CHIMERIC ANTIGEN RECEPTORS TARGETING G-PROTEIN COUPLED RECEPTOR AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application Serial No. 62/088,286, filed December 5, 2014, the content of which is incorporated by reference in its entirety, and to which priority is claimed.

INTRODUCTION

The presently disclosed subject matter provides for methods and compositions for treating cancer. It relates to chimeric antigen receptors (CARs) that specifically target a G-protein coupled receptor (*e.g.*, a G-protein coupled receptor family C group 5 member D (GPRC5D)), immunoresponsive cells comprising such CARs, and methods of using such cells for treating cancer (e.g., multiple myeloma).

BACKGROUND OF THE INVENTION

Cell-based immunotherapy is a therapy with curative potential for the treatment of cancer. T cells and other immune cells may be modified to target tumor antigens through the introduction of genetic material coding for artificial or synthetic receptors for antigen, termed Chimeric Antigen Receptors (CARs), specific to selected antigens. Targeted T cell therapy using CARs has shown recent clinical success in treating hematologic malignancies.

Multiple myeloma (MM) is the second most common hematologic malignancy.[9] Approximately 25% of patients have high-risk cytogenetics, which portends a median survival of less then 2 years.[10,11] While recent strides have been made, regardless of cytogenetics, the disease is still considered incurable outside the immuno-therapeutic graft versus myeloma (GvM) effect of an allogeneic transplant. However, allogeneic transplants are limited by ineligibility and high rates of transplant-associated morbidity and mortality.[12] Similar to the GvM effect, a potentially curative T cell effect may be achieved with minimal toxicity through autologous adoptive T cell therapy.

Myeloma may be an ideal disease to test adoptive T cell therapy. First, as indicated above, allogeneic transplants demonstrate that the T cell can be a curative treatment, even with minimal or no concomitant chemotherapy such as after non-myeloablative transplants or post-transplantation donor lymphocyte infusions.

Second, conditioning chemotherapy, possibly through the mechanism of depleting regulatory T cells (Tregs), enhances the efficacy of adoptive T cell therapy,[5,13] as such, the immediate post-autologous transplant period could be an optimal time to administer T cells, and myeloma is one of the few diseases where autologous stem cell transplantation is the standard of care. Third, the immunomodulatory drug lenalidomide may improve CAR based therapy, as has been shown in mice,[14] and lenalidomide is commonly used to treat MM. Fourth, adoptive T cell therapy works best in bone marrow predominant disease such as ALL,[7,8] when compared to solid tumors or extra-medullary CLL,[5] and similar to ALL, myeloma is a disease of the bone marrow.

While there are various reasons to expect that adoptive T cell therapy may work well in MM, expanding adoptive T cell therapy to myeloma also poses unique challenges. Unlike other B-cell malignancies, CD19 expression is seen in only 2% of myeloma patients.[15] Furthermore, unlike CD19, the common extracellular immunophenotypic markers in myeloma (CD138, CD38, and CD56) are all co-expressed on other essential cell types, and we predict CARs to any of these targets would lead to unacceptable "off tumor, on target" toxicity[7] which can be fatal even in targets where antibodies are well tolerated, as was the case with a HER2 targeted CAR.[16] To address these challenges, we have identified extracellular targets with predicted high MM and limited essential normal tissue expression that may be optimal targets for adoptive T cell therapy of MM. Accordingly, there are needs for novel therapeutic strategies to design CARs targeting antigens that are highly expressed in MM cells and limited expression in normal tissues for treating multiple myeloma, which strategies capable of inducing potent tumor eradication with minimal toxicity and immunogenicity.

SUMMARY OF THE INVENTION

The presently disclosed subject matter generally provides chimeric antigen receptors (CARs) that specifically target a G-protein coupled receptor, immunoresponsive cells comprising such CARs, and uses of these CARs and immunoresponsive cells for treating multiple myeloma.

The presently disclosed subject matter provides CARs. In one non-limiting example, the CAR comprises an extracellular antigen-binding domain, a transmembrane domain and an intracellular domain, where the extracellular antigen-

binding domain specifically binds to a G-protein coupled receptor. In certain embodiments, the G-protein coupled receptor is a G-protein coupled receptor family C group 5 member D (GPRC5D). In certain embodiments, the extracellular antigen-binding domain specifically binds to GPRC5D with a binding affinity (K_D) of from about 1 x 10^{-9} M to about 3 x 10^{-6} M. In certain embodiments, the extracellular antigen-binding domain is a single-chain variable fragment (scFv). In certain embodiments, the extracellular antigen-binding domain is a murine scFv. In certain embodiments, the extracellular antigen-binding domain is a human scFv. In certain embodiments, the extracellular antigen-binding domain is a Fab, which is optionally crosslinked. In certain embodiments, the extracellular binding domain is a $F(ab)_2$. In certain embodiments, any of the foregoing molecules can be comprised in a fusion protein with a heterologous sequence to form the extracellular antigen-binding domain.

In certain embodiments, the extracellular antigen-binding domain comprises a heavy chain variable region comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOS:1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386.

In certain embodiments, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOS:2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387.

In certain embodiments, the extracellular antigen-binding domain comprises (a) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous

to an amino acid sequence selected from the group consisting of SEQ ID NO: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386; and (b) a light chain variable region comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387.

In certain embodiments, the extracellular antigen-binding domain comprises a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386, and conservative modifications thereof.

In certain embodiments, the extracellular antigen-binding domain comprises a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387, and conservative modifications thereof.

In certain embodiments, the extracellular antigen-binding domain comprises (a) a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS:1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386, and conservative modifications thereof, and (b) a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387, and conservative modifications thereof.

In certain embodiments, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having a sequence selected from the group consisting of: SEQ ID NOS:1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386. In certain embodiments, the extracellular antigen-binding domain comprises a light

chain variable region comprising amino acids having a sequence selected from the group consisting of: SEQ ID NOS:2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387. In certain embodiments, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:53. In certain embodiments, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:57. In certain embodiments, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:61. In certain embodiments, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:65. In certain embodiments, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:69. In certain embodiments, the extracellular antigen-binding domain comprises a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:54. In certain embodiments, the extracellular antigen-binding domain comprises a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:58. In certain embodiments, the extracellular antigen-binding domain comprises a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:62. In certain embodiments, the extracellular antigen-binding domain comprises a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:66. In certain embodiments, the extracellular antigen-binding domain comprises a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:70. In certain embodiments, the extracellular antigen-binding domain comprises (a) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:1, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:2; (b) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:5, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:6; (c) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:9, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:10; (d) a heavy chain variable region comprising amino acids having a sequence

set forth in SEQ ID NO:13, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:14; (e) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:17, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:18; (f) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:21, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:22; (g) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:25, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:26; (h) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:29, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:30; (i) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:33, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:34; (j) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:37, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:38; (k) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:41, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:42; (l) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:45, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:46; (m) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:49, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:50; (n) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:53, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:54; (o) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:57, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:58; (p) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:61, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:62; (q) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:65, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID

NO:66; (r) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:69, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:70; (s) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:73, an da light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:74; (t) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:77, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:78; (u) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:81, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:82; (v) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:85, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:86; (w) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:89, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:90; (x) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:93, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:94, (y) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:302, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:303; (z) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:314, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:315; (aa) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:326, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:327; (ab) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:338, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:339; (ac) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:350, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:351; (ad) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:362, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:363; (ae) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID

NO:374, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:375; or (af) a heavy chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:386, and a light chain variable region comprising amino acids having a sequence set forth in SEQ ID NO:387. In certain embodiments, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:53; and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:54. In certain embodiments, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:57; and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:58. In certain embodiments, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:61; and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:62. In another embodiment, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:65; and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:66. In yet another embodiment, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:69; and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:70.

In certain embodiments, the extracellular antigen-binding domain comprises both of said heavy and light chains, optionally with a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. For example, in certain non-limiting embodiments, the extracellular antigen-binding domain comprises (i) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:57 and (ii) a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:58, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the extracellular antigen-binding domain comprises (i) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:61 and (ii) a light chain variable region comprising amino acids having the sequence set forth in

SEQ ID NO:62, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the extracellular antigen-binding domain comprises (i) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:53 and (ii) a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:54, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the extracellular antigen-binding domain comprises (i) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:61 and (ii) a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:62, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the extracellular antigen-binding domain comprises (i) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:65 and (ii) a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:66, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the extracellular antigen-binding domain comprises (i) a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:69 and (ii) a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:70, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region.

In certain embodiments, the extracellular antigen-binding domain comprises (a) a heavy chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 126, 132, 138, 144, 150, 156, 162, 168, 174, 180, 186, 192, 198, 204, 210, 216, 222, 228, 234, 240, 246, 252, 258, 264, 306, 318, 330, 342, 354, 366, 378, and 390; and (b) a light chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 129, 135, 141, 147, 153, 159, 165, 171, 177, 183, 189, 195, 201, 207, 213, 219, 225, 231, 237, 243, 249, 255, 261, 267, 309, 321, 333, 345, 357, 369, 381, and 393.

In certain embodiments, the heavy chain variable region CDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 125, 131,

137, 143, 149, 155, 161, 167, 173, 179, 185, 191, 197, 203, 209, 215, 221, 227, 233, 239, 245, 251, 257, 263, 305, 317, 329, 341, 353, 365, 377, and 389, and conservative modifications thereof; and (b) the light chain variable region CDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 128, 134, 140, 146, 152, 158, 164, 170, 176, 182, 188, 194, 200, 206, 212, 218, 224, 230, 236, 242, 248, 254, 260, 266, 308, 320, 332, 344, 356, 368, 380, and 392, and conservative modifications thereof.

In certain embodiments, the heavy chain variable region CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 124, 130, 136, 142, 148, 154, 160, 166, 172, 178, 184, 190, 196, 202, 208, 214, 220, 226, 232, 238, 244, 250, 256, 262, 304, 316, 328, 340, 352, 364, 376, and 388, and conservative modifications thereof; and (b) the light chain variable region CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 127, 133, 139, 145, 151, 157, 163, 169, 175, 181, 187, 193, 199, 205, 211, 217, 223, 229, 235, 241, 247, 253, 259, 265, 307, 319, 331, 343, 355, 367, 379, and 391, and conservative modifications thereof.

In certain embodiments, the extracellular antigen-binding domain comprises: (a) a heavy chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 124, 130, 136, 142, 148, 154, 160, 166, 172, 178, 184, 190, 196, 202, 208, 214, 220, 226, 232, 238, 244, 250, 256, 262, 304, 316, 328, 340, 352, 364, 376, and 388; (b) a heavy chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 125, 131, 137, 143, 149, 155, 161, 167, 173, 179, 185, 191, 197, 203, 209, 215, 221, 227, 233, 239, 245, 251, 257, 263, 305, 317, 329, 341, 353, 365, 377, and 389; (c) a heavy chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 126, 132, 138, 144, 150, 156, 162, 168, 174, 180, 186, 192, 198, 204, 210, 216, 222, 228, 234, 240, 246, 252, 258, 264, 306, 318, 330, 342, 354, 366, 378, and 390; (d) a light chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 127, 133, 139, 145, 151, 157, 163, 169, 175, 181, 187, 193, 199, 205, 211, 217, 223, 229, 235, 241, 247, 253, 259, 265, 307, 319, 331, 343, 355, 367, 379, and 391; (e) a light chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 128, 134, 140, 146, 152, 158, 164, 170, 176, 182, 188, 194, 200, 206, 212, 218, 224, 230, 236, 242, 248, 254, 260, 266, 308,

320, 332, 344, 356, 368, 380, and 392; and (f) a light chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 129, 135, 141, 147, 153, 159, 165, 171, 177, 183, 189, 195, 201, 207, 213, 219, 225, 231, 237, 243, 249, 255, 261, 267, 309, 321, 333, 345, 357, 369, 381, and 393.

In certain embodiments, the extracellular antigen-binding domain comprises (a) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 124 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 125 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 126 or conservative modifications thereof; (b) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 130 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 131 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 132 or conservative modifications thereof; (c) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 136 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 137 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 138 or conservative modifications thereof; (d) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 142 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 143 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 144 or conservative modifications thereof; (e) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 148 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 149 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 150 or conservative modifications thereof; (f) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 154 or

conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 155 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 156 or conservative modifications thereof; (g) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 160 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 161 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 162 or conservative modifications thereof; (h) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 166 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 167 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 168 or conservative modifications thereof; (i) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 172 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 173 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 174 or conservative modifications thereof; (j) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 178 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 179 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 180 or conservative modifications thereof; (k) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 184 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 185 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 186 or conservative modifications thereof; (l) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 190 or conservative modifications thereof; a heavy chain variable region CDR2 comprising

amino acids having the sequence set forth in SEQ ID NO: 191 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 192 or conservative modifications thereof; (m) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 196 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 197 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 198 or conservative modifications thereof; (n) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 202 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 203 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 204 or conservative modifications thereof; (o) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 208 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 209 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 210 or conservative modifications thereof; (p) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 214 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 215 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 216 or conservative modifications thereof; (q) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 220 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 221 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 222 or conservative modifications thereof; (r) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 226 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 227 or conservative

modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 228 or conservative modifications thereof; (s) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 232 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 233 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 234 or conservative modifications thereof; (t) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 238 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 239 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 240 or conservative modifications thereof; (u) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 244 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 245 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 246 or conservative modifications thereof; (v) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 250 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 251 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 252 or conservative modifications thereof; (w) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 256 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 257 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 258 or conservative modifications thereof; (x) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 262 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 263 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino

acids having the sequence set forth in SEQ ID NO: 264 or conservative modifications thereof; (y) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 304 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 305 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 306 or conservative modifications thereof; (z) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 316 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 317 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 318 or conservative modifications thereof; (aa) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 328 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 329 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 330 or conservative modifications thereof; (ab) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 340 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 341 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 342 or conservative modifications thereof; (ac) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 352 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 353 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 354 or conservative modifications thereof; (ad) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 364 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 365 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 366 or conservative modifications

thereof; (ae) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 376 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 377 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 378 or conservative modifications thereof; or (af) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 388 or conservative modifications thereof; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 389 or conservative modifications thereof; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 390 or conservative modifications thereof . In certain embodiments, the extracellular antigen-binding domain comprises: a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 202; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 203; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 204. In certain embodiments, the extracellular antigen-binding domain comprises: a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 208; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 209; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 210. In another non-limiting embodiment, the extracellular antigen-binding domain comprises: a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 214; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 215; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 216. In yet another non-limiting embodiment, the extracellular antigen-binding domain comprises: a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 220; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 221; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 222. In another embodiment, the extracellular antigen-binding domain comprises: a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 226; a heavy

chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 227; and a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 228.

In certain embodiments, the extracellular antigen-binding domain comprises: (a) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 127 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:129 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 130 or conservative modifications thereof; (b) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 133 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:134 or conservative modifications thereof; and a light chain variable region CDR3 comprising SEQ ID NO: 135 or conservative modifications thereof; (c) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 139 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:140 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 141 or conservative modifications thereof; (d) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 145 or conservative modifications thereof; a light chain variable region CDR2 comprising SEQ ID NO:146 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 147 or conservative modifications thereof; (e) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 151 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:152 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 153 or conservative modifications thereof; (f) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 157 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:158 or conservative modifications

thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 159 or conservative modifications thereof; (g) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 163 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:164 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 165 or conservative modifications thereof; (h) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 169 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:170 or conservative modifications thereof; and a light chain variable region CDR3 comprising SEQ ID NO: 171 or conservative modifications thereof; (i) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 175 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:176 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 177 or conservative modifications thereof; (j) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 181 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:182 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 183 or conservative modifications thereof; (k) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 187 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:188 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 189 or conservative modifications thereof; (l) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 193 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:194 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 195 or

conservative modifications thereof; (m) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 199 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:200 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 201 or conservative modifications thereof; (n) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 205 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:206 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 207 or conservative modifications thereof; (o) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 211 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:212 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 213 or conservative modifications thereof; (p) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 217 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:218 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 219 or conservative modifications thereof; (q) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 223 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:224 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 225 or conservative modifications thereof; (r) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 229 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:230 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 231 or conservative modifications thereof; (s) a light chain variable region CDR1

comprising amino acids having the sequence set forth in SEQ ID NO: 235 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:236 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 237 or conservative modifications thereof; (t) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 241 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:242 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 243 or conservative modifications thereof; (u) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 247 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:248 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 249 or conservative modifications thereof; (v) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 253 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:254 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 255 or conservative modifications thereof; (w) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 259 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:260 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 261 or conservative modifications thereof; (x) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 265 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:266 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 267 or conservative modifications thereof; (y) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 307 or

conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 308 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 309 or conservative modifications thereof; (z) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 319 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:320 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 321 or conservative modifications thereof; (aa) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 331 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 332 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 333 or conservative modifications thereof; (ab) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 343 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:344 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 345 or conservative modifications thereof; (ac) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 355 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 356 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 357 or conservative modifications thereof; (ad) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 367 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 368 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 369 or conservative modifications thereof; (ae) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 379 or conservative modifications thereof; a light chain variable region CDR2 comprising

amino acids having the sequence set forth in SEQ ID NO: 380 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 381 or conservative modifications thereof; or (af) a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 391 or conservative modifications thereof; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 392 or conservative modifications thereof; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 393 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises: a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 205; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:206; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 207. In certain embodiments, the extracellular antigen-binding domain comprises: a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 211; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:212; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 213. In certain embodiments, the extracellular antigen-binding domain comprises: a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 217; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:218; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 219. In another non-limiting embodiment, the extracellular antigen-binding domain comprises: a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 223; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:224; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 225. In yet another non-limiting embodiment, the extracellular antigen-binding domain comprises: a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 229; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:230; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 231.

