7±7.6	28±15.6	3.3±20	N.D.
<i>AS302553VH5bbz</i>	67.8±4.5	52±8.8	39.5±5.5	N.D.
<i>AS302553VH6bbz</i>	32.7±20.7	20.7±4.3	20.8±10.8	N.D.
AS302558bbz	27±25.5	N.D.	27 ± 20.4	N.D.
<i>AS302558VH4bbz</i>	37±22.9	N.D.	18 ± 24	N.D.
<i>AS302558VH5bbz</i>	75±7.9	43.3±12.1	54.7 ± 24.8	N.D.
<i>AS302558VH6bbz</i>	69±8.9	30±18.5	65±8.7	N.D.
<i>AS302558VH7bbz</i>	60.7±22.5	42.3±2.5	60±6.6	N.D.
<i>AS302558VH8bbz</i>	66.3±8.1	42.7±11	33.7±9.1	N.D.
<i>AS302558VH9bbz</i>	72.7±8.7	43.3±10.3	24.7±17	N.D.
AS308506bbz	73±3.5	17.7±3.2	9±12.5	N.D.
<i>AS308506VH4bbz</i>	73.7±3.2	27±4.4	16±11.8	N.D.
<i>AS308506VH5bbz</i>	69±8.2	30.7±6.7	20.3±11.9	N.D.
<i>AS308506VH6bbz</i>	63.3±5.9	28.7±1.2	18±10.8	N.D.
AS310012bbz	41.7±6.7	N.D.	N.D.	N.D.
<i>AS310012VH4bbz</i>	22.3±7.6	N.D.	N.D.	N.D.
<i>AS310012VH5bbz</i>	26.7±4.2	N.D.	N.D.	N.D.
<i>AS310012VH6bbz</i>	41.7±4.6	N.D.	N.D.	N.D.
<i>AS310012VH7bbz</i>	47.3±1.5	N.D.	N.D.	N.D.
<i>AS310012VH8bbz</i>	17.3±3.2	N.D.	N.D.	N.D.
N.D., not determined; Bold , CAR construct using camelid sdAb as GPRC5D binding moiety; <i>Italic</i> , CAR construct using humanized variants as GPRC5D binding moiety with functional activity comparable or better than that of camelid counterpart.				

The cytotoxicity of seven CAR constructs using humanized GPRC5D binding moieties was further tested on MM.1S-Luc cells (with luciferase marker). CAR-T cells were co-incubated with MM.1S-Luc cells, at a 1:2 E:T ratio for 20-24 hours. To assay the cytotoxicity of CAR-T cells on tumor cells, ONE-Glo™ Luciferase Assay System (PROMEGA, Cat. # B6120) were prepared according to manufacturer's protocol and added to the co-cultured cells to detect the remaining luciferase activity in the wells. The remaining luciferase activity directly correlated to

the number of viable target cells in the well. Specific cytotoxicity was calculated using the formula: $\text{Specific Cytotoxicity}\% = 100\% \times (1 - (\text{RLU}_{\text{sample}} - \text{RLU}_{\text{min}}) / (\text{RLU}_{\text{UnT}} - \text{RLU}_{\text{min}}))$. $\text{RLU}_{\text{sample}}$ represents the luciferase activity as measured in the well with CAR-T cells transduced with GPRC5D CAR of the disclosure. RLU_{min} refers to the luciferase activity determined in the well added with Triton X-100 at a final concentration of 1% at the start of the cytotoxicity assay, and RLU_{UnT} refers to the luciferase activity determined in the well with untransduced T cells.

As shown in FIG.8, all monospecific GPRC5D CAR-T cells showed potent killing effects to MM.1S-Luc cells.

10 **EXAMPLE 6 Real-time cellular analysis (RTCA) assay**

The real-time cytotoxicity potency of GPRC5D CAR-T cells co-cultured with tumor cells expressing low levels of GPRC5D (Hep3B2.1-7-5D, Hep3B2.1-7(ATCC, Cat. #HB-8064) cells were transduced with lentivirus containing GPRC5D) was measured using the RTCA assay. Tumor cells with low GPRC5D expression (6×10^3 cells/well) were seeded in 96-well E-plates and monitored overnight using an RTCA analyzer. The target cells were then incubated with GPRC5D CAR-T or UnT cells at an E:T ratio of 1:1, respectively, during which cytotoxicity potency of T cells was detected in real time. The cell index, which indicates the activity, adhesion, and number of the target cells, was normalized (Normalized cell index, $\text{NCI} = \text{real-time cell index} / \text{cell index at a time point before adding effector cells}$). Specific cytotoxicity was calculated using the formula: $\text{Specific Cytotoxicity}\% = 100\% \times (1 - \text{NCI}_{\text{sample}} / \text{NCI}_{\text{UnT}})$.

As shown in FIG 9, the cell index of tumor cells with low GPRC5D expression co-cultured with UnT cells increased over time, with a normalized cell index of 1.32 after 90 hours of incubation and at the end of the experiment. The monospecific GPRC5D CAR-T cells showed cytotoxicity on tumor cells with low GPRC5D expression at different extents with the extension of time. At the end of the experiment, the specific cytotoxicity of monospecific GPRC5D CAR-T cells were greater than 90%. After 90 hours of co-culture, the normalized cell indexes of monospecific GPRC5D CAR-T cells were 0.12 (AS300399VH7bbz), 0.11 (AS302399VH4bbz), 0.06 (AS302553VH5bbz), and 0.05 (AS302558VH5bbz). The specific cytotoxicity of monospecific GPRC5D CAR-T cells were 90.74% (AS300399VH7bbz), 91.32% (AS302399VH4bbz), 95.40% (AS302553VH5bbz), and 96.55% (AS302558VH5bbz), respectively.

SEQUENCES

SEQ ID NO.	Description	Sequence
1	human GPRC5D	MYKDCIESTGDYFLLCDAEGPWGIIIESLAILGIVVTILLLLAFLFLMRKIQDCSQWNVLPQTQLLFLLSVLGLFGLAFIIELNQQTAPVRYFLFGVLFALCFSCLLAHAS

		NLVKLVRGCVSFSWTTILCIAIGCSLLQIIATEYVTLIMTRGMMFVNMTPCQLNV DFVVLVYVFLMALTFVSKATFCGPCENWKQHGRILFITVLFSSIIWVWVISM LLRGNPQFQRQPQWDDPVVCIALVTNAWVFLLYIVPELCILYRSCRQECPLQG NACPVTAHQHSFQVENQELSRARDSGAEEDVALTSYGTPIQPQTVDPTQECFIP QAKLSPOQDAGGV
2	cynomolgus GPRC5D	MYKDCIESTGDYFLPCDSEGPWGIVLESAILGIVVTILLLLAFLFLMRKIQDCSQ WNVLPQTQLFLLSVLGLFGLAFIIFQLNQQTAPVRYFLFGVLFALCFSCLLAHA SNLVKLVRGRVSFSWTTILCIAIGCSLLQVIIAIEYVTLIMTRGMMFVHMTPTYQLN VDFVVLVYVFLMALTFVSKATFCGPCENWKQHGRILFITVLFSSIIWVWVISM MLRGNPQFQRQPQWDDPVVCIALVTNAWVFLLYIVPELCILYRSCRQECPSQ GHACPVTAHQHSFQVENQELSRDC
3	mouse GPRC5D	MYEDCVKSTEDYYLFCDNEGPWAIVLESIAVIGIVVTILLLLAFLFLMRKVQDCS QWNVLPQTQLFLLAVLGLFGLTFIIFQLNHQTAPVRYFLFGVLFALCFSCLLAHA SNLVKLVRGRVSFCWTTILFIAIGVSLQIIAIEYVTLIMTRGLMFEHMTPTYQLN VDFVCLLYVFLMALTFVSKATFCGPCENWKQHGRILFITVLFSSIIWVWVISM MLRGNPQLQRQPHWDDAVICIGLVTNAWVFLLYIIPELSILYRSCRQECPTQG NVCQVPVYQRSFRMDTQEPTEC
4	AS300395	QVQLVESGGGSVQAGGSLRLSCVASGYTGSRNMSGWFRQAPGKEREAVARIWS RLDNTDYADSVKGRFTISRDNKNTVYLMNSLKPEDTAMYYCALDPYRLGLD ASEYTYWGQGTQVTVSS
5	AS300395/AS3077 75CDR1	GYTGSRNMSG
6	AS300395/AS3077 75CDR2	RIWSRLDNTD
7	AS300395CDR3	DPYRLGLDASEYTY
8	AS300396	QVRLVESGGGSVQAGGSLRLSCAASGYISRYCMAWFRQAPGKEREVATISS AGMTSYADSVKGRFTISKDNKNTLYLEMNGLKPEDTAMYYCAADSDFRCAR NVNDYWGQGTQVTVSS
9	AS300396CDR1	GYISRYCMA
10	AS300396CDR2	TISSAGMTS
11	AS300396CDR3	DSDFRCARNVNDY
12	AS300398	QVHLVESGGGSVQAGGSLRLSCAASGNTASILYMAWFRQAPGKEREGVADIAT SGGGTFYADSVKGRFTISADNAKNTVYLMNSLRPDSAMYYCAARGGRLGLG YWGGYRYWGQGTQVTVSS
13	AS300398CDR1	GNTASILYMA
14	AS300398CDR2	DIATSGGGTF
15	AS300398CDR3	RGRLGLGYWGGYRY
16	AS300399	QVHLVESGGGSVEAGGSLRLSCAASGYTVSNHCMAWFRQAPGKEREWVASIGT DGILSYADSVKGRFTISKDNKNTLYLQMSLKPADTAMYYCAAVFTWWDWDR SCRRGAGMDYWGRGTLVTISS
17	AS300399CDR1	GYTVSNHCMA
18	AS300399CDR2	SIGTDGILS
19	AS300399CDR3	VERTWWDWDRSCRRGAGMDY
20	AS300409	QVQLKESGGGSVQTGGSLRLSCAASSVAFGRITLAWFRQAPGKQREGVAIYT GSSITSYADSAKGRFTISQDNKNTVYLMNSLKPEDTGMYYCAARLGRTRLAP SDYNYWGQGTQVTVSS
21	AS300409CDR1	SVAFGRTTLA
22	AS300409CDR2	AIYTGSSITS
23	AS300409CDR3	RLGRTRLAPSDYNY
24	AS300413	QVQLEESGGGSVQAGGSLKLSCAASGIIFSNCGLAWYRQAPGKERELVSSISRRG TTIYADSVKGRATISRDNKNTMYLQMNNLADEDTAVYSCCTTEPQLGLCARDW GQGTQVTVSS
25	AS300413CDR1	GIIFSNCGLA
26	AS300413CDR2	SISRRGTI
27	AS300413CDR3	EPQLGLCARD
28	AS300424	QVQLAESGGDSVQAGGSLRLSCAASGYTSSGNMAWFRQAPGKEREGVAVISV LGSTQYADSVKGRFTISQDNKNTVYLMNSLKPEDTAMYYCALKRRLGISLSS RAFDWGRGTQVTVSS
29	AS300424CDR1	GYTSSGNMA
30	AS300424CDR2	VISVLGSTQ
31	AS300424CDR3	KRRLGISLSSRAFDS

32	AS300435	QVHLVESGGGSVQAGGSLRLSCAISDY TARAGCIGWFRQPPGKEREWVARIARG SGTTYADSVKGRFTISQDNTKTTVYLQMDSLKPEDTAMYYCAAQGDRLCARN AYSYWGQGTQVTVSS
33	AS300435CDR1	DYTARAGCIG
34	AS300435CDR2	RIARGSGTTY
35	AS300435CDR3	QGDRLCARNAYS
36	AS300441	QVRLVESGGGSVQAGGSLRLSCDASGFQHS SCAGWFRQSPGKQREGVAAIYA RRGSTYYADSVNGRFTVSRD NAKNTVYLQIDSLKPEDTAMYYCAAKIFRGCGP DTWYG YDVWGQGTQVTVSS
37	AS300441CDR1	GFQHS SCAG
38	AS300441CDR2	AIYARRGSTY
39	AS300441CDR3	KIFRGCGPDTWYG YDV
40	AS300442	QVHLVESGGGSVQAGGSLRLSCAVSGFSLNWRRYCMRWFRQAPGQEREELAT RGIDGSTRYDDSVKGRFSISVDYEKNTLYLQMNSLKPEDTAMYYCAADYFCNV RTRYWGQGTQVTVSS
41	AS300442CDR1	GFSLNWRRYCMR
42	AS300442CDR2	TRGIDGSTR
43	AS300442CDR3	DYFCNV RTRY
44	AS300447	QVHLVESGGGSVQAGGSLRLSCAISGYTFSGVCMGWVRQAPGKELEKVATSTS GGATWYPDSVEGRFTISKGD TENILYLQMDSLKPEDTGIIYCSVWRRPHCTGTK GYYWGQGTQVTVSS
45	AS300447CDR1	GYTFSGVCMG
46	AS300447CDR2	TSTSGGATW
47	AS300447CDR3	WRRPHCTGTKGYY
48	AS300452	QVKLVESGGGSVQAGGSLRLSCAASGYCMGWFRQVPGKEREGVAYIDSGST LYASSVKGRFSISKDNANTLYLQMNSLKPEDTAMYYCAADLSYLRCP RARGG MYYGFPYWGQGTQVTVSS
49	AS300452CDR1	GYYCMG
50	AS300452CDR2	YIDSGSTL
51	AS300452CDR3	DLSYLRCP RARGGMYYGFPY
52	AS300461	QVQLEESGGGSVQAGGSLRLSCAASGYTSSSACTGWFRSPGKEREA VASISTG GSLTYAASVKGRFTISQDNANTVYLQMNSLKPEDTAMYYCAASRDRLCSYF SRYVYWGHTQVTVSS
53	AS300461CDR1	GYTSSSACTG
54	AS300461CDR2	SISTGGSLTY
55	AS300461CDR3	SRDLRCSYFSRYVY
56	AS300463	QVQLKESGGGSVQTGGSLRLSCAASRIA FGR TTLAWFRQAPGKQREGVAAIYTG SRATSYADSAKGRFTISQDNANTVYLQMNSLKPEDTGMYICAARLG TTRLAP SDYNYWGQGTQVTVSS
57	AS300463CDR1	RIA FGR TTLA
58	AS300463CDR2	AIYTGSRATS
59	AS300463CDR3	RLG TTRLAPSDYNY
60	AS300469	EVQLVESGGGSVQAGGSLRLSCAASGYASSNMYMGWFRQVPGKEREGVAVVT PTFGNTAYADSVKGRFTASRD NAKNVVYLQMNSLKPEDSAMYCAAKTRLGV TLSPGVYKYWGQGTQVTVSS
61	AS300469CDR1	GYASSNMYMG
62	AS300469CDR2	VVTPTFGNTA
63	AS300469CDR3	KTRLGVTLSPGVYKY
64	AS300477	QVQLKESGGGSVQAGGSLRLSCVASTYPVTRGYCLGWFRQAPGKEREGVARIT TFTLD TYHDSVKGRFTISRDN AKRTVDLQMNSLKPEDTAMYYCAADRCTAVA AARPQNWGQGTQVTVSS
65	AS300477CDR1	TYPVTRGYCLG
66	AS300477CDR2	RITTF LDTY
67	AS300477CDR3	DRCTAVAAARPQN
68	AS300488	QVKLVESGGGSVQAGGSLRLSCAYSGITYSRYLLGWFRQAPGKEREGVAAISVG RTNYAESVKGRFTISQDNASTIYLQMNNLKPEDTAVVYCAAGLLRLTSWDNL LGGSYNYWGQGTQVTVSS

69	AS300488CDR1	GITYSRYLLG
70	AS300488CDR2	AISVGRTN
71	AS300488CDR3	GLLRLTSWDNLLGGSYNY
72	AS300494	EVQLVESGGGLVQAGESLR LSCAASGIMFSINVMGWYRQAPGKQRELVA AFTD GGSANYADSVKGRFTISRDN AKNTVSLQMNSLKPEDTAVYYC NARLYGRMRW GQGTQVTVSS
73	AS300494CDR1	GIMFSINVMG
74	AS300494CDR2	AFTDGGSAN
75	AS300494CDR3	RLYGRMR
76	AS300506	AVQLVESGGGLVQPGGSLRLSCAASGIVLSTMGWYRQAPGKQRELVA TITYGG STS YTDSVNGRFTISR ENAKNTVYLQMNSLKPEDTAVYYCYA VRQRTYWGQGT QVTVSS
77	AS300506CDR1	GIVLSTMG
78	AS300506CDR2	TITYGGSTS
79	AS300506CDR3	VRQRTY
80	AS300513	EVQLVESGGGLVQPGGSLRLSCAASGIHFSRNKMAWYRQAPGKQRELVA AITSG GSTNYADSVKGRFTISRDN AHNTMYLQMNSLKPEDTAVYYC NADSRPYSIRGG LYWGQGTQVTVSS
81	AS300513/AS3006 14CDR1	GIHFSRNKMA
82	AS300513CDR2	AITSGGSTN
83	AS300513CDR3	DSRPYSIRGGLY
84	AS300524	AVQLVESGGGLVQAGGSLRLSCATSGIHFSNYAMGWYRRAPGKQRELVA TITRR GSTNYADSVKGRFTISRDN AKNTVYLQMNSLKPEDTAVYYC NADPYKLWGE G YWGQGTQVTVSS
85	AS300524CDR1	GIHFSNYAMG
86	AS300524CDR2	TITRRGSTN
87	AS300524CDR3	DPYKLWGE GY
88	AS300527	DVQLVESGGGLVQPGGSLRLSCAASGIISAYVMGWYRQAPGKQREMVA ISIG SNTNYADSVKGRFTISRDN AKNTVYLQMNSLKPEDTAVYYC TARRTNNYWGQ GTQVTVSS
89	AS300527CDR1	GIISAYVMG
90	AS300527CDR2	ISISGSNTN
91	AS300527CDR3	RRTNNY
92	AS300529	QVQLVESGGGLVQAGGSLRLSCAASGILSSAYAMGWYRQAPGNQREWVA SITG GSTNYADSVKGRFTISRDN ARNTVYLQMNLKPEDTAVYYC NARRSSNFWGQ GTQVTVSS
93	AS300529CDR1	GILSSAYAMG
94	AS300529CDR2	SITGGSTN
95	AS300529CDR3	RRSSNF
96	AS300533	AVQLVESGGGLVQAGGSLRLSCAASGGSVSINAMGWYRQASGKQRELVA GISS GGSTNYADSVKGRFTISR EYGLNTYLQMNSLKPEDTAVYYC NLGGKQGRSFE VWGQGT LVTVSS
97	AS300533CDR1	GGSVSINAMG
98	AS300533CDR2	GISSGGSTN
99	AS300533CDR3	GGKQGRSFEV
100	AS300535	AVQLVESGGGLVQAGGSLRLSCAVSGIIGYVMGWYRQAPGKQRELVA AITSGG SPTYADSVKGRFTISRDN AKNMGYLQMNSLKFEDTAVYFCNVRRTDYWGQG TQVTVSS
101	AS300535CDR1	GIIGYVMG
102	AS300535CDR2	AITSGGSPT
103	AS300535CDR3	RRTRDY
104	AS300573	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWMYWVRQAPGKALEWVSLIN GRGVLTNYADSVKGRFTI ARDN AKNTLYLQMDSLKSEDAMYCAKDPKGNI ARMRSLTDFGSWGQGTQVTVSS
105	AS300573CDR1	GFTFSNYWMY
106	AS300573CDR2	LINGRGVLTN