In certain embodiments, the extracellular antigen-binding domain comprises: (a) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 124; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 125; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 126; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 127; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:128; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 129; (b) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 130; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 131; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 132; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 133; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:134; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 135; (c) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 136; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 137; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 138; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 139; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:140; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 141; (d) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 142; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 143; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 144; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 145; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:146; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 147; (e) a heavy chain variable region CDR1 comprising amino acids having the sequence set

forth in SEQ ID NO: 148; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 149; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 150; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 151; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:152; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 153; (f) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 154; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 155; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 156; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 157; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:158; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 159; (g) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 160; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 161; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 162; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 163; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:164; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 165; (h) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 166; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 167; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 168; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 169; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:170; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 171; (i) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 172; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 173; a heavy chain variable region

CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 174; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 175; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:176; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 177; (j) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 178; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 179; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 180; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 181; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:182; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 183; (k) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 184; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 185; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 186; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 187; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:188; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 189; (l) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 190; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 191; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 192; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 193; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:194; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 195; (m) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 196; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 197; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 198; a light chain variable region CDR1 comprising amino acids having the sequence set

forth in SEQ ID NO: 199; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:200; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 201; (n) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 202; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 203; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 204; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 205; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:206; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 207; (o) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 208; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 209; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 210; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 211; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:212; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 213; (p) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 214; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 215; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 216; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 217; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:218; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 219; (q) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 220; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 221; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 222; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 223; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:224; and a light chain variable region

CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 225; (r) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 226; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 227; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 228; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 229; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:230; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 231; (s) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 232; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 233; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 234; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 235; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:236; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 237; (t) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 238; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 239; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 240; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 241; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:242; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 243; (u) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 244; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 245; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 246; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 247; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:248; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 249; (v) a heavy chain variable region CDR1 comprising amino acids having the sequence set

forth in SEQ ID NO: 250; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 251; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 252; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 253; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:254; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 255; (w) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 256; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 257; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 258; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 259; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:260; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 261; (x) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 262; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 263; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 264; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 265; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:266; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 267; (y) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 304; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 305; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 306; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 307; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 308; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 309; (z) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 316; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 317; a heavy chain variable region

CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 318; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 319; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 320; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 321; (aa) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 328; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 329; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 330; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 331; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 332; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 333; (ab) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 340; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 341; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 342; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 343; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 344; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 345; (ac) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 352; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 353; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 354; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 355; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 356; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 357; (ad) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 364; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 365; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 366; a light chain variable region CDR1 comprising amino acids having the sequence set

forth in SEQ ID NO: 367; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 368; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 369; (ae) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 376; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 377; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 378; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 379; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 380; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 381; or (af) a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 388; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 389; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 390; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 391; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 392; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 393. In certain embodiments, the extracellular antigen-binding domain comprises: a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 202; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 203; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 204; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 205; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:206; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 207. In certain embodiments, the extracellular antigen-binding domain comprises: a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 208; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 209; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 210; a light chain variable region CDR1 comprising amino acids having the sequence set

forth in SEQ ID NO: 211; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:212; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 213. In certain embodiments, the extracellular antigen-binding domain comprises: a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 214; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 215; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 216; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 217; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:218; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 219. In another non-limiting embodiment, the extracellular antigen-binding domain comprises: a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 220; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 221; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 222; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 223; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:224; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 225. In yet another non-limiting embodiment, the extracellular antigen-binding domain comprises: a heavy chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 226; a heavy chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 227; a heavy chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 228; a light chain variable region CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 229; a light chain variable region CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:230; and a light chain variable region CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 231.In certain embodiments, the human scFv comprises a heavy chain variable region, a light chain variable region, a linker peptide between the heavy chain variable region and the light chain variable region, and an His-tag and an HA-tag. In

certain embodiments, the amino acid sequence of the His-tag and HA-tag comprises the amino acid sequence of SEQ ID NO:275,which is provided below:

TSGQAGQHHHHHHGAYPYDVPDYAS [SEQ ID NO: 275]

The nucloetide sequence encoding SEQ ID NO: 275 is SEQ ID NO: 276, which is provided below:

ACTAGTGGCCAGGCCGGCCAGCACCATCACCATCACCATGGCGCAT ACCCGTACGACGTTCCGGACTACGCTTCT [SEQ ID NO: 276]

In certain embodiments, the GPRC5D comprises the amino acid sequence set forth in SEQ ID NO:97. In certain embodiments, the extracellular antigen-binding domain binds to one, two, three or four epitope region selected from the group consisting of an epitope region in N-terminal region comprising amino acids 1-27 of SEQ ID NO:97, an epitope region in ECL1 region comprising amino acids 85-93 of SEQ ID NO:97, an epitope region in ECL2 region comprising amino acids 145-167 of SEQ ID NO:97, and an epitope region in ECL3 region comprising amino acids 226-239 of SEQ ID NO:97. In certain embodiments, the extracellular antigen-binding domain binds to an epitope region comprising amino acids 16-23 of SEQ ID NO:97. In certain embodiments, the extracellular antigen-binding domain binds to an epitope region comprising amino acids 15-23 of SEQ ID NO:97. In certain embodiments, the extracellular antigen-binding domain binds to an epitope region comprising amino acids 16-25 of SEQ ID NO:97. In certain embodiments, the extracellular antigen-binding domain binds to an epitope region comprising amino acids 10-17 of SEQ ID NO:97. In certain embodiments, the extracellular antigen-binding domain binds to an epitope region comprising amino acids 5-17 of SEQ ID NO:97. In certain embodiments, the extracellular antigen-binding domain binds to an epitope region comprising amino acids 85-95 of SEQ ID NO:97. In certain embodiments, the extracellular antigen-binding domain binds to an epitope region comprising amino acids 157-164 of SEQ ID NO:97. In certain embodiments, the extracellular antigen-binding domain binds to an epitope region comprising amino acids 157-167 of SEQ ID NO:97. In certain embodiments, the extracellular antigen-binding domain binds to an epitope region comprising amino acids 230-237 of SEQ ID NO:97. In certain embodiments, the extracellular antigen-binding domain binds to an epitope region comprising amino acids 229-237 of SEQ ID NO:97. In certain embodiments, the extracellular antigen-binding domain binds to an epitope region comprising amino acids 230-243 of SEQ ID NO:97. In certain embodiments, the extracellular antigen-

binding domain binds to an epitope region comprising amino acids 227-237 of SEQ ID NO:97.

In certain embodiments, the extracellular antigen-binding domain binds to one, two, or three epitope region selected from the group consisting of an epitope region comprising amino acids 16-25 of SEQ ID NO:97, an epitope region comprising amino acids 157-164 of SEQ ID NO:97, and an epitope region comprising amino acids 229-237 of SEQ ID NO:97. For example, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:57 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:58. For example, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 208, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 209, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 210, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 211, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 212, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 213.

In certain embodiments, the extracellular antigen-binding domain binds to one, two, or three epitope region selected from the group consisting of an epitope region comprising amino acids 5-17 of SEQ ID NO:97, an epitope region comprising amino acids 85-95 of SEQ ID NO:97, and an epitope region comprising amino acids 157-164 of SEQ ID NO:97. For example, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:61 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:62. For example, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 214, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 215, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 216, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 217, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 218 and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 219.

In certain embodiments, the extracellular antigen-binding domain binds to one or two epitope region selected from the group consisting of an epitope region comprising amino acids 15-23 of SEQ ID NO:97, and an epitope region comprising amino acids 230-243 of SEQ ID NO:97. For example, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:65 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:66. For example, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 220, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 221, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 222, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 223, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 224, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 225.

In certain embodiments, the extracellular antigen-binding domain binds to one, two, or three epitope region selected from the group consisting of an epitope region comprising amino acids 10-17 of SEQ ID NO:97, an epitope region comprising amino acids 157-167 of SEQ ID NO:97, and an epitope region comprising amino acids 227-237 of SEQ ID NO:97. For example, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:69 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:70. For example, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 226, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 227, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 228, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 229, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 230, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 231.

In accordance with the presently disclosed subject matter, the extracellular antigen-binding domain is covalently joined to a transmembrane domain. The extracellular antigen-binding domain can comprise a signal peptide that is covalently

joined to the 5' terminus of the extracellular antigen-binding domain. In certain embodiments, the transmembrane domain of the CAR comprises a CD8 polypeptide, a CD28 polypeptide, a CD3ζ polypeptide, a CD4 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, a BTLA polypeptide, a synthetic peptide (not based on a protein associated with the immune response), or a combination thereof. In certain embodiments, the transmembrane domain comprises a CD8 polypeptide. In certain embodiments, the transmembrane domain comprises a CD28 polypeptide.

In accordance with the presently disclosed subject matter, the intracellular domain comprises a CD3ζ polypeptide. In certain embodiments, the intracellular domain further comprises at least one signaling region. In certain embodiments, the at least one signaling region comprises a CD28 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a DAP-10 polypeptide, a PD-1 polypeptide, a CTLA-4 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, a BTLA polypeptide, a synthetic peptide (not based on a protein associated with the immune response), or a combination thereof. In certain embodiments, the signaling region is a co-stimulatory signaling region. In certain embodiments, the co-stimulatory signaling region comprises a CD28 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a DAP-10 polypeptide, or a combination thereof. In certain embodiments, the at least one co-stimulatory signaling region comprises a CD28 polypeptide. In certain embodiments, the at least one co-stimulatory signaling region comprises a 4-1BB polypeptide. In certain embodiments, the transmembrane domain comprises a CD28 polypeptide, the intracellular domain comprises a CD3ζ polypeptide, and the co-stimulatory signaling domain comprises a CD28 polypeptide.

In certain embodiments, the CAR is recombinantly expressed. The CAR can be expressed from a vector. In certain embodiments, the vector is a γ-retroviral rector.

The presently disclosed subject matter also provides isolated immunoresponsive cells comprising the above-described CARs. In certain embodiments, the isolated immunoresponsive cell is transduced with the CAR, for example, the CAR is constitutively expressed on the surface of the immunoresponsive cell. In certain embodiments, the isolated immunoresponsive cell is further transduced with at least one co-stimulatory ligand such that the immunoresponsive

cell expresses the at least one co-stimulatory ligand. In certain embodiments, the at least one co-stimulatory ligand is selected from the group consisting of 4-1BBL, CD80, CD86, CD70, OX40L, CD48, TNFRSF14, and combinations thereof. In certain embodiments, the isolated immunoresponsive cell is further transduced with at least one cytokine such that the immunoresponsive cell secrets the at least one cytokine. In certain embodiments, the at least cytokine is selected from the group consisting of IL-2, IL-3, IL-6, IL-7, IL-11, IL-12, IL-15, IL-17, IL-21, and combinations thereof. In some embodiments, the isolated immunoresponsive cell is selected from the group consisting of a T cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a human embryonic stem cell, a lymphoid progenitor cell, a T cell-precursor cell, and a pluripotent stem cell from which lymphoid cells may be differentiated. In certain embodiments, the immunoresponsive cell is a T cell.

The presently disclosed subject matter further provides nucleic acid molecules encoding the presently disclosed CARs, vectors comprising the nucleic acid molecules, and host cells expressing such nucleic acid molecules. In certain embodiments, the nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:397. In certain embodiments, the nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:398. In certain embodiments, the nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:399. In certain embodiments, the nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:400. In certain embodiments, the nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:401. In certain embodiments, the nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:402. In certain embodiments, the nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:403. In certain embodiments, the nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:406. In certain embodiments, the nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:407. In certain embodiments, the nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:408. In certain embodiments, the vector is a γ-retroviral vector. In certain embodiments, the host cell is a T cell.

The presently disclosed subject matter further provides use of an effective amount of the immunoresponsive cell as described herein, in the manufacture of a medicament for reducing tumor burden in a subject with multiple myeloma.

The presently disclosed subject matter further provides use of an effective amount of the immunoresponsive cell as described herein, in the manufacture of a medicament for increasing or lengthening survival of a subject having multiple myeloma.

The presently disclosed subject matter further provides a chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain that binds to a G-protein coupled receptor family C group 5 member D (GPRC5D), a transmembrane domain and an intracellular domain, wherein the extracellular antigen-binding domain comprises:

(a) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 124, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 125 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 126; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129;

(b) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 133, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 134 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 135;

(c) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 136, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 137 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 138; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 139, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 140 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 141;

(d) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 142, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 143 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 144; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 145, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 146 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 147;

(e) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 148, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 149 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 150; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 151, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 152 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 153;

(f) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 154, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 155 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 156; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 157, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 158 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 159;

(g) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 160, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 161 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 162; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 163, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 164 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 165;

(h) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 166, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 167 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 168; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 169, a CDR2

comprising the amino acid sequence set forth in SEQ ID NO: 170 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 171;

(i) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 172, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 173 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 174; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 175, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 176 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 177;

(j) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 178, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 179 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 180; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 181, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 182 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 183;

(k) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 184, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 185 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 186; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 187, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 188 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 189;

(l) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 190, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 191 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 192; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 193, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 194 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 195;

(m) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 196, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 197 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 198; and a light chain variable region comprising a

CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 199, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 200 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 201;

(n) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 202, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 203 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 204; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 205, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 206 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 207;

(o) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 208, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 209 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 210; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 211, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 212 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 213;

(p) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 214, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 215 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 216; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 217, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 218 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 219;

(q) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 220, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 221 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 222; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 223, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 224 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 225;

(r) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 226, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 227 and a CDR3 comprising the amino acid

sequence set forth in SEQ ID NO: 228; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 229, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 230 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 231;

(s) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 232, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 233 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 234; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 235, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 236 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 237;

(t) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 238, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 239 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 240; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 241, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 242 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 243;

(u) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 244, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 245 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 246; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 247, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 248 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 249;

(v) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 250, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 251 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 252; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 253, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 254 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 255;

(w) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 256, a CDR2 comprising the amino acid

sequence set forth in SEQ ID NO: 257 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 258; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 259, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 260 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 261;

(x) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 262, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 263 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 264; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 265, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 266 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 267;

(y) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 304, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 305 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 306; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 307, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 308 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 309;

(z) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 316, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 317 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 318; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 319, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 320 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 321;

(aa) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 328, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 329 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 330; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 331, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 332 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 333;

(ab) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO:340, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 341 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 342; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 343, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 344 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 345;

(ac) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 352, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 353 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 354; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 355, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 356 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 357;

(ad) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 364, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 365 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 366; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 367, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 368 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 369;

(ae) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 376, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 377 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 378; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 379, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 380 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 381;or

(af) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 388, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 389 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 390; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 391, a CDR2

comprising the amino acid sequence set forth in SEQ ID NO: 393 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 393

The presently disclosed subject matter further provides a chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain that binds to a G-protein coupled receptor family C group 5 member D (GPRC5D), a transmembrane domain and an intracellular domain, wherein the extracellular antigen-binding domain comprises:

(a) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:1, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:2;

(b) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:5, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:6;

(c) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:9, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:10;

(d) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:13, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:14;

(e) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:17, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:18;

(f) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:21, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:22;

(g) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:25, and a light

chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:26;

(h) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:29, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:30;

(i) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:33, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:34;

(j) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:37, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:38;

(k) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:41, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:42;

(l) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:45, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:46;

(m) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:49, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:50;

(n) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:53, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:54;

(o) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:57, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:58;

(p) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:61, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:62;

(q) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:65, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:66;

(r) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:69, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:70;

(s) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:73, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:74;

(t) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:77, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:78;

(u) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:81, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:82;

(v) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:85, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:86;

(w) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:89, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:90;

(x) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:93, and a light

chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:94;

(y) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:302, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:303;

(z) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:314, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:315;

(aa) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:326, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:327;

(ab) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:338, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:339;

(ac) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:350, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:351;

(ad) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:362, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:363;

(ae) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:374, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:375; or

(af) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:386, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:387.

The presently disclosed subject matter further provides an immunoresponsive cell comprising the CAR as described herein.

The presently disclosed subject matter further provides a nucleic acid molecule encoding the chimeric antigen receptor (CAR) as described herein.

The presently disclosed subject matter further provides a method for producing an immunoresponsive cell that binds to a G-protein coupled receptor family C group 5 member D (GPRC5D), comprising introducing into the immunoresponsive cell a nucleic acid molecule as described herein.

Furthermore, the presently disclosed subject matter provides methods of using the above-described immunoresponsive cell for reducing tumor burden in a subject. For example, the presently disclosed subject matter provides methods of treating reducing tumor burden in a subject, where the method comprises administering an effective amount of the presently disclosed immunoresponsive cell to the subject, thereby inducing tumor cell death in the subject. In certain embodiments, the method reduces the number of the number of tumor cells. In another embodiment, the method reduces tumor size. In yet another embodiment, the method eradicates the tumor in the subject. In certain embodiments, the subject is a human. In certain embodiments, the immunoresponsive cell is a T cell. In certain embodiments, the tumor is multiple myeloma or Waldenstrom's Macroglobulinemia. In certain embodiments, the tumor is multiple myeloma.

Furthermore, the presently disclosed subject matter provides methods of using the above-described immunoresponsive cell for increasing or lengthening survival of a subject having neoplasia. For example, the presently disclosed subject matter provides methods of increasing or lengthening survival of a subject having neoplasia, where the method comprises administering an effective amount of the presently disclosed immunoresponsive cell to the subject, thereby increasing or lengthening survival of the subject. In certain embodiments, the neoplasia is multiple myeloma or Waldenstrom's Macroglobulinemia. In certain embodiments, the neoplasia is multiple myeloma. In certain embodiments, the method reduces or eradicates tumor burden in the subject.

The presently disclosed subject matter also provides methods for producing an immunoresponsive cell that binds to a G-protein coupled receptor. In one non-limiting example, the method comprises introducing into the immunoresponsive cell a nucleic acid sequence that encodes a chimeric antigen receptor (CAR), which comprises an extracellular antigen-binding domain, a transmembrane domain and an intracellular domain, wherein the extracellular antigen-binding domain specifically binds to a G-protein coupled receptor. In certain embodiments, the G-protein coupled receptor is a G-protein coupled receptor family C group 5 member D (GPRC5D). In a specific non-limiting embodiment, the extracellular antigen-binding domain is an scFv.

The presently disclosed subject matter further provides pharmaceutical compositions comprising an effective amount of the presently disclosed

immunoresponsive cells and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical compositions are for treating a neoplasia. In certain embodiments, the neoplasia is multiple myeloma or Waldenstrom's Macroglobulinemia. In certain embodiments, the neoplasia is multiple myeloma.

The presently disclosed subject matter further provides kits for treating a neoplasia, comprising the presently disclosed immunoresponsive cells. In certain embodiments, the kit further include written instructions for using the immunoresponsive cell for treating a neoplasia. In certain embodiments, the neoplasia is multiple myeloma or Waldenstrom's Macroglobulinemia. In certain embodiments, the neoplasia is multiple myeloma.

BRIEF DESCRIPTION OF THE FIGURES

The following Detailed Description, given by way of example, but not intended to limit the invention to specific embodiments described, may be understood in conjunction with the accompanying drawings.

Figure 1 shows a chimeric antigen receptor targeting a G-protein coupled receptor in accordance with one non-limiting embodiment of the presently disclosed subject matter.

Figure 2 depicts the human GPRC5D expression in normal tissues and human cancer cell lines.

Figure 3 depicts the expression of the presently disclosed GPRC5D CAR on human T cells.

Figure 4 depicts the killing activity of the presently disclosed GPRC5D for 3T3 cells overexpressing GPRC5D.

Figure 5 depicts the killing activity of the presently disclosed GPRC5D for a human multiple myeloma cell line.

Figure 6 shows a chimeric antigen receptor targeting GPRC5D in accordance with one non-limiting embodiment of the presently disclosed subject matter.

Figure 7 depicts a nucleic acid molecule that encodes a GPRC5D-targeted CAR in accordance with one non-limiting embodiment of the presently disclosed subject matter.

Figure 8 depicts a nucleic acid molecule that encodes a GPRC5D-targeted CAR in accordance with one non-limiting embodiment of the presently disclosed subject matter.

Figure 9 depicts a nucleic acid molecule that encodes a GPRC5D-targeted CAR in accordance with one non-limiting embodiment of the presently disclosed subject matter.

Figure 10 depicts the cytotoxicity of GPRC5D targeted CAR T cells for human multiple myeloma cell lines.

Figure 11 depicts induction of cytokine secretion of GPRC5D targeted CAR T cells.

Figure 12 depicts anti-tumor activity of GPRC5D targeted CAR T cells.

Figures 13A and 13B depict the killing activity of GPRC5D targeted CAR T cells. (A) Shows the percent of GFP^+ tumor line at time 0. (B) Shows the killing the percent of GFP^+ tumor line at time 36 hours.

Figure 14 illustrates the CLIPS technology. The CLIPS reaction takes place between bromo groups of the CLIPS scaffold and thiol sidechains of cysteines. The reaction is fast and specific under mild conditions. Using this elegant chemistry, native protein sequences are transformed into CLIPS constructs with a range of structures. From left to right: two different single T2 loops, T3 double loop, conjugated T2+T3 loops, stabilized beta sheet, and stabilized alpha helix (Timmerman et al., J. Mol. Recognit. 2007; 20: 283-29).

Figure 15 illustrates combinatorial clips library screening. The target protein (left) containing a discontinuous conformational epitope is converted into a matrix library (middle). Combinatorial peptides are synthesized on a proprietary minicard and chemically converted into spatially defined CLIPS constructs (right).

Figure 16 depicts T3 looped CLIPSTM construct.

Figures 17A-17D illustrates heat map technology. (A) Table of combined peptides, with two sub-sequences indicated as “Loop 1” and “Loop 2”. (B) Data from A displayed as a matrix. (C) Color bar indication of the heat map representation. (D) Heat map visualization of data from A.

Figure 18 shows intensity profiles recorded for ET150-2. Lines are drawn from the starting residue to the ending residue of a single peptide on the height at which the signal for that peptide is recorded.

Figure 19 shows heatmap analysis of data recorded for ET150-5 under high stringency conditions.

Figure 20 shows intensity profiles recorded for ET150-18.

Figure 21 shows intensity profiles recorded for ET150-8.

Figure 22 depicts schematic drawing of GPCR containing seven transmembrane helices (TM) and 3 extracellular regions (ECLs). With colored arrows binding sites for each antibody is depicted.

Figure 23 depicts scatterplot analysis of all data recorded for each sample. On the diagonal is the statistical data distribution.

Figure 24 depicts FACS analysis of anti-GPRC5D antibodies.

Figure 25 depicts FACS analysis of anti-GPRC5D antibodies.

Figure 26 depicts a nucleic acid molecule that encodes a GPRC5D-targeted CAR in accordance with one non-limiting embodiment of the presently disclosed subject matter.

Figure 27 depicts a nucleic acid molecule that encodes a GPRC5D-targeted CAR in accordance with one non-limiting embodiment of the presently disclosed subject matter.

DETAILED DESCRIPTION OF THE INVENTION

The presently disclosed subject matter generally provides chimeric antigen receptors (CARs) targeting a G-protein coupled receptor (*e.g.*, a G-protein coupled receptor family C group 5 member D (GPRC5D)). In one non-limiting example, the CAR comprises an extracellular antigen-binding domain, a transmembrane domain and an intracellular domain, where the extracellular antigen-binding domain specifically binds to a G-protein coupled receptor. The presently disclosed subject matter also provides immunoresponsive cells (*e.g.*, T cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a human embryonic stem cell, a lymphoid progenitor cell, a T cell-precursor cell, and a pluripotent stem cell from which lymphoid cells may be differentiated) expressing the CARs targeting a G-protein coupled receptor, and methods of using such immunoresponsive cells for treating cancer, e.g., multiple myeloma.

I. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton et al., Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988); The Glossary of Genetics, 5th Ed., R.

Rieger et al. (eds.), Springer Verlag (1991); and Hale & Marham, The Harper Collins Dictionary of Biology (1991). As used herein, the following terms have the meanings ascribed to them below, unless specified otherwise.

As used herein, the term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.*, the limitations of the measurement system. For example, "about" can mean within 3 or more than 3 standard deviations, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, preferably up to 10%, more preferably up to 5%, and more preferably still up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value.

As used herein, the term "cell population" refers to a group of at least two cells expressing similar or different phenotypes. In non-limiting examples, a cell population can include at least about 10, at least about 100, at least about 200, at least about 300, at least about 400, at least about 500, at least about 600, at least about 700, at least about 800, at least about 900, at least about 1000 cells expressing similar or different phenotypes.

As used herein, the term "antibody" means not only intact antibody molecules, but also fragments of antibody molecules that retain immunogen-binding ability. Such fragments are also well known in the art and are regularly employed both *in vitro* and *in vivo*. Accordingly, as used herein, the term "antibody" means not only intact immunoglobulin molecules but also the well-known active fragments $F(ab')_2$, and Fab. $F(ab')_2$, and Fab fragments that lack the Fe fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding of an intact antibody (Wahl et al., *J. Nucl. Med.* 24:316-325 (1983). The antibodies of the invention comprise whole native antibodies, bispecific antibodies; chimeric antibodies; Fab, Fab', single chain V region fragments (scFv), fusion polypeptides, and unconventional antibodies.

As used herein, the term "single-chain variable fragment" or "scFv" is a fusion protein of the variable regions of the heavy (V_H) and light chains (V_L) of an immunoglobulin (e.g., mouse or human) covalently linked to form a V_H::VL heterodimer. The heavy (V_H) and light chains (V_L) are either joined directly or joined by a peptide-encoding linker (e.g., 10, 15, 20, 25 amino acids), which connects the N-

terminus of the V_H with the C-terminus of the V_L, or the C-terminus of the V_H with the N-terminus of the V_L. The linker is usually rich in glycine for flexibility, as well as serine or threonine for solubility. The linker can link the heavy chain variable region and the light chain variable region of the extracellular antigen-binding domain. Non-limiting examples of linkers are disclosed in Shen et al., Anal. Chem. 80(6):1910-1917 (2008) and WO 2014/087010, the contents of which are hereby incorporated by reference in their entireties. In certain embodiments, the linker is a G4S linker.

In a non-limiting example, the linker comprises amino acids having the sequence set forth in SEQ ID NO:897 as provided below.

GGGGSGGGGSGGGGS [SEQ ID NO:284]. In certain embodiments, the nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:284 is set forth in SEQ ID NO:285, which is provided below:

GGTGGAGGTGGATCAGGTGGAGGTGGATCTGGTGGAGGTGGATCT [SEQ ID NO:285].

In another non-limiting example, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98 as provided below.

SRGGGGSGGGGSGGGGSLEMA [SEQ ID NO:98]

In certain embodiments, the nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:98 is set forth in SEQ ID NO:99, which is provided below:

tctagaggtggtggtggtagcggcggcggcggctctggtggtggtggatccctcgagatggcc [SEQ ID NO:99]

Despite removal of the constant regions and the introduction of a linker, scFv proteins retain the specificity of the original immunoglobulin. Single chain Fv polypeptide antibodies can be expressed from a nucleic acid comprising V_H - and V_L -encoding sequences as described by Huston, et al. (Proc. Nat. Acad. Sci. USA, 85:5879-5883, 1988). See, also, U.S. Patent Nos. 5,091,513, 5,132,405 and 4,956,778; and U.S. Patent Publication Nos. 20050196754 and 20050196754. Antagonistic scFvs having inhibitory activity have been described (see, e.g., Zhao et al., Hyrbidoma (Larchmt) 2008 27(6):455-51; Peter et al., J Cachexia Sarcopenia Muscle 2012 August 12; Shieh et al., J Imunol2009 183(4):2277-85; Giomarelli et al., Thromb Haemost 2007 97(6):955-63; Fife eta., J Clin Invst 2006 116(8):2252-61; Brocks et al., Immunotechnology 1997 3(3):173-84; Moosmayer et al., Ther Immunol 1995 2(10:31-40). Agonistic scFvs having stimulatory activity have been described (see, e.g., Peter et al., J Bioi Chern 2003 25278(38):36740-7; Xie et al., Nat Biotech 1997

15(8):768-71; Ledbetter et al., Crit Rev Immunol1997 17(5-6):427-55; Ho et al., BioChim Biophys Acta 2003 1638(3):257-66).

As used herein, "F(ab)" refers to a fragment of an antibody structure that binds to an antigen but is monovalent and does not have a Fc portion, for example, an antibody digested by the enzyme papain yields two F(ab) fragments and an Fc fragment (e.g., a heavy (H) chain constant region; Fc region that does not bind to an antigen).

As used herein, "$F(ab')_2$" refers to an antibody fragment generated by pepsin digestion of whole IgG antibodies, wherein this fragment has two antigen binding (ab') (bivalent) regions, wherein each (ab') region comprises two separate amino acid chains, a part of a H chain and a light (L) chain linked by an S-S bond for binding an antigen and where the remaining H chain portions are linked together. A "F(ab')2" fragment can be split into two individual Fab' fragments.

As used herein, the term "vector" refers to any genetic element, such as a plasmid, phage, transposon, cosmid, chromosome, virus, virion, etc., which is capable of replication when associated with the proper control elements and which can transfer gene sequences into cells. Thus, the term includes cloning and expression vehicles, as well as viral vectors and plasmid vectors.

As used herein, the term "expression vector" refers to a recombinant nucleic acid sequence, i.e. recombinant DNA molecule, containing a desired coding sequence and appropriate nucleic acid sequences necessary for the expression of the operably linked coding sequence in a particular host organism. Nucleic acid sequences necessary for expression in prokaryotes usually include a promoter, an operator (optional), and a ribosome binding site, often along with other sequences. Eukaryotic cells are known to utilize promoters, enhancers, and termination and polyadenylation signals.

As used herein, “CDRs” are defined as the complementarity determining region amino acid sequences of an antibody which are the hypervariable regions of immunoglobulin heavy and light chains. See, e.g., Kabat et al., Sequences of Proteins of Immunological Interest, 4th U. S. Department of Health and Human Services, National Institutes of Health (1987). Generally, antibodies comprise three heavy chain and three light chain CDRs or CDR regions in the variable region. CDRs provide the majority of contact residues for the binding of the antibody to the antigen or epitope. In certain embodiments, the CDRs regions are delineated using the Kabat

system (Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242).

As used herein, the term "affinity" is meant a measure of binding strength. Without being bound to theory, affinity depends on the closeness of stereochemical fit between antibody combining sites and antigen determinants, on the size of the area of contact between them, and on the distribution of charged and hydrophobic groups. Affinity also includes the term "avidity," which refers to the strength of the antigen-antibody bond after formation of reversible complexes. Methods for calculating the affinity of an antibody for an antigen are known in the art, comprising use of binding experiments to calculate affinity. Antibody activity in functional assays (e.g., flow cytometry assay) is also reflective of antibody affinity. Antibodies and affinities can be phenotypically characterized and compared using functional assays (e.g., flow cytometry assay).

Nucleic acid molecules useful in the methods of the invention include any nucleic acid molecule that encodes a polypeptide of the invention or a fragment thereof. Such nucleic acid molecules need not be 100% identical with an endogenous nucleic acid sequence, but will typically exhibit substantial identity. Polynucleotides having "substantial identity" to an endogenous sequence are typically capable of hybridizing with at least one strand of a double-stranded nucleic acid molecule. By "hybridize" is meant pair to form a double-stranded molecule between complementary polynucleotide sequences (e.g., a gene described herein), or portions thereof, under various conditions of stringency. (See, e.g., Wahl, G. M. and S. L. Berger (1987) Methods Enzymol. 152:399; Kimmel, A. R. (1987) Methods Enzymol. 152:507).

For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and more preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and more preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30° C, more preferably of at least about 37° C, and most preferably of at least about 42° C. Varying additional parameters, such as

hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred: embodiment, hybridization will occur at 30° C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37° C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42° C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50% formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

For most applications, washing steps that follow hybridization will also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include a temperature of at least about 25° C, more preferably of at least about 42° C, and even more preferably of at least about 68° C. In a preferred embodiment, wash steps will occur at 25° C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42° C. in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 68° C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art. Hybridization techniques are well known to those skilled in the art and are described, for example, in Benton and Davis (Science 196:180, 1977); Grunstein and Rogness (Proc. Natl. Acad. Sci., USA 72:3961, 1975); Ausubel et al. (Current Protocols in Molecular Biology, Wiley Interscience, New York, 2001); Berger and Kimmel (Guide to Molecular Cloning Techniques, 1987, Academic Press, New York); and Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, New York.

By "substantially identical" is meant a polypeptide or nucleic acid molecule exhibiting at least 50% identity to a reference amino acid sequence (for example, any

one of the amino acid sequences described herein) or nucleic acid sequence (for example, any one of the nucleic acid sequences described herein). Preferably, such a sequence is at least 60%, more preferably 80% or 85%, and more preferably 90%, 95% or even 99% identical at the amino acid level or nucleic acid to the sequence used for comparison.

Sequence identity is typically measured using sequence analysis software (for example, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wis. 53705, BLAST, BESTFIT, GAP, or PILEUP/PRETTYBOX programs). Such software matches identical or similar sequences by assigning degrees of homology to various substitutions, deletions, and/or other modifications. In an exemplary approach to determining the degree of identity, a BLAST program may be used, with a probability score between e-3 and e-100 indicating a closely related sequence.

As used herein, the term "analog" refers to a structurally related polypeptide or nucleic acid molecule having the function of a reference polypeptide or nucleic acid molecule.

As used herein, the term "ligand" refers to a molecule that binds to a receptor. In particular, the ligand binds a receptor on another cell, allowing for cell-to-cell recognition and/or interaction.

As used herein, the term "disease" refers to any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ. Examples of diseases include neoplasia or pathogen infection of cell.

As used herein, the term "effective amount" refers to an amount sufficient to have a therapeutic effect. In certain embodiments, an "effective amount" is an amount sufficient to arrest, ameliorate, or inhibit the continued proliferation, growth, or metastasis (e.g., invasion, or migration) of a neoplasia.

As used herein, the term "heterologous nucleic acid molecule or polypeptide" refers to a nucleic acid molecule (e.g., a cDNA, DNA or RNA molecule) or polypeptide that is not normally present in a cell or sample obtained from a cell. This nucleic acid may be from another organism, or it may be, for example, an mRNA molecule that is not normally expressed in a cell or sample.

As used herein, the term "immunoresponsive cell" refers to a cell that functions in an immune response or a progenitor, or progeny thereof.

As used herein, the term "modulate" refers positively or negatively alter. Exemplary modulations include an about 1%, about 2%, about 5%, about 10%, about 25%, about 50%, about 75%, or about 100% change.

As used herein, the term "increase" refers to alter positively by at least about 5% including, but not limited to, alter positively by about 5%, by about 10%, by about 25%, by about 30%, by about 50%, by about 75%, or by about 100%.

As used herein, the term "reduce" refers to alter negatively by at least about 5% including, but not limited to, alter negatively by about 5%, by about 10%, by about 25%, by about 30%, by about 50%, by about 75%, or by about 100%.

As used herein, the term "isolated cell" refers to a cell that is separated from the molecular and/or cellular components that naturally accompany the cell.

As used herein, the term "isolated," "purified," or "biologically pure" refers to material that is free to varying degrees from components which normally accompany it as found in its native state. "Isolate" denotes a degree of separation from original source or surroundings. "Purify" denotes a degree of separation that is higher than isolation. A "purified" or "biologically pure" protein is sufficiently free of other materials such that any impurities do not materially affect the biological properties of the protein or cause other adverse consequences. That is, a nucleic acid or peptide of this invention is purified if it is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Purity and homogeneity are typically determined using analytical chemistry techniques, for example, polyacrylamide gel electrophoresis or high performance liquid chromatography. The term "purified" can denote that a nucleic acid or protein gives rise to essentially one band in an electrophoretic gel. For a protein that can be subjected to modifications, for example, phosphorylation or glycosylation, different modifications may give rise to different isolated proteins, which can be separately purified.

As used herein, the term "secreted" is meant a polypeptide that is released from a cell via the secretory pathway through the endoplasmic reticulum, Golgi apparatus, and as a vesicle that transiently fuses at the cell plasma membrane, releasing the proteins outside of the cell.

As used herein, the term "specifically binds" or "specifically binds to" or "specifically target" is meant a polypeptide or fragment thereof that recognizes and binds a biological molecule of interest (e.g., a polypeptide), but which does not

substantially recognize and bind other molecules in a sample, for example, a biological sample, which naturally includes a polypeptide of the invention.

As used herein, the term "treating" or "treatment" refers to clinical intervention in an attempt to alter the disease course of the individual or cell being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Therapeutic effects of treatment include, without limitation, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastases, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. By preventing progression of a disease or disorder, a treatment can prevent deterioration due to a disorder in an affected or diagnosed subject or a subject suspected of having the disorder, but also a treatment may prevent the onset of the disorder or a symptom of the disorder in a subject at risk for the disorder or suspected of having the disorder.

As used herein, the term "subject" refers to any animal (e.g., a mammal), including, but not limited to, humans, non-human primates, rodents, and the like (e.g., which is to be the recipient of a particular treatment, or from whom cells are harvested).

II. G-protein Coupled Receptor

G protein-coupled receptors ("GPRs"), also known as seven-transmembrane domain receptors, 7TM receptors, heptahelical receptors, serpentine receptor, and G protein-linked receptors, constitute a large protein family of receptors that sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses. GPCRs can be categorized into six classes based on sequence homology and functional similarity: Class A (Rhodopsin-like), Class B (Secretin receptor family), Class C (Metabotropic glutamate/pheromone), Class D (Fungal mating pheromone receptors), Class E (Cyclic AMP receptors), and Class F (Frizzled/Smoothened). In certain embodiments, the GRPs are Class C GRPs. In certain non-limiting embodiments, the Class C GRP is a G-protein coupled receptor family C group 5 member D.

G-protein coupled receptor family C group 5 member D (GPRC5D) is an orphan receptor with no known ligand or function in humans. It is a member of a family of retinoic acid-inducible G-protein-coupled receptors. It is overexpressed in multiple myeloma (MM) cells and is not expressed or expressed in a significantly

lower level in any other cell type, benign or malignant, as shown in Figure 2. Several groups have identified this gene as highly differentially expressed by gene expression profiling of primary MM cells when compared to normal tissue[1] or other hematologic malignancies.[2-4] It has been shown that higher mRNA expression correlates with worse overall survival.[1] Surface staining of Bone marrow aspirates from patients with MM demonstrate plasma cell specific staining.[4] To the knowledge of the inventors, this is the first time GPRC5D has been targeted by any therapeutic. Additionally, to the knowledge of the inventors, this is the first time a CAR targeting any G-protein coupled receptor has been generated.

In certain non-limiting embodiments, GPRC5D is human GPRC5D having the amino acid sequence set forth in SEQ ID NO:97, or fragments thereof.

SEQ ID NO:97 is provided below:

MYKDCIESTGDYFLLCDAEGPWGIILESLAILGIVVTILLLLAFLFLMRKIQDCSQWNVL
PTQLLFLLSVLGLFGLAFAFIIELNQQTAPVRYFLFGVLFALCFSCLLAHASNLVKLVRG
CVSFSWTTILCIAIGCSLLQIIIATEYVTLIMTRGMMFVNMTPCQLNVDFVVLLVYVLFL
MALTFFVSKATFCGPCENWKQHGRLIFITVLFSIIIWVVWISMLLRGNPQFQRQPQWDDP
VVCIALVTNAWVFLLLYIVPELCILYRSCRQECPLQGNACPVTAYQHSFQVENQELSRAR
DSDGAEEDVALTSYGTPIQPQTVDPTQECFIPQAKLSPQQDAGGV
[SEQ ID NO:97]

The N-terminal region of human GPRC5D has amino acids 1-27 of SEQ ID NO:97. The extracellular loop 1 (ECL1) region of human GPRC5D has amino acids 85-93 of SEQ ID NO:97. The extracellular loop 2 (ECL2) region of human GPRC5D has amino acids 145-167 of SEQ ID NO:97. The extracellular loop 3 (ECL3) region of human GPRC5D has amino acids 226-239 of SEQ ID NO:97.

III. Chimeric Antigen Receptor (CAR).

Chimeric antigen receptors (CARs) are engineered receptors, which graft or confer a specificity of interest onto an immune effector cell. CARs can be used to graft the specificity of a monoclonal antibody onto a T cell; with transfer of their coding sequence facilitated by retroviral vectors.

There are three generations of CARs. "First generation" CARs are typically composed of an extracellular antigen binding domain (e.g., a single-chain variable fragments (scFv)) fused to a transmembrane domain, fused to cytoplasmic/intracellular domain of the T cell receptor chain. "First generation" CARs typically have the intracellular domain from the CD3ξ- chain, which is the primary transmitter of signals from endogenous TCRs. "First generation" CARs can

provide *de novo* antigen recognition and cause activation of both $CD4^+$ and $CD8^+$ T cells through their CD3ζ chain signaling domain in a single fusion molecule, independent of HLA-mediated antigen presentation. "Second generation" CARs add intracellular domains from various co-stimulatory molecules (*e.g.*, CD28, 4-1BB, ICOS, OX40) to the cytoplasmic tail of the CAR to provide additional signals to the T cell. "Second generation" CARs comprise those that provide both co-stimulation (e.g., CD28 or 4-1BB) and activation (CD3ζ). Preclinical studies have indicated that "Second Generation" CARs can improve the anti-tumor activity of T cells. For example, robust efficacy of "Second Generation" CAR modified T cells was demonstrated in clinical trials targeting the CD19 molecule in patients with chronic lymphoblastic leukemia (CLL) and acute lymphoblastic leukemia (ALL). "Third generation" CARs comprise those that provide multiple co-stimulation (e.g., CD28 and 4-1BB) and activation (CD3ζ).

In accordance with the presently disclosed subject matter, the CARs comprise an extracellular antigen-binding domain, a transmembrane domain and an intracellular domain, where the extracellular antigen-binding domain binds to a G-protein coupled receptor. In certain embodiments, the G-protein coupled receptor is a GPRC5D. In a specific non-limiting embodiment, the extracellular antigen-binding domain is a scFv. In a specific non-limiting embodiment, the extracellular antigen-binding domain is a Fab, which is optionally crosslinked. In a specific non-limiting embodiment, the extracellular binding domain is a $F(ab)_2$. In a specific non-limiting embodiment, any of the foregoing molecules may be comprised in a fusion protein with a heterologous sequence to form the extracellular antigen-binding domain.

In certain non-limiting embodiments, the extracellular antigen-binding domain of a presently disclsoed CAR has a high binding specificity as well as high binding affinity to the G-protein coupled receptor (*e.g.*, GPRC5D). For example, in such embodiments, the extracellular antigen-binding domain of the CAR (embodied, for example, in a scFv or an analog thereof) binds to GPRC5D with a dissociation constant (K_D) of about 3×10^{-6} M or less. In certain embodiments, the K_D is about 1×10^{-6} M or less, about 1×10^{-7} M or less, about 1×10^{-8} M or less, or about 1×10^{-9} M or less, about 1×10^{-10} M or less, or about 1×10^{-11} M or less. In certain embodiments, the K_D is about 1×10^{-8} M or less. In certain embodiments, the K_D is from about 1×10^{-11} M to about 3×10^{-6} M, such as from about 1×10^{-11} M to about 1×10^{-10} M, from about 1×10^{-10} M to about 1×10^{-9} M, from about 1×10^{-9} M to about

1 x 10^{-8} M, from about 1 x 10^{-8} M to about 1 x 10^{-7} M, or from about 1 x 10^{-7} M to about 1 x 10^{-6} M, or from about 1 x 10^{-6} M to about 3 x 10^{-6} M. In certain embodiments, the K_D is from about 1 x 10^{-9} M to about 1 x 10^{-8} M. In certain embodiments, the K_D is from about 1 x 10^{-9} M to about 1.5 x 10^{-9} M. In certain embodiments, the K_D is about 1.2 x 10^{-9} M. In certain embodiments, the K_D is from about 4 x 10^{-9} M to about 5 x 10^{-9} M. In certain embodiments, the K_D is about 5 x 10^{-9} M. In certain embodiments, the K_D is about 4.8 x 10^{-9} M. In certain embodiments, the K_D is from about 8 x 10^{-9} M to about 9 x 10^{-9} M. In certain embodiments, the K_D is about 8 x 10^{-9} M. In certain embodiments, the K_D is about 8.1 x 10^{-9} M

Binding of the extracellular antigen-binding domain (embodiment, for example, in an scFv or an analog thereof) of a presently disclosed CAR to a G-protein coupled receptor (*e.g.*, GPRC5D) can be confirmed by, for example, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), FACS analysis, bioassay (*e.g.*, growth inhibition), or Western Blot assay. Each of these assays generally detect the presence of protein-antibody complexes of particular interest by employing a labeled reagent (*e.g.*, an antibody, or a scFv) specific for the complex of interest. For example, the scFv can be radioactively labeled and used in a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by such means as the use of a γ counter or a scintillation counter or by autoradiography. In certain embodiments, the GPRC5D-targeted extracellular antigen-binding domain is labeled with a fluorescent marker. Non-limiting examples of fluorescent markers include green fluorescent protein (GFP), blue fluorescent protein (e.g., EBFP, EBFP2, Azurite, and mKalama1), cyan fluorescent protein (e.g., ECFP, Cerulean, and CyPet), and yellow fluorescent protein (e.g., YFP, Citrine, Venus, and YPet). In certain embodiments, the GPRC5D-targeted human scFv is labeled with GFP.