107	AS300573CDR3	DPKGNIARMRSLTDFGS
108	AS300579	DVQLVESGGGLVQAGGSLRLSCVASGIMFGSNDMGWYRQAPGKQRELVAITISGGRTNYADSAKDRFTISRDNAKTTVYLQMNSLKPEDTAVYYCKAERRGIRIYMYWGQGTQVTVSS
109	AS300579CDR1	GIMFGSNDMG
110	AS300579CDR2	TITSGGRTN
111	AS300579CDR3	ERRGIRIYMY
112	AS300614	AVQLVESGGGLVQPGGSLRLSCAVSGIIFSRNKMAWYRQAPGKQRELVAALASGGITNYADSVKGRFTISRDIHNTVYLSMTSLKPEDTAVYYCNADSKPYSIRGNLYWGQGIQVTVSS
113	AS300614CDR2	ALASGGITN
114	AS300614CDR3	DSKPYSIRGNLY
115	AS300629	QVQLVESGGGLVQPGGSLRLSCVASRIMFGIHDMGWYRQAPGNQRELVASITSGRTNYADSVKGRFTISRDNAKQTVSLQMNSLKPEDTARYHCNARSPRSLLYWGQGTQVTVSS
116	AS300629CDR1	RIMFGIHDMG
117	AS300629CDR2	SITSGGRTN
118	AS300629CDR3	RSPRSLLY
119	AS300637	EVQLVESGGGLVQAGGSLRLSCAASGIIFGSSTMGWYRQVPGKQRELVAITITFNGGTNYADSVRGRFTISRDNAKNTVYLQMNSLEPEDTAVYYCNAFRRINYYWGKGLVTVSS
120	AS300637/AS302597CDR1	GIIFGSSTMG
121	AS300637CDR2	TITFNGGTN
122	AS300637CDR3	FRRINYY
123	AS302369	QVHLVESGGGSVQAGGSLRLSCAASGITISSRCMGWFRQAPGKERERVAHIYTG DGTYYADSVKGRFTISQDNAKNTVYLQMDSLKPGDTAMYFCAAQYRRFLSTCQNDNYWGQGTQVTVSS
124	AS302369CDR1	GITISSRCMG
125	AS302369CDR2	HIYTG DGTYY
126	AS302369CDR3	QYRRFLSTCQNDNY
127	AS302372	QVQLVESGGGSVQAGGSLRLSCAASGFTYSSYSMAWFRQAPGKEREGVAGVYTLGLSTYYADSVKGRFTISHDNAKKTLYLQMNSLKPDDTAMYYCAQARGVSWDLRLNEYNYWGQGTQVTVSS
128	AS302372CDR1	GFTYSSYSMA
129	AS302372CDR2	GVYTLGLSTY
130	AS302372CDR3	ARGRVSWDLRLNEYNY
131	AS302376	QVHLMESGGGSVQAGGSLRLSCVASGYTSSILYMGWFRQAPGKKREGVATITRHTGNTIYAEPVKGRFTISLDNAKNTVYLQMNSLESDDTAMYYCAAQTRLGLSLDDYGYNYRGQGTQVTVSS
132	AS302376CDR1	GYTSSILYMG
133	AS302376CDR2	TITRHTGNTI
134	AS302376CDR3	KTRLGLSLDDYGYNY
135	AS302382	AVQLVESGGGLVQAGESLRLSCTASGIIFGSSVMGWYRQAPGKQRELVAVITTGTTNYADSVKGRFRISRDNARTTVYLQMNSLKPEDTAVYLCNARRRIDYWGQGTQVTVSS
136	AS302382/AS302553CDR1	GIIFGSSVMG
137	AS302382CDR2	VITTGTTN
138	AS302382/AS302554CDR3	RRRIDY
139	AS302396	QVQLVESGGGSVQAGGSLRLSCTASGSTYGRNCMGWFRQTPEKGREGVAAISTAGGSTYYADSVKGRFAISQDNANNTVYLQMNSLKPEDTAMYYCAASRDIRCSYWG RYNYWGQGTQVTVSS
140	AS302396CDR1	GSTYGRNCMG
141	AS302396CDR2	AISTAGGSTY
142	AS302396CDR3	SRDIRCSYWG RYNY
143	AS302399	QVKLVESGGGSVQAGGSLRLSCVASGYAAYSPYCMWFRQAPGKEREGVASIYTGSGATYYPDSVKGRFTISQDKAKDTLYLQMNSLKPEDTAMYYCAAAYDLRSCG

		GTWYRFRHWGQGTQVTVSS
144	AS302399CDR1	GYAYSPYCMA
145	AS302399CDR2	SIYTGSGATY
146	AS302399CDR3	AYDLRSCGGTWYRFRH
147	AS302400	AVQLVDSGGGLVQPGGSLRLSCAASRSIFRLHVMGWYRQAPGKQREL VATITS DSSTNYADSMKGRFTISRDN AKKTVYLQMNLSLKPEDTAVYYCNLKYIGNNNID YWGQGTQVTVSS
148	AS302400CDR1	RSIFRLHVMG
149	AS302400CDR2	TITSDSSTN
150	AS302400CDR3	KYIGNNNIDY
151	AS302433	QVHLVESGGGSVQAGGSLRLSCVASGDTVSTYCMAWFRQAPGKEREEVAAIGS VGSPRYADSVKGRFIMSKDNAKNTLYLQMNLSLKPEDTGMYYCAAHRICVMSRF RPNDWGQGTQVTVSS
152	AS302433CDR1	GDTVSTYCM
153	AS302433CDR2	AIGSVGSPR
154	AS302433CDR3	HRICVMSRFRPND
155	AS302434	QVHLVESGGGSVQAGGSLRLSCVASGYTSTSEYMGWFRQSPGKKREGVAAVV RRTGNTIY AEPVKGRFTISLDNAKNTVYLQMNSLESDDTAMYYCAA KTRLGLSL EEYGYRYWGQGTQVTVSS
156	AS302434CDR1	GYTSTSEYMG
157	AS302434CDR2	AVVRTGNTI
158	AS302434CDR3	KTRLGLSLEEYGYRY
159	AS302447	QVKLVESGGGSVQAGGSLRLSCVSGGFFYSRYCMNWVRQAPGKEREGVASIDS GGSTNYADSVKGRFTISKDNAKNILSLQMNSLTPEDTAMYYCVAAYTCRSGIQT RGKYAGQGTQVTVSS
160	AS302447CDR1	GFFYSRYCMN
161	AS302447CDR2	SIDSGGSTN
162	AS302447CDR3	AYTCRSGIQTGRKY
163	AS302468	QVRLVESGGGSVQAGGSLRLSCAASGFFINRYCMAWFRQAPGKEREGVAFINSG GTTTYADSVKGRFTASKDNAKAILYLQMNLSLKPEDTAMYYCARLAVGCYRDS VGLWGRGTQVTVSS
164	AS302468CDR1	GFFINRYCMA
165	AS302468CDR2	FINSGGTTT
166	AS302468CDR3	LAVGCYRDSVGL
167	AS302480	DVQLVESGGGLVQPGGSLRLSCVLSGSIFSNYQMSWYRQTPGKQREW VATITRR GTTTYVASVKGRFTISRDN AKSTVYLQMNLSLKPEDTAVYLCNALWGGEYDYW GQGTQVTVSS
168	AS302480CDR1	GSIFSNYQMS
169	AS302480CDR2	TITRRGTTT
170	AS302480CDR3	LWGGEYDY
171	AS302493	QVHLVESGGGSVQAGGSLRLSCAVSSDTYCNGWFRQAPGKEREGVADIASDGT TSYSDSVKGRFTISKDNAKNTVFLQMNLSLKPEDTAMYYCAASRDVRCRYFPRR GYRYWGQGTQVTVSS
172	AS302493CDR1	SDTYCNG
173	AS302493CDR2	DIASDGTTS
174	AS302493CDR3	SRDVRCRYFPRRGYRY
175	AS302504	QVHLVESGGGSVQAGGSLRLSCAASGYVNSRAYMGWFRQAPGKEQEWVAAIH TGSGVTFLEP VKGRFTISRDN AKNTLFLQMNLSLKPEDTAMYYCAAGNSRLGT WNLRNYYNYWGQGTQVTVSS
176	AS302504CDR1	GYVNSRAYMG
177	AS302504CDR2	AIHTGSGVTF
178	AS302504CDR3	GNSRLGTWNLRNYYNY
179	AS302509	QVQLEESGGGSVQAGGSLRLSCAASGTIYTSNCMGWFRQAPGKEREGVATILA GGGSAVYADSVKGRFTISR DYAKNTVYLQMNGLKPEDTAMYYCAA STDLRCL YSLSSGYRYKYWGQGTQVTVSS
180	AS302509CDR1	GTIYTSNCMG

181	AS302509CDR2	TILAGGGS AV
182	AS302509CDR3	STDRLCLYSLSSGYRYKY
183	AS302516	QVKLVESGGGSVQAGGSLRLSCAASGYTSSYTRMGWFRQAPGKEREAVAGIYT AGGYTTYADSVKGRFTISQDRTEENTVYLQMNDLKPEDTAMYYCAAGRGDLRL QFSPSTYGYWGQGTQVTVSS
184	AS302516CDR1	GYTSSYTRMG
185	AS302516CDR2	GIYTAGGYTY
186	AS302516CDR3	GRGDLRLQFSPSTYGY
187	AS302553	AVQLVESGGGLVQAGGSLRLSCVASGIIFGS SVMGWYRQVPGKQRELAATITYD GNTNYAESVKGRFTISRDN AKRTVWLQMDSLKPEDTAVYYCNAYRRYNYWGQ GTQVTVSS
188	AS302553CDR2	TITYDGNTN
189	AS302553CDR3	YRRYNY
190	AS302554	AVQLVESGGGLVQAGGSLRLSCAASGIIFSSSTMGWYRQAPGKQREL VADITYV GGTNYADSVKGRFTISRDN AKRTVYLQMNSLRPEDTAVYYCNARRRIDYWGQ GTQVTVSS
191	AS302554CDR1	GIIFSSSTMG
192	AS302554CDR2	DITYVGGTN
193	AS302558	AVQLVESGGGLVQAGRSLRLSCVADGSIFLSAMGWYRQAPGNQREL VAAIST NGESTQYANSAKGRFTIYRDNAKNTVYLQMNSLKPEDTAVYYCIAAPSFVVALI PSRIRSWGQGTQVTVSS
194	AS302558CDR1	GSIFLSAMG
195	AS302558CDR2	AISTNGESTQ
196	AS302558CDR3	APSFVVALIPSRIRS
197	AS302560	AVQLVESGGGLVQPGGSLRLACAASGSIFRLNVMGWYRQAPGKQREL VATITS DSLNTNYADSMKGRFTISRDN AKKTVYLQMNNLKPEDTAVYYCHFKEYIGFNN IDYWGQGTQVTVSS
198	AS302560CDR1	GSIFRLNVMG
199	AS302560CDR2	TITSDSLNTN
200	AS302560CDR3	KYIGFNNIDY
201	AS302564	AVQLVESGGGLVQAGESLRLSCTASGIIGIVMGWYRQAPGKQREL VATVTAT DRTNYADSVKGRFTISRGSTRNTVHLQMNSLTPEDTAVYYCKVSRARDYWGQG TQVTVSS
202	AS302564CDR1	GIIGIVMG
203	AS302564CDR2	TVTATDRTN
204	AS302564CDR3	SRARDY
205	AS302571	AVQLVESGGGLVQAGGSLTLSCAASGIMFSRYTMGWYRQAPGKQREL VATITQ GGTNYADSVKGRFTISR DSTINTDLQMNSLKPEDSGVYYCNARHLWRQQNDY WGQGTQVTVSS
206	AS302571CDR1	GIMFSRYTMG
207	AS302571CDR2	TITQGGTN
208	AS302571CDR3	RHLWRQQNDY
209	AS302575	AVQLVESGGGLVQAGGSLRLSCAASGTIFMSSTMGWYRQAQ GKQREL VATITY SGITNYADSVKGRFTISRDN AKHTSHLQMNSLKPEDTAVYYCTSSRRDITYWGQ GTQVTVSS
210	AS302575CDR1	GTIFMSSTMG
211	AS302575CDR2	TITYSGITN
212	AS302575CDR3	SRRDITY
213	AS302597	QVQLVESGGGLVQPGGSLRLSCAASGIIFGSSTMGWYRQAPGKQREL VATITYG GGTNYADSVKGRFTISRDN AKNTVYLQMNSLKPEDTAVYFCNAKRRQDYWGK GTLVTVSL
214	AS302597CDR2	TITYGGTN
215	AS302597CDR3	KRRQDY
216	AS302599	QVQLVESGGGLVQAGGSLRLSCAASGILSASNI AWYRQAPGKQREL VAGISAG GRINYADSVKGRFTISRDN AKMTFYLQMNSLNPEDTAVYYCNVQRTYNYWGQ GTQVTVSS
217	AS302599CDR1	GILSASNIA

218	AS302599CDR2	GISAGGRIN
219	AS302599CDR3	QRTYNY
220	AS302643	AVQLVESGGGLVQAGGSLRLSCAASGIFFSRYTVGWYRQVPGKQREL VADITSL GNTKYVD AVQGRFTISRDN AKNTVYLQMDSLKPEDTAVYYCTTRGSWDRVYW GGGTQVTVSS
221	AS302643CDR1	GIFFSRYTVG
222	AS302643CDR2	DITSLGNTK
223	AS302643CDR3	RGSWDRVY
224	AS302654	QVKLEESGGGLVQAGGSLRLSCLGSGMIFSAFAMGWYRQAPGKQREL VASIVS GSSTNYADSVKGRFTISRDN AKNTVYLQMNSLKPEDTAVYYCNAQRTYSYWG QGTQVTVSS
225	AS302654CDR1	GMIFSAFAMG
226	AS302654CDR2	SIVSGSSTN
227	AS302654CDR3	QRTYSY
228	AS302656	AVQLVESGGGLVQAGGSLRLSCTTSGHIVSAYIMAWYRQAPGKQRD L VASITGG TATNYADSVKGRFTISRDN AKNTVYLQMNSLKPEDTAVYYCSAERTRRHWGQ GTQVTVSS
229	AS302656CDR1	GHIVSAYIMA
230	AS302656CDR2	SITGGTATN
231	AS302656CDR3	ERTRRH
232	AS302721	AVQLVDSGGGVVQAGGSLRLSCAASGSIPILHRMGYYRQAPGKQREL VASITNS GSTDYHDSVRGRFTISRDS AKNTVFLQMNSLKPEDTAVFYCNFQSLRSMRNYW GGGTQVTVSS
233	AS302721CDR1	GSIPILHRMG
234	AS302721CDR2	SITNSGSTD
235	AS302721CDR3	QSLRSMRNY
236	AS302735	QVQLVESGGGLVQAGGSLRLSCVASGIHFSSNAMGWYRQAPGKQREWVAHVT WDGITNYADSVKDRFTISRDN AKQT VYLQMNSLRPEDTAVYYCNARRSYSYW GGGTQVTVSS
237	AS302735CDR1	GIHFSSNAMG
238	AS302735CDR2	HVTWDGITN
239	AS302735CDR3	RRSYSY
240	AS307553	EVQLVESGGGSVQAGGSLRLSCTASGYSGSCGMAWYRQAPGKEREL VSRISST GDTYYGDSVKGRFTISRDN SKKTVYLQMNSLKPEDTAMYYCNPSTGLRCAR APWGQGTQVTVSS
241	AS307553CDR1	GYSGSCGMA
242	AS307553CDR2	RISSTGDTY
243	AS307553CDR3	PSTGLRCARAP
244	AS307587	QVQLEESGGGSVQAGGSLRLSCAASGYIVSSGCMGWFRQVQKERE GVAAIGS DGITGYADSVKGRFTISED NAMNTLYLQMNDLKPEDTAMYYCAA VLPGVPRSG LSGSCRFGGRYYG MNYWGK GTLVTISS
245	AS307587CDR1	GYIVSSGCMG
246	AS307587CDR2	AIGSDGITG
247	AS307587CDR3	VLPGVPRSGLSGSCRFGGRYYG MNY
248	AS307626	QVQLAESGGGSVQPGGSLRLSCAASGSTDSSNWLGWFRQAPGKEREGVAAIGR LPINPYADSVRGRFTISRDN AKNTVYLQMNSLKPEDTAIYYCAAA SLTTWLR GRAYGGGTQVTVDS
249	AS307626CDR1	GSTDSSNWL G
250	AS307626CDR2	AIGRLPINPY
251	AS307626CDR3	AASLTTWLRGRAY
252	AS307672	QVQLQESGGGSVQAGGSLRLSCSASLYSISR SYMAWFRQTPGKEREGIAAIVPSA ATTYAASVKGRFTISKDNAENILY LQMYDLKPDDTAMYYCAGSGSVDLRYLLR SNRYNDWGRGTQVTVSS
253	AS307672CDR1	LYSISR SYMA
254	AS307672CDR2	AIVPSAATT
255	AS307672CDR3	SGSVDLRYLLRSNRYND

256	AS307685	QVHLVESGGGSVQAGGSLRLSCVASGYTTGMAWFRGAPGKEREGVATISTRGG VTNYADSVKGRFTISRDRAKNTVYLMNSLQPEDTAMYYCAARTGGVWPFRIE AGDFGVWGQGTQVTVSS
257	AS307685CDR1	GYTTGMA
258	AS307685CDR2	TISTRGGVTN
259	AS307685CDR3	RTGGVWPFRIEAGDFGV
260	AS307703	QVQLVESGGGSVQAGGSLRLSCSASGYSISRSYMAWFRQTPGKEREGIAAIVPSG ATTYADSVKGRFTISKDNAENILYLMNSLKPDDTAMYYCARSVSVDLRYLLRS NRYSYWGRGTQVTVSS
261	AS307703CDR1	GYSISRSYMA
262	AS307703CDR2	AIVPSGATT
263	AS307703CDR3	SVSVDLRYLLRSNRYSY
264	AS307775	QVQLKESGGGSVQAGGSLRLSCVASGYTGSRNMGWFRQAPGKEREAARIWS RLDNTDYADSVKGRFTISRDNKNTVYLMNSLKPEDTAMYYCAAGPLYLGLR ASEYTYWGQGTQVTVSS
265	AS307775CDR3	GPLYLGLRASEYTY
266	AS307816	EVQLAESGGGSVQAGGSLRLSCGASGLPGAMAWFRQAPGKEREGVAAITGGGR TTYADSVKGRFTISKDNAKNTLYLMNSLEAEDTAMYYCAAYLRGWSSQMR SEDYTYWGQGTQVTVSS
267	AS307816CDR1	GLPGAMA
268	AS307816CDR2	AITGGGRTT
269	AS307816CDR3	YLRRGWSSQMRSEDYTY
270	AS307854	QVHLVESGGGSVQAGGSLRLSCATSGYAYCMTWYRQAPGKEREFVSGFGQNG SPLYTDSVKGRFTISRDNANMVSLQMNSLKPEDTAMYYCKAFADLRFCGKEYW GQGTQVTVTS
271	AS307854CDR1	GYAYCMT
272	AS307854CDR2	GFGQNGSPL
273	AS307854CDR3	FADLRFCGKEY
274	AS307858	EVQLVESGGGSVQAGGSLRLSCAASGYTASMSCMGWFRQAPGKEREGVASIVT STGRNTYIDSVKGRFTISQDNAKNTVYLMNSLKPEDTAMYYCAAASDLRCGW GFVTGSRGYKYWGQGTQVTVSS
275	AS307858CDR1	GYTASMSCMG
276	AS307858CDR2	SIVTSTGRTN
277	AS307858CDR3	ASDLRCGWGFVTGSRGYKY
278	AS307879	QVQLAESGGGSVQAGGSLRLSCAASGELRNLNALGWFRQAPGKEREGVAELYR GSTYYVDSVKGRFTISQDNAKNTFYLMNNLKPEDTAMYYCAAKRGLRGWVP LLAREYNYWGQGTQVTVSS
279	AS307879CDR1	GELRNLNALG
280	AS307879CDR2	ELYRGSTY
281	AS307879CDR3	KRGLRGWVPLLAREYNY
282	AS307926	QMQLVESGGESVQAGGSLRLSCAASGFTVSSSCMGWFRQYPGKEREAATFNN RGTTSTYDSVKGRFTISKDNAKNTLYLMNSLKPEDTAMYYCAANIDIRCPWM PNFRYWGQGTQVTVSS
283	AS307926CDR1	GFTVSSSCMG
284	AS307926CDR2	TFNNRGTTT
285	AS307926CDR3	NIDIRCPWMPNFRY
286	AS307927	QVKLVESGGGSVQAGGSLRLSCAVSSLTYYRRWFRQAPGKEREGVA AISIRGGS TYYADSVKGRFTISTNNAKNTMYLQLNSLKPBDTAMYYCAAGVRSGLDLEEDK YEYWGQGTQVIVSS
287	AS307927CDR1	SLTYRRA
288	AS307927CDR2	AISIRGGSTY
289	AS307927CDR3	GVRSGLDLEEDKYEY
290	AS307946	QVKLVESGGGSVQAGGSLRLSCAASGNTVYMAWFRQAPGKEREGVATIAPTER GVLYANSVKGRFTISRDNKNTVYLMNSLKLEDSAMYYCAAGNRLGLSLSEG SFLYWGQGTQVTVSS
291	AS307946CDR1	GNTVYMA
292	AS307946CDR2	TIAPTERGVL