In certain embodiments, the extracellular antigen-binding domain of a presently disclosed CAR comprises a single-chain variable fragment (scFv). In one specific embodiment, the extracellular antigen-binding domain of a presently disclosed CAR comprises a human scFv that specifically binds to human GPRC5D. In another specific embodiment, the extracellular antigen-binding domain of a presently disclosed CAR comprises a murine scFv that specifically binds to human

GPRC5D. In certain embodiments, the scFv are identified by screening scFv phage library with cells (e.g., 3T3 cells) that express GPRC5D.

Extracellular Antigen-Binding Domain of A CAR

In certain embodiments, the extracellular antigen-binding domain (*e.g.*, scFv) comprises a heavy chain variable region comprising amino acids having a sequence selected from the group consisting of: SEQ ID NOS:1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, and 93. The nucleic acid sequences encoding the amino acid sequence of SEQ ID NOS:1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, and 93 are 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, 47, 51, 55, 59, 63, 67, 71, 75, 79, 83, 87, 91, and 95, respectively. In some embodiments, the extracellular antigen-binding domain (*e.g.*, scFv) comprises a light chain variable region comprising amino acids having a sequence selected from the group consisting of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, and 94. The nucleic acid sequences encoding the amino acid sequence of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, and 94 are 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, 84, 88, 92, and 96, respectively. The sequences of SEQ ID NOS:1-96 are described in the following Tables 1-24.

In certain embodiments, the extracellular antigen-binding domain (*e.g.*, scFv) comprises heavy and light chain variable regions comprising amino acid sequences that are homologous to the amino acid sequences described herein and as disclosed in Tables 1-24. For example, and not by way of limitation, the extracellular antigen-binding domain (*e.g.*, scFv) comprises a heavy chain variable region comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386.

In certain embodiments, the extracellular antigen-binding domain (*e.g.*, scFv) comprises a light chain variable region comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99%

homologous to an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387.

In certain embodiments, the extracellular antigen-binding domain (*e.g.*, scFv) comprises (a) a heavy chain variable region comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386; and (b) a light chain variable region comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387.

The presently disclosed subject matter further provides extracellular antigen-binding domains (*e.g.*, scFv) that comprise heavy chain variable region and light chain variable region CDRs, *e.g.*, CDR1s, CDR2s and CDR3s, as disclosed herein in Tables 1-24. The CDR regions are delineated using the Kabat system (Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). The presently disclosed subject matter further provides extracellular antigen-binding domains (*e.g.*, scFv) that comprise conservative modifications of the antibody sequences disclosed herein. For example, and not by way of limitation, an extracellular antigen-binding domains (*e.g.*, scFv) of the presently disclosed subject matter comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 sequences and a light chain variable region comprising CDR1, CDR2 and CDR3 sequences, wherein one or more of these CDR sequences comprise specified amino acid sequences disclosed herein, or conservative modifications thereof, and wherein the extracellular antigen-binding domains retain the desired functional properties.

In certain embodiments, the presently disclosed subject matter provides an extracellular antigen-binding domain (*e.g.*, scFv) comprising a heavy chain variable region, wherein the heavy chain variable region comprises: (a) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 124, 130, 136, 142, 148, 154, 160, 166, 172, 178, 184, 190, 196, 202, 208, 214, 220, 226, 232, 238, 244, 250, 256, 262, 304, 316, 328, 340, 352, 364, 376, and 388, and conservative modifications thereof; (b) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 125, 131, 137, 143, 149, 155, 161, 167, 173, 179, 185, 191, 197, 203, 209, 215, 221, 227, 233, 239, 245, 251, 257, 263, 305, 317, 329, 341, 353, 365, 377, and 389, and conservative modifications thereof; and (c) a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 126, 132, 138, 144, 150, 156, 162, 168, 174, 180, 186, 192, 198, 204, 210, 216, 222, 228, 234, 240, 246, 252, 258, 264, 306, 318, 330, 342, 354, 366, 378, and 390, and conservative modifications thereof.

In certain embodiments, the extracellular antigen-binding domain (*e.g.*, scFv) comprises a light chain variable region, wherein the light chain variable region comprises: (a) a CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 127, 133, 139, 145, 151, 157, 163, 169, 175, 181, 187, 193, 199, 205, 211, 217, 223, 229, 235, 241, 247, 253, 259, 265, 307, 319, 331, 343, 355, 367, 379, and 391, and conservative modifications thereof; (b) a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 128, 134, 140, 146, 152, 158, 164, 170, 176, 182, 188, 194, 200, 206, 212, 218, 224, 230, 236, 242, 248, 254, 260, 266, 308, 320, 332, 344, 356, 368, 380, and 392, and conservative modifications thereof; and (c) a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 129, 135, 141, 147, 153, 159, 165, 171, 177, 183, 189, 195, 201, 207, 213, 219, 225, 231, 237, 243, 249, 255, 261, 267, 309, 321, 333, 345, 357, 369, 381, and 393, and conservative modifications thereof.

The presently disclosed subject matter provides an extracellular antigen-binding domain (*e.g.*, scFv) comprising a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein: (a) the heavy chain variable region CDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 126, 132, 138, 144, 150, 156, 162, 168, 174, 180, 186, 192, 198, 204, 210,

216, 222, 228, 234, 240, 246, 252, 258, 264, 306, 318, 330, 342, 354, 366, 378, and 390, and conservative modifications thereof; and (b) the light chain variable region CDR3 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 129, 135, 141, 147, 153, 159, 165, 171, 177, 183, 189, 195, 201, 207, 213, 219, 225, 231, 237, 243, 249, 255, 261, 267, 309, 321, 333, 345, 357, 369, 381, and 393, and conservative modifications thereof; wherein the extracellular antigen-binding domain specifically binds to a GPRC5D polypeptide (e.g., a human GPRC5D polypeptide). In certain embodiments, the heavy chain variable region CDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 125, 131, 137, 143, 149, 155, 161, 167, 173, 179, 185, 191, 197, 203, 209, 215, 221, 227, 233, 239, 245, 251, 257, 263, 305, 317, 329, 341, 353, 365, 377, and 389, and conservative modifications thereof; and (b) the light chain variable region CDR2 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 128, 134, 140, 146, 152, 158, 164, 170, 176, 182, 188, 194, 200, 206, 212, 218, 224, 230, 236, 242, 248, 254, 260, 266, 308, 320, 332, 344, 356, 368, 380, and 392, and conservative modifications thereof; wherein the extracellular antigen-binding domain specifically binds to a GPRC5D polypeptide (e.g., a human GPRC5D polypeptide). In certain embodiments, the heavy chain variable region CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 124, 130, 136, 142, 148, 154, 160, 166, 172, 178, 184, 190, 196, 202, 208, 214, 220, 226, 232, 238, 244, 250, 256, 262, 304, 316, 328, 340, 352, 364, 376, and 388, and conservative modifications thereof; and (b) the light chain variable region CDR1 comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 127, 133, 139, 145, 151, 157, 163, 169, 175, 181, 187, 193, 199, 205, 211, 217, 223, 229, 235, 241, 247, 253, 259, 265, 307, 319, 331, 343, 355, 367, 379, and 391, and conservative modifications thereof; wherein the extracellular antigen-binding domain specifically binds to a GPRC5D polypeptide (e.g., a human GPRC5D polypeptide).

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 100 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-153 scFv (also referred to as "ET150-3 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:1 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:2, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 1. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:1, as shown in Table 1. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:1, as shown in Table 1. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:2, as shown in Table 1. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:2, as shown in Table 1. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:1 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:2, as shown in Table 1. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:124 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:125 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:126 or conservative modifications thereof, as shown in Table 1. In certain embodiments, the extracellular antigen-binding domain comprises a V_L

CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:127 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:128 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:129 or conservative modifications thereof, as shown in Table 1. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:124 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:125 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:126 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:127 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:128 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:129 or conservative modifications thereof, as shown in Table 1. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:124, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:125, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:126, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:127, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:128, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:129.

Table 1

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GYTFTSYY [SEQ ID NO:124]	GYTFTSYY [SEQ ID NO:125]	ARGMYRSLLFYDP [SEQ ID NO:126]
V_L	RSNVGNYY [SEQ ID NO:127]	DNN [SEQ ID NO:128]	GTWDGSLSAHV [SEQ ID NO:129]
Full V_H	QVQLVQSGSELKKPGASVRVSCTASGYTFTSYYMHWVRQAPGQ GLEWMGVINPNAGSTRYAQKFQGRVTMSTDTSTSTAYMDLSSL RSEDTAVYYCARGMYRSLLFYDPWGQGTLVTVSS [SEQ ID NO:1]		
DNA	Caggtgcagctggtgcagtctgggtctgagttgaagaagcctggggcctcagtcagagtctcctgcac ggcttctggatacaccttcaccagttactatatgcactgggtgcgacaggcccctggacaagggcttga gtggatgggagtaatcaaccctaatgctggcagcacaagatacgcacagaaattccagggcagagtca		

	ccatgagcactgacacgtccacgagcacagcctacatggacctgagcagtctgagatctgaggacac ggccgtgtattactgtgcgcgcggtatgtaccgttctctgctgttctacgatccgtggggtcaaggtactct ggtgaccgtctcctca [SEQ ID NO:3]
Full V_L	QSVLTQPPSVSAAPGQKVTIPCSGSRSNVGNYYVSWYQQLPGTA PKLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYFCG TWDGSLSAHVFGTGTKVTVLG [SEQ ID NO:2]
DNA	Cagtctgtgttgacgcagccgccctcagtgtctgcggccccaggacagaaggtcaccatccctgctc tggaagccgttccaacgttgggaattattatgtgtcctggtaccagcaactcccaggaacagcccccaa actcctcatttatgacaataataagcgaccctcagggattcctgaccgattctctggctccaagtctggca cgtcagccaccctgggcatcaccggactccagactggggacgaggccgattatttctgcggaacatgg gatggcagcctgagtgcccatgtcttcggaactgggaccaaggtcaccgtcctaggt [SEQ ID NO:4]
scFv	QSVLTQPPSVSAAPGQKVTIPCSGSRSNVGNYYVSWYQQLPGTA PKLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYFCG TWDGSLSAHVFGTGTKVTVLGSRGGGGSGGGGSGGGGSLEMAQ VQLVQSGSELKKPGASVRVSCTASGYTFTSYYMHWVRQAPGQG LEWMGVINPNAGSTRYAQKFQGRVTMSTDTSTSTAYMDLSSLRS EDTAVYYCARGMYRSLLFYDPWGQGTLVTVSS [SEQ ID NO:100]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 101 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-166 scFv (also referred to as "ET150-16 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:5 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:6, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 2. In certain embodiments, the extracellular antigen-binding domain is a human scFv. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:5, as shown in Table 2. In certain embodiments, the extracellular

antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:5, as shown in Table 2. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:6, as shown in Table 2. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:6, as shown in Table 2. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:5 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:6, as shown in Table 2. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:130 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:131 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:132 or conservative modifications thereof, as shown in Table 2. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:133 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:134 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:135 or conservative modifications thereof, as shown in Table 2. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:130 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:131 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:132 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:133 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:134 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:135 or conservative modifications thereof, as shown in Table 2. In certain

embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:130, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:131, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:132, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:133, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:134, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:135.

Table 2

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFTFSNYA [SEQ ID NO:130]	ISGSGNT [SEQ ID NO:131]	ARGSVRYTDI [SEQ ID NO:132]
V_L	SGAIAGAY [SEQ ID NO:133]	DDN [SEQ ID NO:134]	QSYDYDSSNVL [SEQ ID NO:135]
Full V_H	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGK GLEWVSAISGSGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCARGSVRYTDIWGQGTLVTVSS [SEQ ID NO:5]		
DNA	Gaggtgcagctggtggagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtg cagcctctggattcacctttagcaactatgccatgagttgggtccgccaggctccagggaagggactgg agtgggtctcagctattagtggtagtggtaacacatactacgcagactccgtgaagggccggttcaccat ctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggcc gtatattactgtgcgcgcggttctgttcgttacactgatatctggggtcaaggtactctggtgaccgtctcct ca [SEQ ID NO:7]		
Full V_L	NFMLTQPHSVSESPGKTVSISCTRTSGAIAGAYVQWFQQRPGSAP TTVIYDDNKRPSGVPDRFSGSIDKSSNSASLTISGLKTEDEADYYC QSYDYDSSNVLFGGGTKLTVLG [SEQ ID NO:6]		
DNA	Aattttatgctgactcagccccactcagtgtcggagtctccggggaagacggtaagcatctcctgcacc cgcaccagtggcgccattgccggcgcctatgtgcagtggttccagcagcgcccgggcagtgccccca ccactgtgatctatgacgataacaaaagaccctctggggtccctgatcggttctctgggtccatcgacaa gtcctccaactctgcctccctcaccatctctggactgaagactgaggacgaggctgactattattgtcagt cttatgattatgatagcagcaatgtgctattcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:8]		
scFv	NFMLTQPHSVSESPGKTVSISCTRTSGAIAGAYVQWFQQRPGSAP TTVIYDDNKRPSGVPDRFSGSIDKSSNSASLTISGLKTEDEADYYC QSYDYDSSNVLFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMA EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGK GLEWVSAISGSGNTYYADSVKGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCARGSVRYTDIWGQGTLVTVSS [SEQ ID NO:101]		

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 102 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid

sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-170 scFv (also referred to as "ET150-20 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:9 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:10, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 3. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:9, as shown in Table 3. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:9, as shown in Table 3. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:10, as shown in Table 3. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:10, as shown in Table 3. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:9 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:10, as shown in Table 3. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:136 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:137 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having

the sequence set forth in SEQ ID NO:138 or conservative modifications thereof, as shown in Table 3. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:139 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:140 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:141 or conservative modifications thereof, as shown in Table 3. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:136 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:137 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:138 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:139 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:140 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:141 or conservative modifications thereof, as shown in Table 3. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:136, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:137, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:138, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:139, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:140, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:141.

Table 3

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFTFNNYW [SEQ ID NO:136]	IKQDGSEK [SEQ ID NO:137]	ARSMSTAV [SEQ ID NO:138]
V_L	QSISSY [SEQ ID NO:139]	AAS [SEQ ID NO:140]	QQSYSVPYT [SEQ ID NO:141]
Full V_H	EVQLVQSGGGLVQPGGSLRLSCATSGFTFNNYWMSWVRQAPGK GLEWVANIKQDGSEKYYADSVRGRFTISRDNAKNSLSLQLNNLRA EDTAVYYCARSMSTAWGYDEWGQGTLVTVSS [SEQ ID NO:9]		
DNA	Gaggtgcagctggtgcagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtgc		

	aacctctggattcacctttaataactattggatgagttgggtccgccaggctccagggaaggggctggagt gggtggccaacataaagcaagatggaagtgagaaatactacgcggactctgtgaggggccgattcacc atctccagagacaacgccaagaactcactgtctctgcaattgaacaacctgagagccgaggacacggcc gtgtattactgtgcgcgctctatgtctactgcttggggttacgatgaatggggtcaaggtactctggtgacc gtctcctca [SEQ ID NO:11]
Full V_L	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKL LIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPADFATYYCQQSYS VPYTFGQGTKLEIKR [SEQ ID NO:10]
DNA	Gacatccagttgacccagtctccatcctccctgtctgcatctgtcggagacagagtcaccatcacttgccg ggcaagtcagagcattagcagctatttaaattggtatcaacagaaaccagggaaagcccctaagctcctg atctatgctgcatccagtttgcaaagtggggtcccatcaaggttcagtggcagtggatctgggacagatttc actctcaccatcagcagtctgcaacctgcagattttgcaacttactactgtcaacagagttacagtgtcccgt acacttttggccaggggaccaagctggagatcaaacgt [SEQ ID NO:12]
scFv	DIQLTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKL LIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPADFATYYCQQSYS VPYTFGQGTKLEIKRSRGGGGSGGGGSGGGGSLEMAEVQLVQSG GGLVQPGGSLRLSCATSGFTFNNYWMSWVRQAPGKGLEWVANI KQDGSEKYYADSVRGRFTISRDNAKNSLSLQLNNLRAEDTAVYY CARSMSTAWGYDEWGQGTLVTVSS [SEQ ID NO:102]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 103 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-171 scFv (also referred to as "ET150-21 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:13 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:14, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 4. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:13, as shown in Table 4. In certain embodiments, the extracellular

antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:13, as shown in Table 4. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:14, as shown in Table 4. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:14, as shown in Table 4. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:13 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:14, as shown in Table 4. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:142 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:143 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:144 or conservative modifications thereof, as shown in Table 4. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:145 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:146 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:147 or conservative modifications thereof, as shown in Table 4. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:142 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:143 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:144 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:145 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:146 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:147 or conservative modifications thereof, as

shown in Table 4. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:142, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:143, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:144, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:145, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:146, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:147.

Table 4

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GYTFTSYY [SEQ ID NO:142]	INPSGGST [SEQ ID NO:143]	ARGSSRWGGWTGDY [SEQ ID NO:144]
V_L	SSDVGGYNF [SEQ ID NO:145]	DVS [SEQ ID NO:146]	SSYTSTRTVIFAGGTKVTVL [SEQ ID NO:147]
Full V_H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTRYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGSSRWGGWTGDYWGQGTLVTVSS [SEQ ID NO:13]		
DNA	Caggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtttcctgcaaggcatctggatacaccttcaccagctactatatgcactgggtgcgacaggcccctggacaagggcttgagtggatgggaataatcaaccctagtggtggtagcacaaggtacgcacagaagttccagggcagagtcaccatgaccagggacacgtcaacgagcacagtctacatggagctgagcagcctgagatctgaggacacggccgtgtattactgtgcgcgcggttcttctcgctggggtggttggactggtgattactggggtcaaggtactctggtgaccgtctcctca [SEQ ID NO:15]		
Full V_L	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNFVSWYQQHPGKAPKVMIYDVSKRPSGISNRFSGSKSGNTASLTISGLQVEDEAEYYCSSYTSTRTVIFAGGTKVTVLG [SEQ ID NO:14]		
DNA	Caatctgccctgactcagcctgcctccgtgtctgggtctcctggacagtcgatcaccatctcctgcactggaaccagcagtgacgttggtggttataactttgtctcctggtaccaacagcacccaggcaaagccccaaagtcatgatttatgatgtcagtaagcggccctcagggatttctaatcgcttctctggctccaagtctggcaacacggcctccctgaccatctctgggctccaggttgaggacgaggctgaatattactgcagctcatatacaagcactagaactgtgatattcgccggagggaccaaggtcaccgtcctaggt [SEQ ID NO:16]		
scFv	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNFVSWYQQHPGKAPKVMIYDVSKRPSGISNRFSGSKSGNTASLTISGLQVEDEAEYYCSSYTSTRTVIFAGGTKVTVLG SRGGGGSGGGGSGGGGSLEMAQVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTRYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGSSRWGGWTGDYWGQGTLVTVSS [SEQ ID NO:103]		

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 104 and specifically binds

to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-175 scFv (also referred to as "ET150-25 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:17 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:18, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 5. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:17, as shown in Table 5. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:17, as shown in Table 5. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:18, as shown in Table 5. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:18, as shown in Table 5. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:17 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:18, as shown in Table 5. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:148 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:149 or

conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in0 SEQ ID NO:150 or conservative modifications thereof, as shown in Table 5. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:151 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:152 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:153 or conservative modifications thereof, as shown in Table 5. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:148 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:149 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:150 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:151 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:152 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:153 or conservative modifications thereof, as shown in Table 5. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:148, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:149, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:150, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:151, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:152, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:153.