293	AS307946CDR3	GNRLGLSLSEGSFLY
294	AS307971	QVRLVESGGGSVQAGGSLKLSAASGLIFSNCGMGWYRQAPGKERELVSSISRR GVTGYADSVKGRFTISRDNKTGTVYLSMNSLKTEDAAYVYCATVSNLGLCATY WGQGTQVTVSS
295	AS307971CDR1	GLIFSNCGMG
296	AS307971CDR2	SISRRGVTG
297	AS307971CDR3	VSNLGLCATY
298	AS308386	QVQLVESGGGSVQAGGSLRLSCAASGYTVSNACMGWFRQAPGKEREGVAAIY TRGGSTYYANSVKGRFTISQDNAKNTVYLMNSLKPEDTAMYCAARQWGQR CTVVPDFTYWGQGTQVTVAS
299	AS308386CDR1	GYTVSNACMG
300	AS308386CDR2	AIYTRGGSTY
301	AS308386CDR3	RQWGQRCTVVPDFTY
302	AS308506	QVQLVESGGGSVQAGGSLKLSAASGFIFGACGMAWYRQVPGERELVSSISK DGRTDYADSVKGRFSISQDKTKSALYLMYSLTTEDTGVIYCAASRPRLVVT RCSADTYWGQGTQVTVSS
303	AS308506CDR1	GFIFGACGMA
304	AS308506CDR2	SISKDGRTD
305	AS308506CDR3	SRPIRLVVTRCSADTY
306	AS310012	EVQLVESGGGSVQAGGSLRLSCAASGYTYSRLVMAWFRQAPGKEREGVAVIYT GGGSTYYADSVKGRFTISQDNAKNTVYLMNSLKPEDTAMYYCAAVRRTTMT AIQALSARTYNSWGQGTQVTVSS
307	AS310012CDR1	GYTYSRLVMA
308	AS310012CDR2	VIYTGGSSTY
309	AS310012CDR3	VRRTTMTAIQALSARTYNS
310	AS310027	QVQLEESGGGSVQAGGSLKLSAASGYIFSRGCMGWYRQAPGKEREWISSIRFD GTTSYADSVKGRFTISRDNKNTLYLGMNKLKTDDTAVYLCAKPLCQGVGPA WGQGTQVTVSS
311	AS310027CDR1	GYIFSRGCMG
312	AS310027CDR2	SIRFDGTTS
313	AS310027CDR3	PLCQGVGPA
314	leader sequence	MALPVTALLPLALLLHAARP
315	myc tag	EQKLISEEDL
316	CD8α hinge	TSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD
317	CD8α transmembrane region	IYIWAPLAGTCGVLLSLVITLYC
318	the cytoplasmic portion of the 4-1BB (CD137) molecule	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL
319	the cytoplasmic portion of the CD3ζ molecule	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDRRGRDPEMGGKPRRK NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDAL HMQALPPR
320	G109bbz	MALPVTALLPLALLLHAARPEQKLISEEDLQSALTQPASVSGSPGQSITISCTGT SSDVGGYNYVSWYQQHPGKAPKLMYDVSKRPSGVSNNRFSGSKSGNTASLTISG LQAEDEADYYCSSYTRSTEVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVQ SGAEVKKPGASVKVCKASGYTFTSYMHWVRQAPQGLEWMGIINPSGGSTS YAQKFQGRVTMTRDTSTSTVYMESSLRSEDTAVYYCARGGSKKWSGEKWRR ENFDYWQGQTLTVTSSTSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT RGLDFACDIYWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQ EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVL DKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHD GLYQGLSTATKDTYDALHMQALPPR
321	5E11VH	ELQLEQSGGGLVQPGGSLTLSCAASGFTFSKYAMAWVRQAPTKGLEWVASIST GGVNTYYRDSVKARFTISRDNKNTQYLQMDSLRSEDTATYYCATHTGDYFDY WGQGVMTVSS
322	5E11VL	DIVLTQSPALAVSPGQRATISCRASQSVSISGINLMNWYQQKPGQPKLLIYHASI LASGIPTRFSGSGSTDFLTIDPVQADDIATYYCQQTRESPLTFGSGTNLEIK
323	G109scFv	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMYDVS KRPSGVSNNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTRSTEVFGGGTKLTV

		LGSRRGGGSGGGGSGGGGSGLEMAEVQLVQSGAEVKKPGASVKVSCKASGYTF TSYYMHVWRQAPQGLEWMIINPSGGSTSYAQKFQGRVTMTDRDTSSTVYIM ELSSLRSEDATVYYCARGGSKWSGEKWRRENFQYWGQGLTVTVSS
324	chimeric DB1	ENASTSRGCGDLLPQYVSLCDLDAIWGSLAILGIVVTILLALLAFFLMRKIQDCS QWNVLPQTQLLFLSVLGLFGLAFAFIIELNQQTAPVRYFLFGVLFALCFSCLLAH ASNLVKLVRCVSVFSWTTILCIAIGCSLLQIIIAIEYVTLIMTRGMMFVNMTPCQL NVDFVLLVYVLFMLALTFFVSKATFCGPCENWKQHGRLIFITVLFSSIIHVVVWIS MLLRGNPQFQRQPQWDDPVVCIALVTNAWVFLLLYIVPELCILYRSCRQECPLQ GNACPVTAAYQHSFQVENQELSRDC
325	chimeric DA2	MYKDCIESTGDYFLLCDAEGPWGIIIESLAILGIVVTILLALLAFFLMRKIQDCSQ WNVLPQTQLLFLSVLGLFGLAFAFIIELDGSGTPTRFLFGVLFALCFSCLLAHASN LVKLVRGCVSVFSWTTILCIAIGCSLLQIIIAIEYVTLIMTRGMMFVNMTPCQLNVD FVLLVYVLFMLALTFFVSKATFCGPCENWKQHGRLIFITVLFSSIIHVVVWISMLI RGNPQFQRQPQWDDPVVCIALVTNAWVFLLLYIVPELCILYRSCRQECPLQGNA CPVTAYQHSFQVENQELSRDC
326	chimeric DA3	MYKDCIESTGDYFLLCDAEGPWGIIIESLAILGIVVTILLALLAFFLMRKIQDCSQ WNVLPQTQLLFLSVLGLFGLAFAFIIELNQQTAPVRYFLFGVLFALCFSCLLAHAS NLVKLVRCVSVFSWTTILCIAIGCSLLQIIIAEYIVLTMTNRNVTNVVSELSAPRRNE DVDFVLLVYVLFMLALTFFVSKATFCGPCENWKQHGRLIFITVLFSSIIHVVVWIS MLLRGNPQFQRQPQWDDPVVCIALVTNAWVFLLLYIVPELCILYRSCRQECPLQ GNACPVTAAYQHSFQVENQELSRDC
327	chimeric DB4	MYKDCIESTGDYFLLCDAEGPWGIIIESLAILGIVVTILLALLAFFLMRKIQDCSQ WNVLPQTQLLFLSVLGLFGLAFAFIIELNQQTAPVRYFLFGVLFALCFSCLLAHASN NLVKLVRCVSVFSWTTILCIAIGCSLLQIIIAIEYVTLIMTRGMMFVNMTPCQLNVD DFVLLVYVLFMLALTFFVSKATFCGPCENWKQHGRLIFITVLFSSIIHVVVWISMLI LLFGNVKLQQGDWANDPTPVVCIALVTNAWVFLLLYIVPELCILYRSCRQECPL QGNACPVTAAYQHSFQVENQELSRDC
328	AS300399VH4	EVQLVESGGGLVQPGGSLRLSCAASGYTVSNHCMAWFRQAPGKLEWVSSIGT DGILSYADSVKGRFTISRDNNSKNTLYLQMNSLRAEDTAVYYCAAVFRTWWDRS CRRGAGMDYWGGQGLTVTVSS
329	AS300399VH5	EVQLVESGGGLVQPGGSLRLSCAASGYTVSNHCMAWFRQAPGKLEWVASIGT DGILSYADSVKGRFTISRDNNSKNTLYLQMNSLRAEDTAVYYCAAVFRTWWDRS CRRGAGMDYWGGQGLTVTVSS
330	AS300399VH6	EVQLVESGGGLVQPGGSLRLSCAASGYTVSNHCMAWFRQAPGKLEWVASIGT DGILSYADSVKGRFTISKDNSKNTLYLQMNSLRAEDTAVYYCAAVFRTWWDRS CRRGAGMDYWGGQGLTVTVSS
331	AS300399VH7	EVQLVESGGGLVQPGGSLRLSCAASGYTVSNHCMAWFRQAPGKEREWVASIGT DGILSYADSVKGRFTISKDNSKNTLYLQMNSLRAEDTAVYYCAAVFRTWWDRS CRRGAGMDYWGGQGLTVTVSS
332	AS300399VH8	EVQLVESGGGLVQPGGSLRLSCAASGYTVSNHCMAWFRQAPGKEREWVASIGT DGILSYADSVKGRFTISKDNSKNTLYLQMNSLRAEDTAVYYCAAVFRTWWDRS CRRGAGMDYWGGQGLTVTVSS
333	AS300399VH9	EVQLVESGGGLVQPGGSLRLSCAASGYTVSNHCMAWFRQAPGKEREWVASIGT DGILSYADSVKGRFTISKDNSKNTLYLQMDSLRAEDTAVYYCAAVFRTWWDRS CRRGAGMDYWGGQGLTVTVSS
334	AS300413VH4	EVQLVESGGGLVQPGGSLRLSCAASGIIFSNCGLAWYRQAPGKGLELVSSISRRG TTIYADSVKGRFTISRDNNSKNTLYLQMNSLRAEDTAVYYCTTEPQLGLCARDWG QGTLTVTVSS
335	AS300413VH5	EVQLVESGGGLVQPGGSLRLSCAASGIIFSNCGLAWYRQAPGKGLELVSSISRRG TTIYADSVKGRFTISRDNNSKNTLYLQMNSLRAEDTAVYSCCTTEPQLGLCARDWG QGTLTVTVSS
336	AS300413VH6	EVQLVESGGGLVQPGGSLRLSCAASGIIFSNCGLAWYRQAPGKGLELVSSISRRG TTIYADSVKGRATISRDNNSKNTLYLQMNSLRAEDTAVYSCCTTEPQLGLCARDWG QGTLTVTVSS
337	AS300413VH7	EVQLVESGGGLVQPGGSLRLSCAASGIIFSNCGLAWYRQAPGKERELVSSISRRG TTIYADSVKGRATISRDNNSKNTLYLQMNSLRAEDTAVYSCCTTEPQLGLCARDWG QGTLTVTVSS
338	AS300452VH4	EVQLVESGGGLVQPGGSLRLSCAASGYCYMGWFRQAPGKGLEGVSYIDSFGST LYADSVKGRFTISRDNNSKNTLYLQMNSLRAEDTAVYYCAADLSYLRCPRRGG MYYGFPYWGQGLTVTVSS
339	AS300452VH5	EVQLVESGGGLVQPGGSLRLSCAASGYCYMGWFRQAPGKGLEGVAYIDSFGST LYADSVKGRFTISRDNNSKNTLYLQMNSLRAEDTAVYYCAADLSYLRCPRRGG MYYGFPYWGQGLTVTVSS
340	AS300452VH6	EVQLVESGGGLVQPGGSLRLSCAASGYCYMGWFRQAPGKGLEGVSYIDSFGST LYADSVKGRFTISKDNSKNTLYLQMNSLRAEDTAVYYCAADLSYLRCPRRGG MYYGFPYWGQGLTVTVSS
341	AS300452VH7	EVQLVESGGGLVQPGGSLRLSCAASGYCYMGWFRQAPGKEREGVAYIDSFGST LYADSVKGRFTISRDNNSKNTLYLQMNSLRAEDTAVYYCAADLSYLRCPRRGG MYYGFPYWGQGLTVTVSS