Table 5

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GSTFSSYA [SEQ ID NO:148]	ISGRGRST [SEQ ID NO:149]	ARYYKSKDH [SEQ ID NO:150]
V_L	RSNIGTNY [SEQ ID NO:151]	RNH [SEQ ID NO:152]	AAWDDNLSGVV [SEQ ID NO:153]
Full V_H	EVQLVETGGGLVQPGGSLRLSCAASGSTFSSYAMSWVRQAPGKG LEWVSAISGRGRSTYYADSVKGRFTISRDNSKNTLYLQMNSLRA		

	EDTAVYYCARYYKSSKDHWGQGTLVTVSS [SEQ ID NO:17]
DNA	Gaggtgcagctggtggagactgggggaggcttggtacagcctgggggtccctgagactctcctgtg cagcctctggatccacctttagcagctatgccatgagctgggtccgccaggctccagggaaggggctg gagtgggtctcagctattagtggtcgtggtcgtagcacatactacgcagactccgtgaagggccggttc accatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacac ggccgtatattactgtgcgcgctactacaaatcttctaaagatcattggggtcaaggtactctggtgaccg tctcctca [SEQ ID NO:19]
Full V_L	QSVLTQPPSLSGAPGQRVTISCSGSRSNIGTNYVSWXQQLPGTAP KLLIYRNHQWPSGVPDRFTGSKSGTSASLAISGLRSEDEADYYCA AWDDNLSGVVFGGGTKLTVLG [SEQ ID NO:18]
DNA	Cagtctgtgttgacgcagccgccctcactgtctggggccccagggcagagggtcaccatctcttgttcc ggaagcaggtccaacatcggaactaattatgtatcctggnaccagcaactcccaggaacggcccccaa actcctcatctataggaatcatcagtggccctcaggggtccctgaccgattcactggctccaagtctggc acctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattactactgtgcagcatgg gatgacaatttgagtggtgtggtgttcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:20]
scFv	QSVLTQPPSLSGAPGQRVTISCSGSRSNIGTNYVSWXQQLPGTAP KLLIYRNHQWPSGVPDRFTGSKSGTSASLAISGLRSEDEADYYCA AWDDNLSGVVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMA EVQLVETGGGLVQPGGSLRLSCAASGSTFSSYAMSWVRQAPGKG LEWVSAISGRGRSTYYADSVKGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCARYYKSSKDHWGQGTLVTVSS [SEQ ID NO:104]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 105 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-154 scFv (also referred to as "ET150-4 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:21 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:22, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 6. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%,

about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:21, as shown in Table 6. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:21, as shown in Table 6. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:22, as shown in Table 6. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:22, as shown in Table 6. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:21 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:22, as shown in Table 6. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:154 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:155 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:156 or conservative modifications thereof, as shown in Table 6. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:157 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:158 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:159 or conservative modifications thereof, as shown in Table 6. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:154 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:155 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:156 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:157 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:158 or

conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:159 or conservative modifications thereof, as shown in Table 6. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:154, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:155, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:156, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:157, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:158, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:159.

Table 6

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	AYTFTDYY [SEQ ID NO:154]	INPKSGRT [SEQ ID NO:155]	ARVYGYSRWSGFD L [SEQ ID NO:156]
V_L	SSNIGSNY [SEQ ID NO:157]	RNN [SEQ ID NO:158]	AAWDDSLSGYV [SEQ ID NO:159]
Full V_H	QVQLVQSGAEVQRPGASVRVSCKAIAYTFTDYYIHWVRQAPGQ GPEWMGWINPKSGRTQYAPKFQDRVTLARETPISTASMELRGLT SDDTAVYYCARVYGYSRWSGFDLWGQGTLVTVSS [SEQ ID NO:21]		
DNA	Caggtccagctggtgcagtctggggctgaggtgcagaggcctggggcctcagtgagggtctcctgca aggctattgcgtacaccttcaccgactactatatccactgggtgcgacaggcccctggacaagggcctg agtggatggggtggatcaaccctaaaagtggtcgcacacagtatgcaccgaagtttcaagacagggtc accctggccagggagacgcccatcagcacagcctccatggagctgcgcggactgacatctgacgac acggccgtgtattactgtgcgcgcgtttacggttactctcgttggtctggtttcgatctgtggggtcaaggt actctggtgaccgtctcctca [SEQ ID NO:23]		
Full V_L	QAVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAP KLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCA AWDDSLSGYVFGTGTKVTVLG [SEQ ID NO:22]		
DNA	Caggctgtgctgactcagccaccctcagcgtctgggacccccgggcagagggtcaccatctcttgttct ggaagcagctccaacatcggaagtaattatgtatactggtaccagcagctcccaggaacggcccccaa actcctcatctataggaataatcagcggccctcaggggtccctgaccgattctctggctccaagtctggc acctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgtgcagcatgg gatgacagcctgagtggttatgtcttcggaactgggaccaaggtcaccgtcctaggt [SEQ ID NO:24]		
scFv	QAVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAP KLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCA AWDDSLSGYVFGTGTKVTVLGSRGGGGSGGGGSGGGGSLEMAQ VQLVQSGAEVQRPGASVRVSCKAIAYTFTDYYIHWVRQAPGQGP EWMGWINPKSGRTQYAPKFQDRVTLARETPISTASMELRGLTSD DTAVYYCARVYGYSRWSGFDLWGQGTLVTVSS [SEQ ID NO:105]		

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 106 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-156 scFv (also referred to as "ET150-6 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:25 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:26, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 7. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:25, as shown in Table 7. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:25, as shown in Table 7. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:26, as shown in Table7. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:26, as shown in Table 7. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:25 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:26, as shown in Table 7. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the

sequence set forth in SEQ ID NO:160 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:161 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:162 or conservative modifications thereof, as shown in Table 7. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:163 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:164 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:165 or conservative modifications thereof, as shown in Table 7. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:160 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:161 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:162 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:163 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:164 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:165 or conservative modifications thereof, as shown in Table 7. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:160, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:161, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:162, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:163, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:164, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:165.

Table 7

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GYTFTTYY [SEQ ID NO:160]	INPNGGGT [SEQ ID NO: 161]	ARGHKVYKSHPTGG YDR [SEQ ID NO:162]
V_L	SRDVGGYNY [SEQ	EVS [SEQ ID	SSYTSSSTLD [SEQ ID

	ID NO:163]	NO:164]	NO:165]
Full V_H	QVQLVQSGAEVKQPGASVKVSCQASGYTFTTYYMHWVRQAPGQ GLEWMGIINPNGGGTFYAQKFQDRVTMTRDTSTGTVYMELSSLRS DDTAVYYCARGHKVYKSHPTGGYDRWGQGTLVTVSS [SEQ ID NO:25]		
DNA	Caggtgcagctggtgcaatctggggctgaggtgaagcagcctggggcctcagtgaaggtttcctgccag gcatctggatacaccttcaccacttattatatgcactgggtgcgacaggcccctggacaagggcttgagtg gatgggaataatcaaccctaatggtggtggcacattctacgcacagaagttccaggacagagtcaccatg accagggacacgtccacgggcacagtctacatggaactgagcagcctgagatctgacgacactgccgtg tattactgtgcgcgcggtcataaagtttacaaatctcatccgactggtggttacgatcgttggggtcaaggta ctctggtgaccgtctcctca [SEQ ID NO:27]		
Full V_L	QSALTQPASVSGSPGQSITISCTGTSRDVGGYNYVSWYQQYPGKAP KLMIYEVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSS YTSSSTLDFGTGTKVTVLG [SEQ ID NO:26]		
DNA	Caatctgccctgactcagcctgcctccgtgtctgggtctcctggacagtcgatcaccatctcctgcactgga accagccgtgacgttggtggttataactatgtctcctggtaccaacagtacccaggcaaagcccccaaact catgatttatgaggtcagtaagcggccctcaggggtttctaatcgcttctctggctccaagtctggcaacacg gcctccctgaccatctctgggctccaggctgaggacgaggctgattattactgcagctcatataccagtagc agcactttagacttcggaactgggaccaaggtcaccgtcctaggt [SEQ ID NO:28]		
scFv	QSALTQPASVSGSPGQSITISCTGTSRDVGGYNYVSWYQQYPGKAP KLMIYEVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSS YTSSSTLDFGTGTKVTVLGSRGGGGSGGGGSGGGGSLEMAQVQL VQSGAEVKQPGASVKVSCQASGYTFTTYYMHWVRQAPGQGLEW MGIINPNGGGTFYAQKFQDRVTMTRDTSTGTVYMELSSLRSDDTA VYYCARGHKVYKSHPTGGYDRWGQGTLVTVSS [SEQ ID NO:106]		

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 107 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-157 scFv (also referred to as "ET150-7 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:29 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:30, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 8. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%,

about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:29, as shown in Table 8. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:29, as shown in Table 8. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:30, as shown in Table 8. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:30, as shown in Table 8. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:29 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:30, as shown in Table 8. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:166 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:167 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:168 or conservative modifications thereof, as shown in Table 8. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:169 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:170 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:171 or conservative modifications thereof, as shown in Table 8. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:166 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:167 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:168 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the

sequence set forth in SEQ ID NO:169 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:170 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:171 or conservative modifications thereof, as shown in Table 8. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:166, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:167, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:168, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:169, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:170, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:171.

Table 8

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GGTFSSYA [SEQ ID NO:166]	IIPIFGTA [SEQ ID NO: 167]	ARSHVAWSLLDY [SEQ ID NO: 168]
V_L	SSNIGSNY [SEQ ID NO: 169]	RNN [SEQ ID NO: 170]	AAWDDSLSGVV [SEQ ID NO: 171]
Full V_H	EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQG LEWMGGIIPIFGTAKYAQKFQGRVTITADESTSTAYMELSSLRSED TAVYYCARSHVAWSLLDYWGQGTLVTVSS [SEQ ID NO:29]		
DNA	Gaggtccagctggtgcagtctggggctgaggtgaagaagcctgggtcctcggtgaaggtctcctgca aggcttctggaggcaccttcagcagctatgctatcagctgggtgcgacaggcccctggacaagggctt gagtggatgggagggattatccctatctttggtacagcaaaatatgcacagaagttccagggcagagtc acgattaccgcggacgaatccacgagcacagcctacatggagctgagcagcctgagatctgaggaca cggccgtgtattactgtgcgcgctctcatgttgcttggtctctgctggattactggggtcaaggtactctgg tgaccgtctcctca [SEQ ID NO:31]		
Full V_L	SYELTQPPSASGTPGQRVTISCSGSSSNIGSNYVSWYQQLPGTAPK LLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAA WDDSLSGVVFGGGTKLTVLG [SEQ ID NO:30]		
DNA	Tcctatgagctgactcagccaccctcagcgtctgggacccccgggcagagggtcaccatctcttgttct ggaagcagctccaacatcggaagtaattatgtatcctggtaccagcagctcccaggaacggcccccaa actcctcatctataggaataatcagcggccctcaggggtccctgaccgattctctggctccaagtctggc acctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgtgcagcatgg gatgacagcctgagtggtgtggtattcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:32]		
scFv	SYELTQPPSASGTPGQRVTISCSGSSSNIGSNYVSWYQQLPGTAPK LLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAA WDDSLSGVVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMAEV QLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLE WMGGIIPIFGTAKYAQKFQGRVTITADESTSTAYMELSSLRSEDT		

	AVYYCARSHVAWSLLDYWGQGTLVTVSS [SEQ ID NO:107]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 108 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-159 scFv (also referred to as "ET150-9 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:33 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:34, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 9. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:33, as shown in Table 9. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:33, as shown in Table 9. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:34, as shown in Table 9. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:34, as shown in Table 9. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:33 and a V_L comprising amino acids having the sequence set forth in

SEQ ID NO:34, as shown in Table 9. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:172 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:173 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:174 or conservative modifications thereof, as shown in Table 9. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:175 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:176 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:177 or conservative modifications thereof, as shown in Table 9. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:172 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:173 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:174 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:175 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:176 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:177 or conservative modifications thereof, as shown in Table 9. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:172, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:173, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:174 a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:175, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:176, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:177.

Table 9

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3

V_H	GGTFSSYA [SEQ ID NO:172]	MNPNSGNT [SEQ ID NO:173]	ARYQSYKGSQSDS [SEQ ID NO:174]
V_L	SSNIGSNY[SEQ ID NO:175]	RNN [SEQ ID NO:176]	AAWDDSLSGWV [SEQ ID NO:177]
Full V_H	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQG LEWMGWMNPNSGNTGYAQKFQGRVTMTRNTSISTAYMELSSLR SEDTAVYYCARYQSYKGSQSDSWGQGTLVTVSS [SEQ ID NO:33]		
DNA	Caggtgcagctggtgcagtctggggctgaggtgaagaagcctgggtcctcagtgaaggtctcctgca aggcttctggaggcaccttcagcagctatgctatcagctgggtgcgacaggcccctggacaagggctt gagtggatgggatggatgaaccctaacagtggtaacacaggctatgcacagaagttccagggcagag tcaccatgaccaggaacacctccataagcacagcctacatggagctgagcagcctgagatctgaggac acggccgtgtattactgtgcgcgctaccagtcttacaaaggttctcagtctgattcttggggtcaaggtact ctggtgaccgtctcctca [SEQ ID NO:35]		
Full V_L	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAP KLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCA AWDDSLSGWVFGGGTKLTVLG [SEQ ID NO:34]		
DNA	Cagtctgtgttgacgcagccaccctcagcgtctgggacccccgggcagagggtcaccatctcttgttct ggaagcagctccaacatcggaagtaattatgtatactggtaccagcagctcccaggaacggcccccaa actcctcatctataggaataatcagcggccctcaggggtccctgaccgattctctggctccaagtctggc acctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgtgcagcatgg gatgacagcctgagtggttgggtgttcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:36]		
scFv	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNYVYWYQQLPGTAP KLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCA AWDDSLSGWVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMA QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQG LEWMGWMNPNSGNTGYAQKFQGRVTMTRNTSISTAYMELSSLR SEDTAVYYCARYQSYKGSQSDSWGQGTLVTVSS [SEQ ID NO:108]		

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 109 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-160 scFv (also referred to as "ET150-10 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:37 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:38, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or

full length human IgG with V_H and V_L regions or CDRs selected from Table 10. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:37, as shown in Table 10. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:37, as shown in Table 10. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:38, as shown in Table 10. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:38, as shown in Table 10. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:37 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:38, as shown in Table 10. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:178 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:179 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:180 or conservative modifications thereof, as shown in Table 10. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:181 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:182 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:183 or conservative modifications thereof, as shown in Table 10. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:178 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the

sequence set forth in SEQ ID NO:179 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:180 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:181 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:182 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:183 or conservative modifications thereof, as shown in Table 10. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:178, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:179, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:180, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:181, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:182, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:183.

Table 10

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GYTFTSYY[SEQ ID NO:178]	INPSGGST [SEQ ID NO:179]	ARGGSKKWSGEKW RRENFDY [SEQ ID NO:180]
V_L	SSDVGGYNY [SEQ ID NO:181]	DVS [SEQ ID NO:182]	SSYTRSSTEV [SEQ ID NO:183]
Full V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARGGSKKWSGEKWRRENFDYWGQGTLVTVSS [SEQ ID NO:37]		
DNA	Gaggtccagctggtacagtctggggctgaggtgaagaagcctggggcctcagtgaaggtttcctgcaa ggcatctggatacaccttcaccagctactatatgcactgggtgcgacaggcccctggacaagggcttga gtggatgggaataatcaaccctagtggtggtagcacaagctacgcacagaagttccagggcagagtcac catgaccagggacacgtccacgagcacagtctacatggagctgagcagcctgagatctgaggacacg gccgtgtattactgtgcgcgcggtggttctaaaaaatggtctggtgaaaaatggcgtcgtgaaaacttcga ttactggggtcaaggtactctggtgaccgtctcctca [SEQ ID NO:39]		
Full V_L	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKA PKLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS SYTRSSTEVFGGGTKLTVLG [SEQ ID NO:38]		
DNA	Caatctgccctgactcagcctgcctccgtgtctgggtctcctggacagtcgatcaccatctcctgcactgg aaccagcagtgacgttggtggttataactatgtctcctggtaccaacagcacccaggcaaagcccccaaa ctcatgatttatgatgtcagtaagcggccctcaggggtttctaatcgcttctctggctccaagtctggcaaca cggcctccctgaccatctctgggctccaggctgaggacgaggctgattattactgcagctcatatacaag aagcagcactgaggtattcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:40]		

scFv	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKA PKLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCS SYTRSSTEVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMAEVQ LVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLE WMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDT AVYYCARGGSKKWSGEKWRRENFDYWGQGTLVTVSS [SEQ ID NO:109]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 110 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-161 scFv (also referred to as "ET150-11 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:41 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:42, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 11. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:41, as shown in Table 11. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:41, as shown in Table 11. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:42, as shown in Table 11. In certain embodiments, the extracellular antigen-binding domain

comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:42, as shown in Table 11. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:41 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:42, as shown in Table 11. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:184 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 185 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 186 or conservative modifications thereof, as shown in Table 11. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 187 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 188 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 189 or conservative modifications thereof, as shown in Table 11. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 184 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 185 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 186 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 187 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 188 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 189 or conservative modifications thereof, as shown in Table 11. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 184, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 185, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 186, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 187, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 188, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 189.

Table 11

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	EYTFTRHI [SEQ ID NO: 184]	INPGNGNT [SEQ ID NO: 185]	ARLPDQ [SEQ ID NO: 186]
V_L	SSNIGSNT [SEQ ID NO: 187]	RNN [SEQ ID NO: 188]	AAWDDSLSGL [SEQ ID NO:189]
Full V_H	QMQLVQSGAEVKKPGASVKVSCKASEYTFTRHILHWVRQAPGQ SLEWMGWINPGNGNTKYSQKFQVRVTFTRDTSASTVYMELSSLR SEDTAVYYCARLPDQWGQGTLVTVSS [SEQ ID NO:41]		
DNA	Cagatgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtttcctgcaa ggcttctgaatacaccttcactaggcatattctacattgggtgcgccaggctcccggacaaagccttgagt ggatgggatggatcaacccaggcaatggtaatacaaaatattcacagaagttccaggtcagagtcacctt taccagggacacatccgcgagcacagtctatatggagctgagcagcctgagatctgaagacacggcc gtgtattactgtgcgcgcctgccggatcagtggggtcaaggtactctggtgaccgtctcctca [SEQ ID NO:43]		
Full V_L	SYVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPK LLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAA WDDSLSGLFGTGTKVTVLG [SEQ ID NO:42]		
DNA	Tcctatgtgctgactcagccaccctcagcgtctgggacccccgggcagagggtcaccatctcttgttct ggaagcagctccaacatcggaagtaatactgtaaactggtaccagcagctcccaggaacggccccca aactcctcatctataggaataatcagcggccctcaggggtccctgaccgattctctggctccaagtctgg cacctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgtgcagcatg ggatgacagcctgagtggtctcttcggaactgggaccaaggtcaccgtcctaggt [SEQ ID NO:44]		
scFv	SYVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPK LLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAA WDDSLSGLFGTGTKVTVLGSRGGGGSGGGGSGGGGSLEMAQMQ LVQSGAEVKKPGASVKVSCKASEYTFTRHILHWVRQAPGQSLEW MGWINPGNGNTKYSQKFQVRVTFTRDTSASTVYMELSSLRSEDT AVYYCARLPDQWGQGTLVTVSS [SEQ ID NO:110]		

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 111 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-162 scFv (also referred to as "ET150-12 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:45 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:46, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker

comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 12. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:45, as shown in Table 12. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:45, as shown in Table 12. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:46, as shown in Table 12. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:46, as shown in Table 12. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:45 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:46, as shown in Table 12. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:190 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 191 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 192 or conservative modifications thereof, as shown in Table 12. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 193 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 194 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 195 or conservative modifications thereof, as shown in Table 12. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1

comprising amino acids having the sequence set forth in SEQ ID NO: 190 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 191 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 192 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 193 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 194 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 195 or conservative modifications thereof, as shown in Table 12. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 190, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 191, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 192, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 193, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 194, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 195.

Table 12

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFTFGDYG [SEQ ID NO: 190]	INWNGGST [SEQ ID NO: 191]	ARSKQDY [SEQ ID NO: 192]
V_L	SRDAGGYNY [SEQ ID NO: 193]	EVT [SEQ ID NO: 194]	SSYGGSNNFRV [SEQ ID NO:195]
Full V_H	EVQLVESGGGVVRPGGSLRLSCAASGFTFGDYGMSWVRQAPGK GLEWVSGINWNGGSTGYADSVKGRFTISRDNAKNSLYLQMNSLR AEDTAVYYCARSKQDYWGQGTLVTVSS [SEQ ID NO:45]		
DNA	Gaggtgcagctggtggagtctgggggaggtgtggtacggcctgggggtccctgagactctcctgtg cagcctctggattcacctttggtgattatggcatgagctgggtccgccaagctccagggaaggggctgg agtgggtctctggtattaattggaatggtggtagcacaggttatgcagactctgtgaagggccgattcacc atctccagagacaacgccaagaactccctgtatctgcaaatgaacagtctgagagccgaggacacggc cgtatattactgtgcgcgctctaaacaggattactggggtcaaggtactctggtgaccgtctcctca [SEQ ID NO:47]		
Full V_L	QSALTQPPSASGSPGQSVTISCTGTSRDAGGYNYFSWYQQHPGKA PKLLIYEVTKRPSGVPDRFSGSKSGKTASLTVSGLQADDEAVYYC SSYGGSNNFRVFGGGTKLTVLG [SEQ ID NO:46]		
DNA	Cagtctgccctgactcagcctccctccgcgtccgggtctcctggacagtcagtcaccatctcctgcactg gaaccagcagggacgctggtggttataattatttctcctggtaccaacaacacccaggcaaagccccca aactcctgatttatgaggtcactaagcggccctcaggggtccctgatcgcttctctggctccaagtctggc aagacggcctccctgaccgtctctgggctccaggctgacgatgaggctgtatattactgcagctcatatg		

	gaggcagcaacaactttcgggtgttcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:48]
scFv	QSALTQPPSASGSPGQSVTISCTGTSRDAGGYNYFSWYQQHPGKA PKLLIYEVTKRPSGVPDRFSGSKSGKTASLTVSGLQADDEAVYYC SSYGGSNNFRVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMA EVQLVESGGGVVRPGGSLRLSCAASGFTFGDYGMSWVRQAPGK GLEWVSGINWNGGSTGYADSVKGRFTISRDNAKNSLYLQMNSLR AEDTAVYYCARSKQDYWGQGTLVTVSS [SEQ ID NO:111]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 112 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-163 scFv (also referred to as "ET150-13 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:49 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:50, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 13. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:49, as shown in Table 13. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:49, as shown in Table 13. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:50, as shown in Table 13. In certain embodiments, the extracellular antigen-binding domain

comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:50, as shown in Table 13. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:49 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:50, as shown in Table 13. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:196 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 197 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 198 or conservative modifications thereof, as shown in Table 13. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 199 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:200 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:201 or conservative modifications thereof, as shown in Table 13. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 196 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 197 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 198 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 199 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:200 or conservative modifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:201 or conservative modifications thereof, as shown in Table 13. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 196, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 197, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 198 a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 199, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:200, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:201.

Table 13

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFSFSGTA[SEQ ID NO: 196]	ISSTGRST [SEQ ID NO: 197]	ARVSFDY [SEQ ID NO: 198]
V_L	SSNIGAGYD [SEQ ID NO: 199]	GNS [SEQ ID NO:200]	QSYDSSLSGSYV [SEQ ID NO:201]
Full V_H	EVQLVETGGNLVQPGASLRLSCAASGFSFSGTAMHWVRQAPGK GLEWVSTISSTGRSTYYRDSVKGRFTISRDNSKNTLYLQMNSLRG EDTAVYYCARVSFDYWGQGTLVTVSS [SEQ ID NO:49]		
DNA	Gaggtgcagctggtggagactgggggaaacttggtacagccgggggcgtccctgagactctcctgtg cagcctctggattcagctttagtggcactgccatgcactgggtccgccaggctccagggaaggggctg gaatgggtctcgactattagtagtactgggcgtagcacatactacagagactccgtgaagggccggttc accatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagaggcgaggacac ggccgtatattactgtgcgcgcgtttctttcgattactggggtcaaggtactctggtgaccgtctcctca [SEQ ID NO:51]		
Full V_L	QSVVTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTA PKLLIYGNSNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYC QSYDSSLSGSYVFGTGTKLTVLG [SEQ ID NO:50]		
DNA	Cagtctgtcgtgacgcagccgccctcagtgtctggggccccagggcagagggtcaccatctcctgca ctgggagcagctccaacatcggggcaggttatgatgtacactggtaccagcagcttccaggaacagcc cccaaactcctcatctatggtaacagcaatcggccctcaggggtccctgaccgattctctggctccaagt ctggcacctcagcctccctggccatcactgggctccaggctgaggatgaggctgattattactgccagt cctatgacagcagcctgagtggctcctacgtcttcggaactgggaccaagctgaccgtcctaggt [SEQ ID NO:52]		
scFv	QSVVTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTA PKLLIYGNSNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYC QSYDSSLSGSYVFGTGTKLTVLGSRGGGGSGGGGSGGGGSLEMA EVQLVETGGNLVQPGASLRLSCAASGFSFSGTAMHWVRQAPGK GLEWVSTISSTGRSTYYRDSVKGRFTISRDNSKNTLYLQMNSLRG EDTAVYYCARVSFDYWGQGTLVTVSS [SEQ ID NO:112]		

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 113 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-151 scFv (also referred to as "ET150-1 scFv").

In certain embodiments, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:53 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:54, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the

sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 14. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:53, as shown in Table 14. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:53, as shown in Table 14. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:54, as shown in Table 14. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:54, as shown in Table 14. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:53 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:54, as shown in Table 14. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:202 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:203 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 204 or conservative modifications thereof, as shown in Table 14. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 205 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 206 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 207 or conservative modifications thereof, as shown in Table 14. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1

comprising amino acids having the sequence set forth in SEQ ID NO: 202 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 203 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 204 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 205 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 206 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 207 or conservative modifications thereof, as shown in Table 14. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 202, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 203, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 204, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 205, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 206, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 207.

Table 14

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFTFSSYA [SEQ ID NO: 202]	ISGRGRST [SEQ ID NO: 203]	ARYYHAGAFDL [SEQ ID NO: 204]
V_L	SSDVGGYNY [SEQ ID NO: 205]	DVS [SEQ ID NO: 206]	SSYTSSSTLV [SEQ ID NO: 207]
Full V_H	EVQLVESGGAFVQPGGSLRLSCAASGFTFSSYAMTWVRQAPGKG LEWVSTISGRGRSTFYADSVKGRFTISRDNSKNTLYLQMNSLRAE DTAVYYCARYYHAGAFDLWGQGTLVTVSS [SEQ ID NO:53]		
DNA	Gaggtgcagctggtggagtctgggggagcctttgtacagcctgggggtccctgagactctcctgtgc agcctctggattcacctttagcagctatgccatgacctgggtccgccaggctccagggaagggcctgga atgggtctcgactattagtggtcgtggtcgtagcacattctacgcagactccgtgaagggccggtttacca tctccagagacaattccaagaacacgctatatctgcaaatgaacagtctgagagccgaggacacggcc gtatattactgtgcgcgctactaccatgctggtgctttcgatctgtggggtcaaggtactctggtgaccgtc tcctca [SEQ ID NO:55]		
Full V_L	QSVVTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKA PKLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYC SSYTSSSTLVFGGGTKLTVLG [SEQ ID NO:54]		
DNA	Cagtctgtcgtgacgcagcctgcctccgtgtctgggtctcctggacagtcgatcaccatctcctgcactg gaaccagcagtgacgttggtggttataactatgtctcctggtaccaacagcacccaggcaaagccccca aactcatgatttatgatgtcagtaagcggccctcaggggtttctaatcgcttctctggctccaagtctggca acacggcctccctgaccatctctgggctccaggctgaggacgaggctgattattactgcagctcatatac		

	aagcagcagcactttggtattcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:56]
scFv	QSVVTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKA PKLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYC SSYTSSSTLVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMAEV QLVESGGAFVQPGGSLRLSCAASGFTFSSYAMTWVRQAPGKGLE WVSTISGRGRSTFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDT AVYYCARYYHAGAFDLWGQGTLVTVSS [SEQ ID NO:113]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 114 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-152 scFv (also referred to as "ET150-2 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:57 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:58, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 15. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:57, as shown in Table 15. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:57, as shown in Table 15. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:58, as shown in Table 15. In certain embodiments, the extracellular antigen-binding domain

comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:58, as shown in Table 15. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:57 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:58, as shown in Table 15. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:208 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 209 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 210 or conservative modifications thereof, as shown in Table 15. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 211 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 212 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 213 or conservative modifications thereof, as shown in Table 15. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 208 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 209 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 210 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 211 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 212 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 213 or conservative modifications thereof, as shown in Table 15. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 208, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 209, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 210, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 211, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 212, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 213.

Table 15

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GYTFNRYA [SEQ ID NO: 208]	ISAYNGNS [SEQ ID NO: 209]	ARMAYDS [SEQ ID NO: 210]
V_L	SNDVGAYKY [SEQ ID NO: 211]	DVF [SEQ ID NO: 212]	FSLTSSNTYV [SEQ ID NO: 213]
Full V_H	QMQLVQSGAEVKKPGASVKVSCKASGYTFNRYAITWVRQAPGQ GLEWMGWISAYNGNSHYAQKLQGRVTMTTDTSTGTAYMELRRL RSDDTAVYYCARMAYDSWGQGTLVTVSS [SEQ ID NO:57]		
DNA	Cagatgcagctggtgcagtctggagctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaa ggcttctggttacacctttaacagatatgctatcacctgggtgcgacaggcccctggacaaggccttgagt ggatgggatggatcagcgcttacaatggtaattcacactatgcacagaagctccagggcagagtcaccat gaccacagacacatccacgggcacagcctatatggagctgaggaggctgagatctgacgacacggcc gtgtattactgtgcgcgcatggcttacgattcttggggtcaaggtactctggtgaccgtctcctca [SEQ ID NO:59]		
Full V_L	QSVLTQPASVSGSPGQSLTISCTGTSNDVGAYKYVSWYQQYPGKA PKLILYDVFKRPSGVSNRFSGSKSDNTASLTISGLQAEDEADYYCF SLTSSNTYVFGTGTKVTVLG [SEQ ID NO:58]		
DNA	Cagtctgtgttgacgcagcctgcctccgtgtctgggtctcctggacagtcgctcaccatctcctgcactgg aaccagcaatgacgttggtgcttataagtatgtctcctggtatcaacagtacccaggcaaagcccccaaac tcatactttatgatgtctttaagcggccctcaggggtctctaatcgcttctctggctccaagtctgacaacac ggcctccctgaccatctctgggctccaggctgaggacgaggctgattattactgcttctcacttacaagca gtaacacttatgtcttcggaactgggaccaaggtcaccgtcctaggt [SEQ ID NO:60]		
scFv	QSVLTQPASVSGSPGQSLTISCTGTSNDVGAYKYVSWYQQYPGKA PKLILYDVFKRPSGVSNRFSGSKSDNTASLTISGLQAEDEADYYCF SLTSSNTYVFGTGTKVTVLGSRGGGGSGGGGSGGGGSLEMAQMQ LVQSGAEVKKPGASVKVSCKASGYTFNRYAITWVRQAPGQGLEW MGWISAYNGNSHYAQKLQGRVTMTTDTSTGTAYMELRRLRSDD TAVYYCARMAYDSWGQGTLVTVSS [SEQ ID NO:114]		

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 115 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-155 scFv (also referred to as "ET150-5 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFV, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:61 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:62, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain

embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 16. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:61, as shown in Table 16. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:61, as shown in Table 16. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:62, as shown in Table 16. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:62, as shown in Table 16. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:61 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:62, as shown in Table 16. Incertain embodiments certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:214 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 215 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 216 or conservative modifications thereof, as shown in Table 16. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 217 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 218 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 219 or conservative modifications thereof, as shown in Table 16. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ

ID NO: 214 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 215 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 216 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 217 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 218 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 219 or conservative modifications thereof, as shown in Table 16. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 214, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 215, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 216, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 217, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 218 and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 219.

Table 16

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFTFSDYY [SEQ ID NO: 214]	ISSSGSTI [SEQ ID NO: 215]	ARGYGKAYDQ [SEQ ID NO: 216]
V_L	RSNVGGNY [SEQ ID NO: 217]	RSN [SEQ ID NO: 218]	ATWDDSLSGFV [SEQ ID NO: 219]
Full V_H	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKG LEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAE DTAVYYCARGYGKAYDQWGQGTLVTVSS [SEQ ID NO:61]		
DNA	Gaggtgcagctggtggagtctgggggaggcttggtcaagcctggagggtccctgagactctcctgtg cagcctctggattcaccttcagtgactactacatgagctggatccgccaggctccagggaaggggctg gagtgggtttcatacattagtagtagtggtagtaccatatactacgcagactctgtgaagggccgattcac catctccagggacaacgccaagaactcactgtatctgcaaatgaacagcctgagagccgaggacacg gccgtatattactgtgcgcgcggttacggtaaagcttacgatcagtggggtcaaggtactctggtgaccg tctcctca [SEQ ID NO:63]		
Full V_L	QSVLTQPPSASGTPGQRVTISCSGSRSNVGGNYVFWYQQVPGATP KLLIYRSNQRPSGVPDRFAGSKSGSSASLAISGLRSEDEADYYCAT WDDSLSGFVFGTGTKVTVLG [SEQ ID NO:62]		
DNA	Cagtctgtgttgactcagccaccctcagcgtctgggacccccggacagagggtcaccatctcttgttct ggaagcaggtccaacgtaggaggtaattatgtattttggtaccagcaagtccccggagcgacccccaa actcctcatctataggagtaatcagcggccctcgggggtccctgaccgattcgctggctccaagtctgg ctcctcagcctccctggccatcagtggactccggtccgaggatgaggctgattattactgtgcaacatgg gatgacagcctgagtggttttgtcttcggaactgggaccaaggtcaccgtcctaggt [SEQ ID		

	NO:64]
scFv	QSVLTQPPSASGTPGQRVTISCSGSRSNVGGNYVFWYQQVPGATP KLLIYRSNQRPSGVPDRFAGSKSGSSASLAISGLRSEDEADYYCAT WDDSLSGFVFGTGTKVTVLGSRGGGGSGGGGSGGGGSLEMAEV QLVESGGGLVKPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLE WVSYISSSGSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARGYGKAYDQWGQGTLVTVSS [SEQ ID NO:115]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 116 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-158 scFv (also referred to as "ET150-8 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:65 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:66, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 17. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:65, as shown in Table 17. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:65, as shown in Table 17. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:66, as shown in Table 17. In certain embodiments, the extracellular antigen-binding domain

comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:66, as shown in Table 17. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:65 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:66, as shown in Table 17. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:220 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 221 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 222 or conservative modifications thereof, as shown in Table 17. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 223 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 224 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 225 or conservative modifications thereof, as shown in Table 17. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 220 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 221 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 222 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 223 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 224 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 225 or conservative modifications thereof, as shown in Table 17. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 220, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 221, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 222, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 223, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 224, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 225.

Table 17

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFTFRSHS [SEQ ID NO: 220]	ISSDSTYT [SEQ ID NO: 221]	ARSGGQWKYYDY [SEQ ID NO: 222]
V_L	SLRSYY [SEQ ID NO: 223]	GKN [SEQ ID NO: 224]	NSRDSSGNPPVV [SEQ ID NO: 225]
Full V_H	QVQLVESGGGLVHPGGSLRLSCAASGFTFRSHSMNWVRQAPGKG LEWVSSISSDSTYTYYADSVKGRFTISRDNAKNSLYLQMNSLRAE DTAVYYCARSGGQWKYYDYWGQGTLVTVSS [SEQ ID NO:65]		
DNA	Caggtgcagctggtggagtctgggggaggcctggtccaccctgggggtccctgagactctcctgtgc agcctctggattcaccttcagaagccatagcatgaactgggtccgccaggctccagggaaggggctgg agtgggtctcatccattagtagtgatagtacttacacatactacgcagactcagtgaagggccgattcacc atctccagagacaacgccaagaactcactgtatctgcaaatgaacagcctgagagccgaggacacggc cgtatattactgtgcgcgctctggtggtcagtggaaatactacgattactggggtcaaggtactctggtgac cgtctcctca [SEQ ID NO:67]		
Full V_L	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVL VIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRD SSGNPPVVFGGGTKLTVLG [SEQ ID NO:66]		
DNA	Tcttctgagctgactcaggaccctgctgtgtctgtggccttgggacagacagtcaggatcacatgccaag gagacagcctcagaagctattatgcaagctggtaccagcagaagccaggacaggcccctgtacttgtca tctatggtaaaaacaaccggccctcagggatcccagaccgattctctggctccagctcaggaaacacag cttccttgaccatcactggggctcaggcggaagatgaggctgactattactgtaactcccgggacagcag tggtaacccccctgtggtattcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:68]		
scFv	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVL VIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRD SSGNPPVVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMAQVQL VESGGGLVHPGGSLRLSCAASGFTFRSHSMNWVRQAPGKGLEWV SSISSDSTYTYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARSGGQWKYYDYWGQGTLVTVSS [SEQ ID NO:116]		

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 117 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-168 scFv (also referred to as "ET150-18 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:69 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:70, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain

embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 18. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:69, as shown in Table 18. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:69, as shown in Table 18. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:70, as shown in Table 18. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:70, as shown in Table 18. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:69 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:70, as shown in Table 18. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:226 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 227 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 228 or conservative modifications thereof, as shown in Table 18. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 229 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 230 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 231 or conservative modifications thereof, as shown in Table 18. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 226 or

conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 227 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 228 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 229 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 230 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 231 or conservative modifications thereof, as shown in Table 18. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 226, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 227, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 228, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 229, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 230, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 231.

Table 18

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFTFSNYA [SEQ ID NO: 226]	INGRGSST [SEQ ID NO: 227]	ARYISRGLGDS [SEQ ID NO: 228]
V_L	NSNIERNY[SEQ ID NO: 229]	DND [SEQ ID NO: 230]	GTWDSSLRGWV [SEQ ID NO: 231]
Full V_H	EVQLVESGGGLIQPGGSLRLSCAASGFTFSNYAMNWVRQAPGKG LEWVSTINGRGSSTIYADSVKGRFTISRDNSKNTLYLQMNSLRAED TATYYCARYISRGLGDSWGQGTLVTV [SEQ ID NO:69]		
DNA	Gaggtgcagctggtggagtccgggggaggcttgatacagcctgggggtccctgagactctcctgtgc agcctctggattcacctttagcaactatgccatgaactgggtccgccaggctccagggaaggggctgga gtgggtctcaactattaatggtcgtggtagtagtacaatctacgcagactccgtgaagggccggttcacca tctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacagcca cgtattactgtgcgcgctacatctctcgtggtctgggtgattcttggggtcaaggtactctggtgaccgtctc ctca [SEQ ID NO:71]		
Full V_L	QSVVTQPPSMSAAPGQQVTISCSGGNSNIERNYVSWYLQLPGTAP KLVIFDNDRRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGT WDSSLRGWVFGGGTKLTVLG [SEQ ID NO:70]		
DNA	Cagtctgtcgtgacgcagccgccctcaatgtctgcggccccaggacagcaagtcaccatctcctgctct ggaggcaactccaacattgagagaaattatgtatcctggtacctccagctccctggaacagccccaaac tcgtcatttttgacaatgataggcgaccctcagggattcctgaccgattctctggctccaagtctggcacgt cagccaccctgggcatcaccggactccagactggggacgaggccgattattactgcggaacatgggat agcagcctgagaggttgggtgttcggcggagggaccaagctgaccgtcctaggt [SEQ ID		

	NO:72]
scFv	QSVVTQPPSMSAAPGQQVTISCSGGNSNIERNYVSWYLQLPGTAP KLVIFDNDRRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGT WDSSLRGWVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMAEV QLVESGGGLIQPGGSLRLSCAASGFTFSNYAMNWVRQAPGKGLE WVSTINGRGSSTIYADSVKGRFTISRDNSKNTLYLQMNSLRAEDT ATYYCARYISRGLGDSWGQGTLVTV [SEQ ID NO:117]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 118 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-164 scFv (also referred to as "ET150-14 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:73 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:74, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 19. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:73, as shown in Table 19. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:73, as shown in Table 19. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:74, as shown in Table 19. In certain embodiments, the extracellular antigen-binding domain

comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:74, as shown in Table 19. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:73 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:74, as shown in Table 19. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:232 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 233 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 234 or conservative modifications thereof, as shown in Table 19. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 235 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 236 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 237 or conservative modifications thereof, as shown in Table 19. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 232 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 233 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 234 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 235 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 236 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 237 or conservative modifications thereof, as shown in Table 19. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 232, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 233, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 234, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 235, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 236, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 237.