342	AS300452VH8	EVQLVESGGGLVQPGGSLRLSCAASGYTCMGWFRQAPGKEREKVAYIDSFSGSTLYADSVKGRFTISKDNSKNTLYLQMNSLRAEDTAVYYCAADLSYLRCPRRGGMYYGFPYWGGTLVTVSS
343	AS302399VH4	EVQLLESGGGLVQPGGSLRLSCAASGYAYSPYCMWFRQAPGKGLEGVSSIYTGSGATYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAAYDLRSCGTWYRFRHWGGTLVTVSS
344	AS302399VH5	EVQLLESGGGLVQPGGSLRLSCAASGYAYSPYCMWFRQAPGKGLEGVASIYTGSGATYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAAYDLRSCGTWYRFRHWGGTLVTVSS
345	AS302399VH6	EVQLLESGGGLVQPGGSLRLSCAASGYAYSPYCMWFRQAPGKGLEGVASIYTGSGATYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAAYDLRSCGTWYRFRHWGGTLVTVSS
346	AS302399VH7	EVQLLESGGGLVQPGGSLRLSCAASGYAYSPYCMWFRQAPGKEREKVASIYTGSGATYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAAYDLRSCGTWYRFRHWGGTLVTVSS
347	AS302509VH4	EVQLLESGGGLVQPGGSLRLSCAASGTIYTSNCMGWFRQAPGKGLEGVSTILAGGSAVYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAASTDLRCLYSLSSGYRYKYWGQTLVTVSS
348	AS302509VH5	EVQLLESGGGLVQPGGSLRLSCAASGTIYTSNCMGWFRQAPGKGLEGVATILAGGSAVYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAASTDLRCLYSLSSGYRYKYWGQTLVTVSS
349	AS302509VH6	EVQLLESGGGLVQPGGSLRLSCAASGTIYTSNCMGWFRQAPGKEREKVATILAGGSAVYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAASTDLRCLYSLSSGYRYKYWGQTLVTVSS
350	AS302553VH4	EVQLVESGGGLVQPGGSLRLSCAASGIHFGSSVMGWYRQAPGKGLELVSTITYDGNNTNYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCNAYRRYNYWGQGTTLVTVSS
351	AS302553VH5	EVQLVESGGGLVQPGGSLRLSCAASGIHFGSSVMGWYRQAPGKGLELAATITYDGNNTNYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCNAYRRYNYWGQGTTLVTVSS
352	AS302553VH6	EVQLVESGGGLVQPGGSLRLSCAASGIHFGSSVMGWYRQAPGKGQRELAATITYDGNNTNYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCNAYRRYNYWGQGTTLVTVSS
353	AS302558VH4	EVQLVESGGGLVQPGGSLRLSCAASGSIFSLSAMGWYRQAPGKGLELVSAISTNGESTQYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCIAAPSFVVALIPSRIRSWGQGTMTVTSS
354	AS302558VH5	EVQLVESGGGLVQPGGSLRLSCAASGSIFSLSAMGWYRQAPGNQLELVSAISTNGESTQYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCIAAPSFVVALIPSRIRSWGQGTMTVTSS
355	AS302558VH6	EVQLVESGGGLVQPGGSLRLSCAASGSIFSLSAMGWYRQAPGNQRELVSAISTNGESTQYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCIAAPSFVVALIPSRIRSWGQGTMTVTSS
356	AS302558VH7	EVQLVESGGGLVQPGGSLRLSCAASGSIFSLSAMGWYRQAPGNQLELVSAISTNGESTQYADSVKGRFTIYRDNSKNTLYLQMNSLRAEDTAVYYCIAAPSFVVALIPSRIRSWGQGTMTVTSS
357	AS302558VH8	EVQLVESGGGLVQPGGSLRLSCAADGSIFSLSAMGWYRQAPGNQLELVSAISTNGESTQYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCIAAPSFVVALIPSRIRSWGQGTMTVTSS
358	AS302558VH9	EVQLVESGGGLVQPGGSLRLSCAADGSIFSLSAMGWYRQAPGNQRELVSAISTNGESTQYADSVKGRFTIYRDNSKNTLYLQMNSLRAEDTAVYYCIAAPSFVVALIPSRIRSWGQGTMTVTSS
359	AS302643VH8	EVQLVESGGGLVQPGGSLRLSCAASGIFFSRYTVGWYRQAPGKGLELVSDITSLGNTKYADSVQGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCTTRGSWDRVYWGGQTLVTVSS
360	AS302643VH9	EVQLVESGGGLVQPGGSLRLSCAASGIFFSRYTVGWYRQAPGKGLELVSDITSLGNTKYVDAVQGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCTTRGSWDRVYWGGQTLVTVSS
361	AS302643VH10	EVQLVESGGGLVQPGGSLRLSCAASGIFFSRYTVGWYRQVPGKGLELVSDITSLGNTKYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCTTRGSWDRVYWGGQTLVTVSS
362	AS302643VH11	EVQLVESGGGLVQPGGSLRLSCAASGIFFSRYTVGWYRQVPGKGLELVSDITSLGNTKYVDAVQGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCTTRGSWDRVYWGGQTLVTVSS
363	AS302643VH12	EVQLVESGGGLVQPGGSLRLSCAASGIFFSRYTVGWYRQVPGKQRELVADITSLGNTKYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCTTRGSWDRVYWGGQTLVTVSS
364	AS307587VH4	EVQLVESGGGLVQPGGSLRLSCAASGYIVSSGCMGWFRQAPGKGLEGVSAIGSDGITGYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAVLPVGPVPSGLSGSCRFGGRYYGMYWGQTLVTVSS

365	AS307587VH5	EVQLVESGGGLVQPGGSLRLSCAASGYIVSSGCMGWFRQAPGKGLEGVSAIGSD GITGYADSVKGRFTISEDNSKNTLYLQMNSLRAEDTAVYYCAA VLPGVPRSGLS GSCRFGGRYYGMNYWGQGLTVTVSS
366	AS307587VH6	EVQLVESGGGLVQPGGSLRLSCAASGYIVSSGCMGWFRQAPGKGLEGVAAIGS DGITGYADSVKGRFTISEDNSKNTLYLQMNSLRAEDTAVYYCAA VLPGVPRSGL SGSCRFGGRYYGMNYWGQGLTVTVSS
367	AS307587VH7	EVQLVESGGGLVQPGGSLRLSCAASGYIVSSGCMGWFRQAPGKEREKVAAIGS DGITGYADSVKGRFTISEDNSKNTLYLQMNSLRAEDTAVYYCAA VLPGVPRSGL SGSCRFGGRYYGMNYWGQGLTVTVSS
368	AS307858VH4	EVQLVESGGGLVQPGGSLRLSCAASGYTASMSCMGWFRQAPGKGLEGVSSIVT STGRNTYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAADLRCGW GFVTGSRGYKYWGQGLTVTVSS
369	AS307858VH5	EVQLVESGGGLVQPGGSLRLSCAASGYTASMSCMGWFRQAPGKGLEGVSSIVT STGRNTYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAADLRCGW GFVTGSRGYKYWGQGLTVTVSS
370	AS307858VH6	EVQLVESGGGLVQPGGSLRLSCAASGYTASMSCMGWFRQAPGKGLEGVASIVT STGRNTYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAADLRCGW GFVTGSRGYKYWGQGLTVTVSS
371	AS307858VH7	EVQLVESGGGLVQPGGSLRLSCAASGYTASMSCMGWFRQAPGKEREKVASIVT STGRNTYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAADLRCGW GFVTGSRGYKYWGQGLTVTVSS
372	AS308386VH4	EVQLVESGGGLVQPGGSLRLSCAASGYTVSNACMGWFRQAPGKGLEGVSAIYT RGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAARQWGQRC TVVPTDFTYWGQGLTVTVSS
373	AS308386VH5	EVQLVESGGGLVQPGGSLRLSCAASGYTVSNACMGWFRQAPGKGLEGVSAIYT RGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAARQWGQRC TVVPTDFTYWGQGLTVTVSS
374	AS308386VH6	EVQLVESGGGLVQPGGSLRLSCAASGYTVSNACMGWFRQAPGKGLEGVAAIYT RGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAARQWGQRC TVVPTDFTYWGQGLTVTVSS
375	AS308386VH7	EVQLVESGGGLVQPGGSLRLSCAASGYTVSNACMGWFRQAPGKEREKVAAIYT RGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAARQWGQRC TVVPTDFTYWGQGLTVTVSS
376	AS308386VH8	EVQLVESGGGLVQPGGSLRLSCAASGYTVSNACMGWFRQAPGKEREKVAAIYT RGGSTYYANSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAARQWGQRC TVVPTDFTYWGQGLTVTVSS
377	AS308506VH4	EVQLVESGGGLVQPGGSLRLSCAASGFIFGACGMAWYRQAPGKGLELVSSISKD GRTDYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAASRPRLV VTR CSADTYWGQGLTVTVSS
378	AS308506VH5	EVQLVESGGGLVQPGGSLRLSCAASGFIFGACGMAWYRQAPGKGLELVSSISKD GRTDYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAASRPRLV VTR CSADTYWGQGLTVTVSS
379	AS308506VH6	EVQLVESGGGLVQPGGSLRLSCAASGFIFGACGMAWYRQAPGKERELVSSISKD GRTDYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAASRPRLV VTR CSADTYWGQGLTVTVSS
380	AS310012VH4	EVQLVESGGGLVQPGGSLRLSCAASGYTYSRLVMAWFRQAPGKGLEGVSVIYT GGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAVRRTTMTA IQALSARTYNSWGQGLTVTVSS
381	AS310012VH5	EVQLVESGGGLVQPGGSLRLSCAASGYTYSRLVMAWFRQAPGKGLEGVAVIYT GGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAVRRTTMTA IQALSARTYNSWGQGLTVTVSS
382	AS310012VH6	EVQLVESGGGLVQPGGSLRLSCAASGYTYSRLVMAWFRQAPGKGLEGVSVIYT GGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAVRRTTMTA IQALSARTYNSWGQGLTVTVSS
383	AS310012VH7	EVQLVESGGGLVQPGGSLRLSCAASGYTYSRLVMAWFRQAPGKGLEGVAVIYT GGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAVRRTTMTA IQALSARTYNSWGQGLTVTVSS
384	AS310012VH8	EVQLVESGGGLVQPGGSLRLSCAASGYTYSRLVMAWFRQAPGKEREKVAVIYT GGGSTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAAVRRTTMTA IQALSARTYNSWGQGLTVTVSS
385	AS310027VH4	EVQLVESGGGLVQPGGSLRLSCAASGYIFSRGCMGWYRQAPGKGLEWVSSIRF DGTTSYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKPLCQGVGPA WGQGLTVTVSS
386	AS310027VH5	EVQLVESGGGLVQPGGSLRLSCAASGYIFSRGCMGWYRQAPGKGLEWISSIRFD GTTSYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAKPLCQGVGPAW GQGLTVTVSS
387	AS310027VH6	EVQLVESGGGLVQPGGSLRLSCAASGYIFSRGCMGWYRQAPGKGLEWVSSIRF DGTTSYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYLCAPKPLCQGVGPA WGQGLTVTVSS