Table 19

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GYTFTSYY [SEQ ID NO: 232]	INPSGGST [SEQ ID NO: 233	ARAGMGMDT [SEQ ID NO: 234]
V_L	SSDVGGYNY [SEQ ID NO: 235]	EVS [SEQ ID NO: 236]	SSYAGSNTLV [SEQ ID NO: 237]
Full V_H	QMQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPG QGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSL RSEDTAVYYCARAGMGMDTWGQGTLVTVSS [SEQ ID NO:73]		
DNA	Cagatgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtttcctgca aggcatctggatacaccttcaccagctactatatgcactgggtgcgacaggcccctggacaagggcttg agtggatgggaataatcaaccctagtggtggtagcacaagctacgcacagaagttccagggcagagtc accatgaccagggacacgtccacgagcacagtctacatggagctgagcagcctgagatctgaggaca cggccgtgtattactgtgcgcgcgctggtatgggtatggatacttggggtcaaggtactctggtgaccgt ctcctca [SEQ ID NO:75]		
Full V_L	QSALTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGK APKLMIYEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYY CSSYAGSNTLVFGGGTKLTVLG [SEQ ID NO:74]		
DNA	Cagtctgccctgactcagcctccctccgcgtccgggtctcctggacagtcagtcaccatctcctgcact ggaaccagcagtgacgttggtggttataactatgtctcctggtaccaacagcacccaggcaaagccccc aaactcatgatttatgaggtcagtaagcggccctcaggggtccctgatcgcttctctggctccaagtctgg caacacggcctccctgaccgtctctgggctccaggctgaggatgaggctgattattactgcagctcatat gcaggcagcaacaccttggtgttcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:76]		
scFv	QSALTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGK APKLMIYEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYY CSSYAGSNTLVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMA QMQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPG QGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSL RSEDTAVYYCARAGMGMDTWGQGTLVTVSS [SEQ ID NO:118]		

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 119 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-165 scFv (also referred to as "ET150-15 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:77 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:78, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker

comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 20. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:77, as shown in Table 20. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:77, as shown in Table 20. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:78, as shown in Table 20. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:78, as shown in Table 20. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:77 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:78, as shown in Table 20. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:238 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 239 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 240 or conservative modifications thereof, as shown in Table 20. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 241 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 242 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 243 or conservative modifications thereof, as shown in Table 20. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1

comprising amino acids having the sequence set forth in SEQ ID NO: 238 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 239 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 240 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 241 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 242 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 243 or conservative modifications thereof, as shown in Table 20. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 238, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 239, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 240, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 241, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 242, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 243.

Table 20

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GYTFTAYS [SEQ ID NO: 238]	INPSSGGA [SEQ ID NO: 239]	ARNVGGQADD [SEQ ID NO: 240]
V_L	SSDIGGYNY [SEQ ID NO: 241]	EVN [SEQ ID NO: 242]	ASFAGRKTLV [SEQ ID NO: 243]
Full V_H	QVQLVQSGAEVKKPGASVKVSCRASGYTFTAYSLHWVRQAPGQ GLEWMGWINPSSGGAVYAQKFQGRVTMTRDTSISTAYMELSGL RSDDTAVYYCARNVGGQADDWGQGTLVTVSS [SEQ ID NO:77]		
DNA	Caggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtctcctgca gggcttctggatacaccttcaccgcctactctttacactgggtgcgacaggcccctggacaagggcttg agtggatgggatggatcaaccctagcagtggtggcgcagtttatgcacagaaatttcagggtagggtca ccatgaccagggacacgtccatcagcacagcctacatggagctgagtggcctgagatctgacgacac ggccgtgtattactgtgcgcgcaacgttggtggtcaggctgatgactggggtcaaggtactctggtgac cgtctcctca [SEQ ID NO:79]		
Full V_L	QSALTQPPSASGSPGQSVTISCTGTSSDIGGYNYVSWYQQHPGKA PKLMIYEVNKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYY CASFAGRKTLVFGGGTKLTVLG [SEQ ID NO:78]		
DNA	Caatctgccctgactcagcctccctccgcgtccgggtctcctggacagtcagtcaccatctcctgcactg gaaccagcagtgacattggtggttataactatgtctcctggtaccaacagcacccaggcaaagccccca aactcatgatttatgaggtcaataagcggccctcaggggtccctgatcgcttctcgggctccaagtctgg caacacggcctccctgaccgtctctgggctccaggctgaggatgaggctgattattactgcgcctcattt		

	gcgggcaggaagacattggtcttcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:80]
scFv	QSALTQPPSASGSPGQSVTISCTGTSSDIGGYNYVSWYQQHPGKA PKLMIYEVNKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYY CASFAGRKTLVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMA QVQLVQSGAEVKKPGASVKVSCRASGYTFTAYSLHWVRQAPGQ GLEWMGWINPSSGGAVYAQKFQGRVTMTRDTSISTAYMELSGL RSDDTAVYYCARNVGGQADDWGQGTLVTVSS [SEQ ID NO:119]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 120 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-167 scFv (also referred to as "ET150-17 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:81 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:82, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 21. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:81, as shown in Table 21. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:81, as shown in Table 21. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:82, as shown in Table 21. In certain embodiments, the extracellular antigen-binding domain

comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:82, as shown in Table 21. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:81 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:82, as shown in Table 21. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:244 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 245 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 246 or conservative modifications thereof, as shown in Table 21. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 247 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 248 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 249 or conservative modifications thereof, as shown in Table 21. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 244 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 245 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 246 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 247 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 248 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 249 or conservative modifications thereof, as shown in Table 21. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 244, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 245, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 246, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 247, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 248, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 249.

Table 21

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GYTFTAYS [SEQ ID NO: 244]	INPSSGGA [SEQ ID NO: 245]	ARNVGGHADD [SEQ ID NO: 246]
V_L	STDIGGYNY [SEQ ID NO: 247]	EVN [SEQ ID NO: 248]	ASFAGRKTLV [SEQ ID NO: 249]
Full V_H	QVQLVQSGAEVKKPGASVKVSCRASGYTFTAYSLHWVRQAPGQ GLEWMGWINPSSGGAVYAQKFQGRVTMTRDTSISTAYMELSGL RSDDTAVYYCARNVGGHADDWGQGTLVTVSS [SEQ ID NO:81]		
DNA	Caggtgcagctggtgcagtctggggctgaggtgaaaaagcctggggcctcagtgaaagtctcctgca gggcttctggatacaccttcaccgcctactctttacactgggtgcgacaggcccctggacaagggcttg agtggatgggatggatcaaccctagcagtggtggcgcagtttatgcacagaaatttcagggtagggtca ccatgaccagggacacgtccatcagcacagcctacatggagctgagtggcctgagatctgacgacac ggccgtgtattactgtgcgcgcaacgttggtggtcacgctgatgactggggtcaaggtactctggtgac cgtctcctca [SEQ ID NO:83]		
Full V_L	QSALTQPPSASGSPGQSVTISCTGTSTDIGGYNYVSWYQHHPSKA PKLMIYEVNKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYY CASFAGRKTLVFGGGTKLTVLG [SEQ ID NO:82]		
DNA	Caatctgccctgactcagcctccctccgcgtccgggtctcctggacagtcagtcaccatctcctgcactg gaaccagcactgacattggtggttataactatgtctcctggtaccaacaccacccaagcaaagccccca aactcatgatttatgaggtcaataagcggccctcaggggtccctgatcgcttctcgggctccaagtctgg caacacggcctccctgaccgtctctgggctccaggctgaggatgaggctgattattactgcgcctcattt gcgggcaggaagacattggtcttcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:84]		
scFv	QSALTQPPSASGSPGQSVTISCTGTSTDIGGYNYVSWYQHHPSKA PKLMIYEVNKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYY CASFAGRKTLVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMA QVQLVQSGAEVKKPGASVKVSCRASGYTFTAYSLHWVRQAPGQ GLEWMGWINPSSGGAVYAQKFQGRVTMTRDTSISTAYMELSGL RSDDTAVYYCARNVGGHADDWGQGTLVTVSS [SEQ ID NO:120]		

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 121 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-169 scFv (also referred to as "ET150-19 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:85 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:86, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker

comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 22. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:85, as shown in Table 22. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:85, as shown in Table 22. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:86, as shown in Table 22. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:86, as shown in Table 22. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:85 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:86, as shown in Table 22. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:250 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 251 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 252 or conservative modifications thereof, as shown in Table 22. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 253 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 254 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 255 or conservative modifications thereof, as shown in Table 22. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1

comprising amino acids having the sequence set forth in SEQ ID NO: 250 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 251 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 252 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 253 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 254 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 255 or conservative modifications thereof, as shown in Table 22. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 250, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 251, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 252, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 253, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 254, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 255.

Table 22

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFTFNTYG [SEQ ID NO: 250]	ISANNGHT [SEQ ID NO: 251]	ARGGYHHQMQRYY KATSVYSDY [SEQ ID NO: 252]
V_L	SSNIGNNY [SEQ ID NO: 253]	DNN [SEQ ID NO: 254]	GTWDSSLSGVV [SEQ ID NO: 255]
Full V_H	QVQLVQSGGEVKKPGASVKVSCKASGFTFNTYGISWVRQAPGQ GLEWMGWISANNGHTKSAQRFQDRVAMATDTSTSTAYMELRSL KFDDTAVYYCARGGYHHQMQRYYKATSVYSDYWGQGTLVTVS S [SEQ ID NO:85]		
DNA	Caggtccagctggtgcagtctggaggtgaggtgaagaagcctggggcctcagtgaaggtctcctgca aggcttctggtttcacctttaacacctatggcatcagttgggtgcgacaggcccctggacaagggcttga gtggatgggatggatcagcgctaacaatggtcacacaaagtctgcacagaggttccaggacagagtcg ccatggccacagacacatccacgagcacggcctacatggagctgaggagcctgaaatttgacgacac ggccgtgtattactgtgcgcgcggtggttaccatcatcagatgcagcggtactacaaagctacttctgttt actctgattactggggtcaaggtactctggtgaccgtctcctca [SEQ ID NO:87]		
Full V_L	QSVVTQPPSVSAAPGQKVTISCSGSSSNIGNNYVSWYQQLPGTAP KLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGT WDSSLSGVVFGGGTKLTVLG [SEQ ID NO:86]		
DNA	Cagtctgtcgtgacgcagccgccctcagtgtctgcggccccaggacagaaggtcaccatctcctgctc tggaagcagctccaacattgggaataattatgtatcctggtaccagcaactcccaggaacagcccccaa		

	actcctcatttatgacaataataagcgaccctcagggattcctgaccgattctctggctccaagtctggca cgtctgccaccctgggcatcaccggactccagactggggacgaggccgattattactgcggaacatgg gatagcagcctgagtggtgtggtattcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:88]
scFv	QSVVTQPPSVSAAPGQKVTISCSGSSSNIGNNYVSWYQQLPGTAP KLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGT WDSSLSGVVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMAQV QLVQSGGEVKKPGASVKVSCKASGFTFNTYGISWVRQAPGQGLE WMGWISANNGHTKSAQRFQDRVAMATDTSTSTAYMELRSLKFD DTAVYYCARGGYHHQMQRYYKATSVYSDYWGQGTLVTVSS [SEQ ID NO:121]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 122 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-172 scFv (also referred to as "ET150-22 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:89 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:90, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 23. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:89, as shown in Table 23. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:89, as shown in Table 23. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or

about 99% homologous to the amino acid sequence set forth in SEQ ID NO:90, as shown in Table 23. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:90, as shown in Table 23. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:89 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:90, as shown in Table 23. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:256 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 257 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 258 or conservative modifications thereof, as shown in Table 23. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 259 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 260 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 261 or conservative modifications thereof, as shown in Table 23. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 256 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 257 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 258 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 259 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 260 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 261 or conservative modifications thereof, as shown in Table 23. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 256, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 257, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 258, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 259, a V_L CDR2 comprising amino acids having the sequence

set forth in SEQ ID NO: 260, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 261.

Table 23

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GYTFTSYY [SEQ ID NO: 256]	INPSGGSS [SEQ ID NO: 257]	ARAGMGMDT [SEQ ID NO: 258]
V_L	SSDVGGYNY [SEQ ID NO: 259]	EVS [SEQ ID NO: 260]	SSYAGSNTLV [SEQ ID NO: 261]
Full V_H	QMQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPG QGLEWMGIINPSGGSSSYAQKFQGRVTMTRDTSTSTVYMELSSL RSEDTAVYYCARAGMGMDTWGQGTLVTVSS [SEQ ID NO:89]		
DNA	Cagatgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtttcctgca aggcatctggatacaccttcaccagctactatatgcactgggtgcgacaggcccctggacaagggcttg agtggatgggaataatcaaccctagtggtggtagctcaagctacgcacagaagttccagggcagagtc accatgaccagggacacgtccacgagcacagtctacatggagctgagcagcctgagatctgaggaca cggccgtgtattactgtgcgcgcgctggtatgggtatggatacttggggtcaaggtactctggtgaccgt ctcctca [SEQ ID NO:91]		
Full V_L	QSALTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGK APKLMIYEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYY CSSYAGSNTLVFGGGTKLTVLG [SEQ ID NO:90]		
DNA	Cagtctgccctgactcagcctccctccgcgtccgggtctcctggacagtcagtcaccatctcctgcact ggaaccagcagtgacgttggtggttataactatgtctcctggtaccaacagcacccaggcaaagccccc aaactcatgatttatgaggtcagtaagcggccctcaggggtccctgatcgcttctctggctccaagtctgg caacacggcctccctgaccgtctctgggctccaggctgaggatgaggctgattattactgcagctcatat gcaggcagcaacaccttggtgttcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:92]		
scFv	QSALTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGK APKLMIYEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYY CSSYAGSNTLVFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMA QMQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPG QGLEWMGIINPSGGSSSYAQKFQGRVTMTRDTSTSTVYMELSSL RSEDTAVYYCARAGMGMDTWGQGTLVTVSS [SEQ ID NO:122]		

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 123 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-173 scFv (also referred to as "ET150-23 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:93 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:94, optionally with (iii) a

linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 24. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:93, as shown in Table 24. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:93, as shown in Table 24. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:94, as shown in Table 24. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:94, as shown in Table 24. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:93 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:94, as shown in Table 24. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:262 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 263 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 264 or conservative modifications thereof, as shown in Table 24. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 265 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 266 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ

ID NO: 267 or conservative modifications thereof, as shown in Table 24. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 262 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 263 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 264 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 265 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 266 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 267 or conservative modifications thereof, as shown in Table 24. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 262, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 263, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 264, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 265 f, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 266, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 267.

Table 24

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GYTFTSYY [SEQ ID NO: 262]	INPSGGST [SEQ ID NO: 263]	ARDVISGFDS [SEQ ID NO: 264]
V_L	SSDVGGYNY [SEQ ID NO: 265]	GVS [SEQ ID NO: 266]	SSYAGVNNLM [SEQ ID NO: 267]
Full V_H	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQ GLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRS EDTAVYYCARDVISGFDSWGQGTLVTVSS [SEQ ID NO:93]		
DNA	Caggtgcagctggtgcaatctggggctgaggtgaagaagcctggggcctcagtgaaggtttcctgcaa ggcatctggatacaccttcaccagctactatatgcactgggtgcgacaggcccctggacaagggcttga gtggatgggaataatcaaccctagtggtggtagcacaagctacgcacagaagttccagggcagagtcac catgaccagggacacgtccacgagcacagtctacatggagctgagcagcctgagatctgaggacactg ccgtgtattactgtgcgcgcgacgttatctctggtttcgattcttggggtcaaggtactctggtgaccgtctc ctca [SEQ ID NO:95]		
Full V_L	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQSPGKAP RLMIYGVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCS SYAGVNNLMFGGGTKLTVLG [SEQ ID NO:94]		
DNA	Cagtctgccctgactcagcctgcctccgtgtctgggtctcctggacagtcgatcaccatctcctgcactgg		

	aaccagcagtgacgttggtggttataactatgtctcctggtaccaacaatccccaggcaaagcccccaga ctcatgatttatggggtcagtaagcggccctctggggtccctgatcgcttctctggctccaagtctggcaac acggcctccctgaccgtctctgggctccaggctgaagatgaggctgattattactgcagctcatatgcagg cgtcaacaatttaatgttcggcggagggaccaagctgaccgtcctaggt [SEQ ID NO:96]
scFv	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQSPGKAP RLMIYGVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCS SYAGVNNLMFGGGTKLTVLGSRGGGGSGGGGSGGGGSLEMAQV QLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGL EWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSED TAVYYCARDVISGFDSWGQGTLVTVSS [SEQ ID NO:123]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 301 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-024 scFv (also referred to as "ET150-174 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:302 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:303, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 25. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:302, as shown in Table 25. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:302, as shown in Table 25. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or

about 99% homologous to the amino acid sequence set forth in SEQ ID NO:303, as shown in Table 25. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:303, as shown in Table 25. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:302 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:303, as shown in Table 25. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:304 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:305 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:306 or conservative modifications thereof, as shown in Table 25. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:307 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:308 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:309 or conservative modifications thereof, as shown in Table 25. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 304 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 305 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 306 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 307 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 308 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 309 or conservative modifications thereof, as shown in Table 25. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 304, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 305, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 306, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 307, a V_L CDR2 comprising amino acids having the sequence

set forth in SEQ ID NO: 308, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 309.

Table 25

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFTFGDYG [SEQ ID NO: 304]	INWNGGST [SEQ ID NO: 305]	ARSKQGY [SEQ ID NO: 306]
V_L	SRDAGGYNY [SEQ ID NO: 307]	EVT [SEQ ID NO: 308]	SSYGGSNNFRV [SEQ ID NO: 309]
Full V_H	EVQLVESGGGVVRPGGSLRLSCAASGFTFGDYGMSWVRQAPGK GLEWVSGINWNGGSTGYADSVKGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCARSKQDYWGQGTLVTVSS [SEQ ID NO:302]		
DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGCCT GGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCT TTGGTGATTATGGCATGAGCTGGGTCCGCCAAGCTCCAGGGAA GGGGCTGGAGTGGGTCTCTGGTATTAATTGGAATGGTGGTAGC ACAGGTTATGCAGACTCTGTGAAGGGCCGATTCACCATCTCCA GAGACAACGCCAAGAACTCCCTGTATCTGCAAATGAACAGTC TGAGAGCCGAGGACACGGCCGTATATTACTGTGCGCGCTCTAA ACAGGATTACTGGGGTCAAGGTACTCTGGTGACCGTCTCCTCA [SEQ ID NO:310]		
Full V_L	MKKTAIAIAVALAGFATVAQAAELQSALTQPPSASGSPGQSVTIS CTGTSRDAGGYNYFSWYQQHPGKAPKLLIYEVTKRPSGVPDRFS GSKSGKTASLTVSGLQADDEAVYYCSSYGGSNNFRVFGGGTKLT VLG [SEQ ID NO:303]		
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGTCTGCCCTGA CTCAGCCTCCCTCCGCGTCCGGGTCTCCTGGACAGTCAGTCAC CATCTCCTGCACTGGAACCAGCAGGGACGCTGGTGGTTATAAT TATTTCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAAC TCCTGATTTATGAGGTCACTAAGCGGCCCTCAGGGGTCCCTGA TCGCTTCTCTGGCTCCAAGTCTGGCAAGACGGCCTCCCTGACC GTCTCTGGGCTCCAGGCTGACGATGAGGCTGTATATTACTGCA GCTCATATGGAGGCAGCAACAACTTTCGGGTGTTCGGCGGAG GGACCAAGCTGACCGTCCTAGGT [SEQ ID NO:311]		
scFv	MKKTAIAIAVALAGFATVAQAAELQSALTQPPSASGSPGQSVTIS CTGTSRDAGGYNYFSWYQQHPGKAPKLLIYEVTKRPSGVPDRFS GSKSGKTASLTVSGLQADDEAVYYCSSYGGSNNFRVFGGGTKLT VLGSRGGGGSGGGGSGGGGSLEMAEVQLVESGGGVVRPGGSLR LSCAASGFTFGDYGMSWVRQAPGKGLEWVSGINWNGGSTGYA DSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARSKQDYW GQGTLVTVSS [SEQ ID NO:301]		
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGTCTGCCCTGA CTCAGCCTCCCTCCGCGTCCGGGTCTCCTGGACAGTCAGTCAC CATCTCCTGCACTGGAACCAGCAGGGACGCTGGTGGTTATAAT TATTTCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAAAC		

	TCCTGATTTATGAGGTCACTAAGCGGCCCTCAGGGGTCCCTGA TCGCTTCTCTGGCTCCAAGTCTGGCAAGACGGCCTCCCTGACC GTCTCTGGGCTCCAGGCTGACGATGAGGCTGTATATTACTGCA GCTCATATGGAGGCAGCAACAACTTTCGGGTGTTCGGCGGAG GGACCAAGCTGACCGTCCTAGGTTCTAGAGGTGGTGGTGGTA GCGGCGGCGGCGGCTCTGGTGGTGGTGGATCCCTCGAGATGG CCGAGGTGCAGCTGGTGGAGTCTGGGGGAGGTGTGGTACGGC CTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCAC CTTTGGTGATTATGGCATGAGCTGGGTCCGCCAAGCTCCAGGG AAGGGGCTGGAGTGGGTCTCTGGTATTAATTGGAATGGTGGTA GCACAGGTTATGCAGACTCTGTGAAGGGCCGATTCACCATCTC CAGAGACAACGCCAAGAACTCCCTGTATCTGCAAATGAACAG TCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGCGCTCT AAACAGGATTACTGGGGTCAAGGTACTCTGGTGACCGTCTCCT CA [SEQ ID NO:312]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 313 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-026 scFv (also referred to as "ET150-176 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:314 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:315, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 26. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:314 as shown in Table 26. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:314, as shown in Table 26. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid

sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:315, as shown in Table 26. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:315, as shown in Table 26. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:314 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:315 as shown in Table 26. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:316 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:317 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:318 or conservative modifications thereof, as shown in Table 26. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:319 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:320 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:321 or conservative modifications thereof, as shown in Table 26. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 316 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 317 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 318 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 319 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 320 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 321 or conservative modifications thereof, as shown in Table 26. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 316, a V_H CDR2 comprising amino acids having the sequence set forth in

SEQ ID NO: 317, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 318, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 319, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 320, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 321.