388	AS310027VH7	EVQLVESGGGLVQPGGSLRLSCAASGYIFSRCGMGWYRQAPGKGLEWISSIRFD GTTSYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYLC AKPLCQGVGPAW GQGTLVTVSS
389	AS310027VH8	EVQLVESGGGLVQPGGSLRLSCAASGYIFSRCGMGWYRQAPGKEREWVSSIRFD GTTSYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYLC AKPLCQGVGPAW GQGTLVTVSS
390	AS310027VH9	EVQLVESGGGLVQPGGSLRLSCAASGYIFSRCGMGWYRQAPGKEREWISSIRFD GTTSYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYLC AKPLCQGVGPAW GQGTLVTVSS

WHAT IS CLAIMED IS

1. An anti-GPRC5D V_HH, comprising:

(1) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 4;

(2) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 8;

(3) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 12;

(4) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 16;

(5) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 20;

(6) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 24;

(7) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 28;

(8) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 32;

(9) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 36;

(10) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 40;

(11) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 44;

(12) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 48;

(13) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 52;

(14) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 56;

(15) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 60;

(16) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 64;

(17) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,

and CDR3, respectively, as set forth in SEQ ID NO: 68;

(18) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 72;

(19) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 76;

(20) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 80;

(21) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 84;

(22) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 88;

(23) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 92;

(24) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 96;

(25) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 100;

(26) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 104;

(27) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 108;

(28) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 112;

(29) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 115;

(30) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 119;

(31) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 123;

(32) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 127;

(33) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 131;

(34) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 135;

(35) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 139;

(36) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 143;

(37) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 147;

(38) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 151;

(39) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 155;

(40) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 159;

(41) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 163;

(42) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 167;

(43) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 171;

(44) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 175;

(45) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 179;

(46) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 183;

(47) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 187;

(48) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 190;

(49) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 193;

(50) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 197;

(51) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 201;

(52) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2,

and CDR3, respectively, as set forth in SEQ ID NO: 205;

(53) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 209;

(54) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 213;

(55) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 216;

(56) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 220;

(57) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 224;

(58) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 228;

(59) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 232;

(60) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 236;

(61) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 240;

(62) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 244;

(63) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 248;

(64) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 252;

(65) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 256;

(66) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 260;

(67) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 264;

(68) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 266;

(69) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 270;

(70) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 274;

(71) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 278;

(72) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 282;

(73) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 286;

(74) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 290;

(75) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 294;

(76) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 298;

(77) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 302;

(78) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 306; or

(79) a CDR1, a CDR2, and a CDR3 having the amino acid sequences of the CDR1, CDR2, and CDR3, respectively, as set forth in SEQ ID NO: 310.

2. The V_{HH} of claim 1, wherein the CDR1, CDR2 or CDR3 are determined according to the AbM numbering scheme, the IMGT numbering scheme, the Kabat numbering scheme, the Chothia numbering scheme, the Contact numbering scheme, or any combination thereof.

3. An anti-GPRC5D V_{HH} , comprising a CDR1, a CDR2, and a CDR3, respectively comprising the amino acid sequences of:

- (1) SEQ ID NO: 5, 6 and 7; or (2) SEQ ID NO: 9, 10 and 11; or
- (3) SEQ ID NO: 13, 14 and 15; or (4) SEQ ID NO: 17, 18 and 19; or
- (5) SEQ ID NO: 21, 22 and 23; or (6) SEQ ID NO: 25, 26 and 27; or
- (7) SEQ ID NO: 29, 30 and 31; or (8) SEQ ID NO: 33, 34 and 35; or
- (9) SEQ ID NO: 37, 38 and 39; or (10) SEQ ID NO: 41, 42 and 43; or
- (11) SEQ ID NO: 45, 46 and 47; or (12) SEQ ID NO: 49, 50 and 51; or
- (13) SEQ ID NO: 53, 54 and 55; or (14) SEQ ID NO: 57, 58 and 59; or
- (15) SEQ ID NO: 61, 62 and 63; or (16) SEQ ID NO: 65, 66 and 67; or
- (17) SEQ ID NO: 69, 70 and 71; or (18) SEQ ID NO: 73, 74 and 75; or
- (19) SEQ ID NO: 77, 78 and 79; or (20) SEQ ID NO: 81, 82 and 83; or

(21) SEQ ID NO: 85, 86 and 87; or (22) SEQ ID NO: 89, 90 and 91; or
(23) SEQ ID NO: 93, 94 and 95; or (24) SEQ ID NO: 97, 98 and 99; or
(25) SEQ ID NO: 101, 102 and 103; or (26) SEQ ID NO: 105, 106 and 107; or
(27) SEQ ID NO: 109, 110 and 111; or (28) SEQ ID NO: 81, 113 and 114; or
(29) SEQ ID NO: 116, 117 and 118; or (30) SEQ ID NO: 120, 121 and 122; or
(31) SEQ ID NO: 124, 125 and 126; or (32) SEQ ID NO: 128, 129 and 130; or
(33) SEQ ID NO: 132, 133 and 134; or (34) SEQ ID NO: 136, 137 and 138; or
(35) SEQ ID NO: 140, 141 and 142; or (36) SEQ ID NO: 144, 145 and 146; or
(37) SEQ ID NO: 148, 149 and 150; or (38) SEQ ID NO: 152, 153 and 154; or
(39) SEQ ID NO: 156, 157 and 158; or (40) SEQ ID NO: 160, 161 and 162; or
(41) SEQ ID NO: 164, 165 and 166; or (42) SEQ ID NO: 168, 169 and 170; or
(43) SEQ ID NO: 172, 173 and 174; or (44) SEQ ID NO: 176, 177 and 178; or
(45) SEQ ID NO: 180, 181 and 182; or (46) SEQ ID NO: 184, 185 and 186; or
(47) SEQ ID NO: 136, 188 and 189; or (48) SEQ ID NO: 191, 192 and 138; or
(49) SEQ ID NO: 194, 195 and 196; or (50) SEQ ID NO: 198, 199 and 200; or
(51) SEQ ID NO: 202, 203 and 204; or (52) SEQ ID NO: 206, 207 and 208; or
(53) SEQ ID NO: 210, 211 and 212; or (54) SEQ ID NO: 120, 214 and 215; or
(55) SEQ ID NO: 217, 218 and 219; or (56) SEQ ID NO: 221, 222 and 223; or
(57) SEQ ID NO: 225, 226 and 227; or (58) SEQ ID NO: 229, 230 and 231; or
(59) SEQ ID NO: 233, 234 and 235; or (60) SEQ ID NO: 237, 238 and 239; or
(61) SEQ ID NO: 241, 242 and 243; or (62) SEQ ID NO: 245, 246 and 247; or
(63) SEQ ID NO: 249, 250 and 251; or (64) SEQ ID NO: 253, 254 and 255; or
(65) SEQ ID NO: 257, 258 and 259; or (66) SEQ ID NO: 261, 262 and 263; or
(67) SEQ ID NO: 5, 6 and 265; or (68) SEQ ID NO: 267, 268 and 269; or
(69) SEQ ID NO: 271, 272 and 273; or (70) SEQ ID NO: 275, 276 and 277; or
(71) SEQ ID NO: 279, 280 and 281; or (72) SEQ ID NO: 283, 284 and 285; or
(73) SEQ ID NO: 287, 288 and 289; or (74) SEQ ID NO: 291, 292 and 293; or
(75) SEQ ID NO: 295, 296 and 297; or (76) SEQ ID NO: 299, 300 and 301; or
(77) SEQ ID NO: 303, 304 and 305; or (78) SEQ ID NO: 307, 308 and 309; or
(79) SEQ ID NO: 311, 312 and 313.

4. The V_HH of any one of claims 1-3, comprising the amino acid sequence of SEQ ID NO: 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, 96, 100, 104, 108, 112, 115, 119, 123, 127, 131, 135, 139, 143, 147, 151, 155, 159, 163, 167, 171, 175, 179, 183, 187, 190, 193, 197, 201, 205, 209, 213, 216, 220, 224, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 266, 270, 274, 278, 282, 286, 290, 294, 298, 302, 306 or 310, or an amino acid

sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

5. The V_HH of any one of claims 1-4, which is camelid, chimeric or humanized.

6. The V_HH of claim 5, comprising the amino acid sequence of SEQ ID NO: 16, 24, 48, 143, 179, 187, 193, 220, 244, 274, 298, 302, 306 or 310, or an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

preferably, the V_HH comprising the amino acid sequence of any one of the followings:

(1) SEQ ID NO: 328, 329, 330, 331, 332 or 333; (2) SEQ ID NO: 334, 335, 336 or 337;

(3) SEQ ID NO: 338, 339, 340, 341 or 342; (4) SEQ ID NO: 343, 344, 345 or 346;

(5) SEQ ID NO: 347, 348 or 349; (6) SEQ ID NO: 350, 351 or 352;

(7) SEQ ID NO: 353, 354, 355, 356, 357 or 358; (8) SEQ ID NO: 359, 360, 361, 362 or 363;

(9) SEQ ID NO: 364, 365, 366 or 367; (10) SEQ ID NO: 368, 369, 370 or 371;

(11) SEQ ID NO: 372, 373, 374, 375 or 376; (12) SEQ ID NO: 377, 378 or 379;

(13) SEQ ID NO: 380, 381, 382, 383 or 384;

(14) SEQ ID NO: 385, 386, 387, 388, 389 or 390.

7. A polypeptide construct, comprising the V_HH of any one of claims 1 to 6.

8. The polypeptide construct of claim 7, wherein the construct is a monospecific molecule, a bispecific molecule, a multispecific molecule, an immunoconjugate, or a fusion protein;

preferably, the monospecific molecule is a sdAb, or antigen binding fragment thereof.

9. The polypeptide construct of claim 7 or 8, wherein the construct comprising an additional polypeptide.

10. The polypeptide construct of claim 9, the additional polypeptide is an immunoglobulin Fc region;

preferably, the immunoglobulin Fc region is an IgG Fc region, e.g., an IgG1, IgG2, IgG3, or IgG4 Fc region.

11. The polypeptide construct of claim 9, the additional polypeptide is an additional binding domain that binds to a second target other than GPRC5D;

preferably, wherein the second target is selected from CD3, CD33, CD19, CD20, CD22, CD30, CD70, CLL-1, BCMA, DLL-3, Claudin 6, Claudin 18.2, GPC3, GPC2, CD229, FcRH5, GUCY2C, mesothelin, HER2, PSMA, or PSCA.

12. The polypeptide construct of claim 11, wherein the additional binding domain is a monovalent antibody fragment, e.g., a Fab, an Fv, a scFv, a sdAb, or a V_HH.

13. A nucleic acid molecule comprising a nucleotide sequence encoding the V_HH of any one of claims 1 to 6, or the polypeptide construct of claims 7 to 12.

14. A vector comprising the nucleic acid molecule of claim 13.

15. A cell comprising the nucleic acid molecule of claim 13, or the vector of claim 14.

16. A method of producing the V_HH of any one of claims 1 to 6, or the polypeptide construct of claims 7 to 12, comprising: culturing a host cell comprising the nucleic acid molecule of claim 13 or the vector of claim 14, or the cell of claim 15 under a condition that allows protein expression, and recovering the V_HH, or the polypeptide construct from a culture of the cultured cell.

17. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain, a transmembrane domain and an intracellular signaling domain, wherein the extracellular antigen-binding domain comprises a first binding moiety that specifically binds to a first antigen or epitope, wherein the first binding moiety comprises the V_HH of any one of claims 1 to 6, or the polypeptide construct of claims 7 to 12.

18. The chimeric antigen receptor of claim 17, wherein the extracellular antigen-binding domain further comprises a second binding moiety that specifically binds to a second antigen or epitope;

preferably, wherein the first antigen or epitope is the same as the second antigen or epitope;

preferably, wherein the first antigen or epitope is different from the second antigen or epitope;

preferably, wherein the first binding moiety and the second binding moiety are linked in tandem.

19. The chimeric antigen receptor of claim 17 or 18, wherein the second binding moiety is an sdAb, an scFv, or an extracellular domain of a receptor;

preferably, wherein the second binding moiety is an anti-tumor antigen sdAb or scFv, and the tumor antigen selected from CD33, CD19, CD20, CD22, CD30, CD70, CLL-1, BCMA, DLL3, Claudin 6, Claudin 18.2, GPC3, GPC2, GPRC5D, CD229, FcRH5, GUCY2C, mesothelin, HER2, PSMA, or PSCA;

preferably, wherein the second binding moiety is an anti-GPRC5D sdAb, and comprises the V_HH of any one of claims 1 to 6, or the polypeptide construct of claims 7 to 12.

20. The chimeric antigen receptor of any one of claims 17 to 19, wherein the CAR further comprising a spacer domain is selected from a hinge domain and/or CH2 and CH3 regions of an immunoglobulin (e.g., IgG1 or IgG4);

preferably, the hinge domain comprises a hinge region of CD8 α , IgG4, PD1, CD152 or CD154;

preferably, the spacer domain comprises a hinge region of CD8 α (e.g., a sequence as set forth in SEQ ID NO: 316).

21. The chimeric antigen receptor of any one of claims 17 to 20, wherein transmembrane domain is selected from one or more transmembrane regions selected from the group consisting of: α , β or ζ chain of T cell receptor, CD3 ϵ , CD3 ζ , CD4, CD5, CD8 α , CD28, CD137, CD152, CD154 and PD1;

preferably, the transmembrane domain comprises a transmembrane region of CD8 α (e.g., a sequence as set forth in SEQ ID NO: 317).

22. The chimeric antigen receptor of any one of claims 17 to 21, wherein the intracellular signaling domain comprises a primary signaling domain and/or a costimulatory signaling domain;

preferably, the intracellular signaling domain comprises a primary signaling domain and at least one costimulatory signaling domain;

preferably, the primary signaling domain comprises an intracellular signaling domain of a protein selected from the group consisting of: CD3 ζ , FcR γ , FcR β , CD3 γ , CD3 δ , CD3 ϵ , CD5, CD22, CD79a, CD79b and CD66d;

preferably, the costimulatory signaling domain comprises an intracellular signaling domain of a protein selected from the group consisting of: CARD11, CD2, CD7, CD27, CD28, CD30, CD54 (ICAM), CD83, CD134 (OX40), CD137 (4-1BB), CD150 (SLAMF1), CD152 (CTLA4), CD223 (LAGS), CD270 (HVEM), CD273 (PD-L2), CD274 (PD-L1), CD278 (ICOS), DAP10 and DAP12;

preferably, the intracellular signaling domain comprises a primary signaling domain and a costimulatory signaling domain, wherein the primary signaling domain comprises an intracellular signaling domain of CD3 ζ (e.g., a sequence as set forth in SEQ ID NO: 319), the costimulatory signaling domain comprises an intracellular signaling domain of CD137 (e.g., a sequence as set forth in SEQ ID NO: 318).

23. The chimeric antigen receptor of any one of claims 17 to 22, wherein the chimeric antigen receptor further comprises a signal peptide and/or a tag;

preferably, the tag is selected from a myc-tag, a His-tag, a short linear peptide sequence from yeast transcription factor GCN4, a leucine zipper sequence or a short linear peptide sequence from a human nuclear protein;

preferably, the tag is a myc-tag, and the myc-tag comprises a sequence as set forth in SEQ ID NO: 315;

preferably, the signal peptide is derived from a molecule selected from the group consisting of CD8 α , GM-CSF receptor α , and IgG1 heavy chain;

preferably, the signal peptide comprises a sequence as set forth in SEQ ID NO: 314;

preferably, the chimeric antigen receptor comprises the following domains in sequence from the N-terminal to the C-terminal: the signal peptide, the tag, the antigen-binding domain, the

spacer domain, the transmembrane domain and the intracellular signaling domain.

24. A dual-chimeric antigen receptor (CAR), comprising:

a first engineered receptor comprising the chimeric antigen receptor of any one of claims 17-23; and

a second engineered receptor comprising: a second extracellular antigen-binding domain a second transmembrane domain and a second intracellular domain;

preferably, wherein the second extracellular antigen-binding domain is an anti-tumor antigen sdAb or scFv, and the tumor antigen selected from BCMA, CD33, CD19, CD20, CD22, CD30, CD70, CLL-1, DLL3, Claudin 6, Claudin 18.2, GPC3, GPC2, GPRC5D, CD229, FcRH5, GUCY2C, mesothelin, HER2, PSMA, or PSCA.

25. A nucleic acid molecule comprising a nucleotide sequence encoding the chimeric antigen receptor of any one of claims 17 to 23 or the dual-chimeric antigen receptor of claim 24.

26. A vector comprising the nucleic acid molecule of claim 25.

27. A host cell, which comprises the nucleic acid molecule of claim 25 or the vector of claim 26;

preferably, the host cell is selected from an immune cell (e.g., human immune cell);

preferably, the immune cell is selected from the group consisting of T lymphocyte, NK cell, monocyte, macrophage or dendritic cell, and any combination thereof.

28. An engineered immune cell, which expresses the chimeric antigen receptor of any one of claims 17 to 23 or the dual-chimeric antigen receptor of claim 24;

optionally, the chimeric antigen receptor or the dual-chimeric antigen receptor is expressed on the surface of the engineered immune cell;

optionally, the engineered immune cell also expresses a chimeric antigen receptor that is not specific for GPRC5D;

preferably, the immune cell is selected from the group consisting of T lymphocyte, NK cell, monocyte, macrophage or dendritic cell and any combination thereof;

preferably, the immune cell is obtained from a patient or a healthy donor.

29. A pharmaceutical composition comprising the V_HH of any one of claims 1 to 6, the polypeptide construct of claims 7 to 12, or the chimeric antigen receptor of any one of claims 17 to 23, or the dual-chimeric antigen receptor of claim 24; and a pharmaceutically acceptable carrier and/or excipient.

30. The pharmaceutical composition of claim 29, which further comprises an additional therapeutic agent;

preferably, the additional therapeutic agent is an anti-tumor agent;

preferably, the additional therapeutic agent is a cytotoxic agent, such as an alkylating agent, an anti-mitotic agent, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, a tyrosine kinase inhibitor, or a radionuclide.

31. A method for preventing and/or treating a disease in a subject, the method comprising administering to a subject in need thereof an effective amount of the V_HH of any one of claims 1 to 6 or the polypeptide construct of claims 7 to 12 or the nucleic acid molecule of claim 13 or 25 or the vector of claim 14 or 26 or the cell of claim 15 or 27 or the chimeric antigen receptor of any one of claims 17 to 23 or the dual-chimeric antigen receptor of claim 24 or the engineered immune cell of claim 28 or the pharmaceutical composition according to claim 29 or 30;

preferably, the disease is tumor or autoimmune disease;

preferably, the tumor expresses GPRC5D;

preferably, the tumor is a solid tumor;

preferably, the tumor is a hematological malignancy, e.g., multiple myeloma;

preferably, the subject is a mammal, such as a human.