Table 26

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFTFSNYA [SEQ ID NO: 316]	ITNSGRST [SEQ ID NO: 317]	ARVTHRRYGSTFDS [SEQ ID NO: 318]
V_L	SSNIGSNT [SEQ ID NO: 319]	SNN [SEQ ID NO: 320]	AAWDDSVNGYV [SEQ ID NO: 321]
Full V_H	QLQLQESGGGSVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGK GLEWVSAITNSGRSTYYADSVKGRFTISRDNSKNTLSLQMSSLRA EDTAVYYCARVTHRRYGSTFDSRGQGTLVTVSS [SEQ ID NO:314]		
DNA	CAGCTGCAGCTGCAGGAGTCGGGGGGAGGCTCGGTACAGCCG GGGGGGTCTCTGAGACTGTCCTGTGCAGCCTCTGGATTCACCT TTAGCAACTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGA AGGGGCTGGAGTGGGTCTCAGCTATCACTAATAGTGGTCGTAG TACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCC AGAGACAATTCCAAGAACACGCTGTCTTTGCAAATGAGCAGC CTGAGAGCCGAAGACACGGCCGTGTATTACTGTGCGCGCGTTA CTCATCGTCGTTACGGTTCTACTTTCGATTCTCGGGGTCAAGGT ACTCTGGTGACCGTCTCCTCA ACTAGTGGCCAGGCCGGCCAGC [SEQ ID NO:322]		
Full V_L	MKKTAIAIAVALAGFATVAQAAELSYELTQPPSASGTPGQRVSIS CSGSSSNIGSNTVNWYQQFPGTAPKLLIHSNNQRPSGVPDRFSGS KSGTSASLAISGPQSEDEADYYCAAWDDSVNGYVFGTGTKVTVL G [SEQ ID NO:315]		
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCTCCTATGAGCTGA CTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCA GCATCTCTTGTTCTGGAAGCAGCTCCAACATCGGGAGTAATAC TGTAAACTGGTACCAACAGTTCCCCGGAACGGCCCCCAAACTC CTCATCCATAGTAATAATCAGCGGCCCTCAGGGGTCCCTGACC GATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCAT CAGTGGGCCCCAGTCTGAGGATGAGGCTGATTATTACTGTGCA GCTTGGGATGACAGTGTGAATGGTTATGTCTTCGGAACTGGGA CCAAGGTCACCGTCCTAGGT [SEQ ID NO:323]		
scFv	MKKTAIAIAVALAGFATVAQAAELSYELTQPPSASGTPGQRVSIS CSGSSSNIGSNTVNWYQQFPGTAPKLLIHSNNQRPSGVPDRFSGS KSGTSASLAISGPQSEDEADYYCAAWDDSVNGYVFGTGTKVTVL		

	GSRGGGGSGGGGSGGGGSLEMAQLQLQESGGGSVQPGGSLRLS CAASGFTFSNYAMSWVRQAPGKGLEWVSAITNSGRSTYYADSV KGRFTISRDNSKNTLSLQMSSLRAEDTAVYYCARVTHRRYGSTF DSRGQGTLVTVSS [SEQ ID NO:313]
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCTCCTATGAGCTGA CTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCA GCATCTCTTGTTCTGGAAGCAGCTCCAACATCGGGAGTAATAC TGTAAACTGGTACCAACAGTTCCCCGGAACGGCCCCCAAACTC CTCATCCATAGTAATAATCAGCGGCCCTCAGGGGTCCCTGACC GATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCAT CAGTGGGCCCCAGTCTGAGGATGAGGCTGATTATTACTGTGCA GCTTGGGATGACAGTGTGAATGGTTATGTCTTCGGAACTGGGA CCAAGGTCACCGTCCTAGGTTCTAGAGGTGGTGGTGGTAGCGG CGGCGGCGGCTCTGGTGGTGGTGGATCCCTCGAGATGGCCCA GCTGCAGCTGCAGGAGTCGGGGGGAGGCTCGGTACAGCCGGG GGGGTCTCTGAGACTGTCCTGTGCAGCCTCTGGATTCACCTTT AGCAACTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGAAG GGGCTGGAGTGGGTCTCAGCTATCACTAATAGTGGTCGTAGTA CATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAG AGACAATTCCAAGAACACGCTGTCTTTGCAAATGAGCAGCCTG AGAGCCGAAGACACGGCCGTGTATTACTGTGCGCGCGTTACTC ATCGTCGTTACGGTTCTACTTTCGATTCTCGGGGTCAAGGTACT CTGGTGACCGTCTCCTCA [SEQ ID NO:324]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 325 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-028 scFv (also referred to as "ET150-178 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:326 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:327, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 27. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%,

about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:325 as shown in Table 27. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:325, as shown in Table 27. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:326, as shown in Table 27. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:326, as shown in Table 27. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:325 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:327 as shown in Table 27. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:328 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:329 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:330 or conservative modifications thereof, as shown in Table 27. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:331 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:332 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:333 or conservative modifications thereof, as shown in Table 27. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 328 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 329 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 330 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 331 or conservative modifications thereof, a V_L

CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 332 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 333 or conservative modifications thereof, as shown in Table 27. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 328, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 329, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 330, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 331, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 332, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 333.

Table 27

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GGTFRSYA [SEQ ID NO: 328]	IIPMLDIT [SEQ ID NO: 329]	ARTYSRSPFHMEDF [SEQ ID NO: 330]
V_L	SSNIGGNT [SEQ ID NO: 331]	RNN [SEQ ID NO: 332]	AAWDASRQGV [SEQ ID NO: 333]
Full V_H	QVQLVQSGAEVKKPGSSVKVSCKASGGTFRSYAITWVRQAPGQGLEWMGRIIPMLDITNYAQKFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARTYSRSPFHMEDFWGQGTLVTVSS [SEQ ID NO:326]		
DNA	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCCGCAGCTATGCTATCACCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAAGGATCATCCCTATGCTTGATATAACAAACTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGCGCACTTACTCTCGTTCTCCGTTCCATATGGAAGATTTCTGGGGTCAAGGTACTCTGGTGACCGTCTCCTCA [SEQ ID NO:334]		
Full V_L	MKKTAIAIAVALAGFATVAQAAELQPVLTQPPSASGTPGQRVTISCSGSSSNIGGNTVSWYQQVPGTAPRLLIFRNNQRPPGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDASRQGVFGGGTKLTVLG [SEQ ID NO:327]		
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGTTTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGCCTGTGCTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCACCATCTCTTGTTCTGGAAGCAGCTCCAATATCGGAGGTAACACTGTCAGCTGGTACCAGCAGGTCCCAGGAACGGCCCCCAGACTCCTCATTTTTAGGAATAATCAACGGCCCCCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCAGTGGGCTCCGGTCTGAGGATGAGGCTGATTATTACTGTGC		

	AGCATGGGACGCCAGTCGACAAGGGGTGTTCGGCGGAGGGAC CAAGCTGACCGTCCTAGGT [SEQ ID NO:335]
scFv	MKKTAIAIAVALAGFATVAQAAELQPVLTQPPSASGTPGQRVTIS CSGSSSNIGGNTVSWYQQVPGTAPRLLIFRNNQRPPGVPDRFSGS KSGTSASLAISGLRSEDEADYYCAAWDASRQGVFGGGTKLTVLG SRGGGGSGGGGSGGGGSLEMAQVQLVQSGAEVKKPGSSVKVSC KASGGTFRSYAITWVRQAPGQGLEWMGRIIPMLDITNYAQKFQG RVTITADKSTSTAYMELSSLRSEDTAVYYCARTYSRSPFHMEDF WGQGTLVTVSS [SEQ ID NO:325]
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGCCTGTGCTGA CTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCA CCATCTCTTGTTCTGGAAGCAGCTCCAATATCGGAGGTAACAC TGTCAGCTGGTACCAGCAGGTCCCAGGAACGGCCCCCAGACT CCTCATTTTTAGGAATAATCAACGGCCCCCAGGGGTCCCTGAC CGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCA TCAGTGGGCTCCGGTCTGAGGATGAGGCTGATTATTACTGTGC AGCATGGGACGCCAGTCGACAAGGGGTGTTCGGCGGAGGGAC CAAGCTGACCGTCCTAGGTTCTAGAGGTGGTGGTGGTAGCGGC GGCGGCGGCTCTGGTGGTGGTGGATCCCTCGAGATGGCCCAG GTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGG TCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCC GCAGCTATGCTATCACCTGGGTGCGACAGGCCCCTGGACAAG GGCTTGAGTGGATGGGAAGGATCATCCCTATGCTTGATATAAC AAACTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGC GGACAAATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCT GAGATCTGAGGACACGGCCGTGTATTACTGTGCGCGCACTTAC TCTCGTTCTCCGTTCCATATGGAAGATTTCTGGGGTCAAGGTA CTCTGGTGACCGTCTCCTCA [SEQ ID NO:336]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 337 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-029 scFv (also referred to as "ET150-179 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:338 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:339, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 28. In

certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:338 as shown in Table 28. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:338, as shown in Table 28. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:339, as shown in Table 28. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:339, as shown in Table 28. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:338 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:339 as shown in Table 28. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:340 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:341 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:342 or conservative modifications thereof, as shown in Table 28. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:343 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:344 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:345 or conservative modifications thereof, as shown in Table 28. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 340 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 341 or conservative modifications thereof, a V_H

CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 342 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 343 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 344 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 345 or conservative modifications thereof, as shown in Table 28. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 340, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 341, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 342, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 343, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 344, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 345.

Table 28

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFTFSSYA[SEQ ID NO: 340]	ISGSGGST [SEQ ID NO: 341]	ARKYQDV [SEQ ID NO: 342]
V_L	SSNIGSNT[SEQ ID NO: 343]	RNN [SEQ ID NO: 344]	AAWDDSLSGRV [SEQ ID NO: 345]
Full V_H	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKG LEWVSAISGSGGSTYYADSVKGRFTISRDNAKNTLYLQMNSLRA EDTAVYYCARKYQDVWGQGTLVTVSS [SEQ ID NO:338]		
DNA	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCT GGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCT TTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGA AGGGGCTGGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTA GCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTC CAGAGACAATGCCAAGAACACGCTGTATCTGCAAATGAACAG CCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGCGCAA ATACCAGGATGTTTGGGGTCAAGGTACTCTGGTGACCGTCTCC TCA [SEQ ID NO:346]		
Full V_L	MKKTAIAIAVALAGFATVAQAAELQSVLTQPPSASGTPGQRVTIS CSGSSSNIGSNTVNWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGS KSGTSASLAISGLRSEDEADYYCAAWDDSLSGRVFGGGTKLTVL G [SEQ ID NO:339]		
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGTCTGTGCTGA CGCAGCCGCCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCA CCATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATAC		

	TGTAAACTGGTACCAGCAGCTCCCAGGAACGGCCCCCAAACT CCTCATCTATAGGAATAATCAGCGGCCCTCAGGGGTCCCTGAC CGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCA TCAGTGGGCTCCGGTCCGAGGATGAGGCTGATTATTACTGTGC AGCATGGGATGACAGCCTGAGTGGTAGGGTGTTCGGCGGAGG GACCAAGCTGACCGTCCTAGGT [SEQ ID NO:347]
scFv	MKKTAIAIAVALAGFATVAQAAELQSVLTQPPSASGTPGQRVTIS CSGSSSNIGSNTVNWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGS KSGTSASLAISGLRSEDEADYYCAAWDDSLSGRVFGGGTKLTVL GSRGGGGSGGGGSGGGGSLEMAEVQLVESGGGLVQPGGSLRLS CAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVK GRFTISRDNAKNTLYLQMNSLRAEDTAVYYCARKYQDVWGQGT LVTVSS [SEQ ID NO:337]
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGTCTGTGCTGA CGCAGCCGCCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCA CCATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATAC TGTAAACTGGTACCAGCAGCTCCCAGGAACGGCCCCCAAACT CCTCATCTATAGGAATAATCAGCGGCCCTCAGGGGTCCCTGAC CGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCA TCAGTGGGCTCCGGTCCGAGGATGAGGCTGATTATTACTGTGC AGCATGGGATGACAGCCTGAGTGGTAGGGTGTTCGGCGGAGG GACCAAGCTGACCGTCCTAGGTTCTAGAGGTGGTGGTGGTAGC GGCGGCGGCGGCTCTGGTGGTGGTGGATCCCTCGAGATGGCC GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCT GGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCT TTAGCAGCTATGCCATGAGCTGGGTCCGCCAGGCTCCAGGGA AGGGGCTGGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTA GCACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTC CAGAGACAATGCCAAGAACACGCTGTATCTGCAAATGAACAG CCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGCGCAA ATACCAGGATGTTTGGGGTCAAGGTACTCTGGTGACCGTCTCC TCA [SEQ ID NO:348]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 349 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-030 scFv (also referred to as "ET150-180 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:350 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:351, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker

comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 29. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:350 as shown in Table 29. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:350, as shown in Table 29. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:351, as shown in Table 29. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:351, as shown in Table 29. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:350 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:351 as shown in Table 29. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:352 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:353 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:354 or conservative modifications thereof, as shown in Table 29. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:355 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:356 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:357 or conservative modifications thereof, as shown in Table 29. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1

comprising amino acids having the sequence set forth in SEQ ID NO: 352 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 353 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 354 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 355 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 356 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 357 or conservative modifications thereof, as shown in Table 29. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 352, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 353, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 354, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 355, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 356, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 357.

Table 29

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GFSFSGTA [SEQ ID NO: 352]	ISSTGRST [SEQ ID NO: 353]	ARPVSSMTLSIQSDG [SEQ ID NO: 354]
V_L	SSNIGAGYD [SEQ ID NO: 355]	GNS [SEQ ID NO: 356]	QSYDSSLRGYV [SEQ ID NO: 357]
Full V_H	QVQLVQSGGGVVQPGRSLRLSCAASGFSFSGTAMHWVRQAPG KGLEWVSTISSTGRSTYYRDSVKGRFTISRDNSKNTLYLQMNSL RGEDTAVYYCARPVSSMTLSIQSDGWGQGTLVTVSS [SEQ ID NO:350]		
DNA	CAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTGGTCCAGCCT GGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCAGC TTTAGTGGCACTGCCATGCACTGGGTCCGCCAGGCTCCAGGG AAGGGGCTGGAATGGGTCTCGACTATTAGTAGTACTGGGCGT AGCACATACTACAGAGACTCCGTGAAGGGCCGGTTCACCATC TCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAAC AGCCTGAGAGGCGAGGACACGGCCGTATATTACTGTGCGCGC CCGGTTTCTTCTATGACTCTGTCTATCCAGTCTGATGGTTGGG GTCAAGGTACTCTGGTGACCGTCTCCTCA [SEQ ID NO:358]		
Full V_L	MKKTAIAIAVALAGFATVAQAAELQSVLTQPPSVSGAPGQRVTI SCTGSSSNIGAGYDVHWYQQLPGRAPKLLIYGNSNRPSGVPDRF SGSKSGTSASLAITGLQAEDEADYYCQSYDSSLRGYVFGTGTKV		

	TVLG [SEQ ID NO:351]
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGTCTGTGTTG ACGCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAGGGTC ACCATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCAGGT TATGATGTACACTGGTACCAGCAGCTTCCAGGAAGAGCCCCC AAACTCCTCATCTATGGTAACAGCAATCGGCCCTCAGGGGTC CCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCC TGGCCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATT ACTGCCAGTCCTATGACAGCAGCCTGAGAGGTTATGTCTTCG GAACTGGGACCAAGGTCACCGTCCTAGGT [SEQ ID NO:359]
scFv	MKKTAIAIAVALAGFATVAQAAELQSVLTQPPSVSGAPGQRVTI SCTGSSSNIGAGYDVHWYQQLPGRAPKLLIYGNSNRPSGVPDRF SGSKSGTSASLAITGLQAEDEADYYCQSYDSSLRGYVFGTGTKV TVLGSRGGGGSGGGGSGGGGSLEMAQVQLVQSGGGVVQPGRS LRLSCAASGFSFSGTAMHWVRQAPGKGLEWVSTISSTGRSTYYR DSVKGRFTISRDNSKNTLYLQMNSLRGEDTAVYYCARPVSSMT LSIQSDGWGQGTLVTVSS [SEQ ID NO:349]
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGTCTGTGTTG ACGCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAGGGTC ACCATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCAGGT TATGATGTACACTGGTACCAGCAGCTTCCAGGAAGAGCCCCC AAACTCCTCATCTATGGTAACAGCAATCGGCCCTCAGGGGTC CCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCC TGGCCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATT ACTGCCAGTCCTATGACAGCAGCCTGAGAGGTTATGTCTTCG GAACTGGGACCAAGGTCACCGTCCTAGGTTCTAGAGGTGGTG GTGGTAGCGGCGGCGGCGGCTCTGGTGGTGGTGGATCCCTCG AGATGGCCCAGGTGCAGCTGGTGCAGTCTGGGGGAGGCGTG GTCCAGCCTGGGAGGTCCCTGAGACTCTCCTGTGCAGCCTCT GGATTCAGCTTTAGTGGCACTGCCATGCACTGGGTCCGCCAG GCTCCAGGGAAGGGGCTGGAATGGGTCTCGACTATTAGTAGT ACTGGGCGTAGCACATACTACAGAGACTCCGTGAAGGGCCGG TTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTG CAAATGAACAGCCTGAGAGGCGAGGACACGGCCGTATATTA CTGTGCGCGCCCGGTTTCTTCTATGACTCTGTCTATCCAGTCT GATGGTTGGGGTCAAGGTACTCTGGTGACCGTCTCCTCA [SEQ ID NO:360]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 361 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-031 scFv (also referred to as "ET150-181 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the

sequence set forth in SEQ ID NO:362 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:363, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 30. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:362 as shown in Table 30. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:362, as shown in Table 30. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:363, as shown in Table 30. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:363, as shown in Table 30. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:362 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:363 as shown in Table 30. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:364 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:365 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:366 or conservative modifications thereof, as shown in Table 30. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:367 or conservative modifications thereof, a V_L CDR2 comprising amino

acids having the sequence set forth in SEQ ID NO:368 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:369 or conservative modifications thereof, as shown in Table 30. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 364 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 365 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 366 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 367 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 368 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 369 or conservative modifications thereof, as shown in Table 30. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 364, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 365, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 366, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 367, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 368, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 369.

Table 30

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GYTFTSYY [SEQ ID NO: 364]	INPSGGST [SEQ ID NO: 365]	ARGQKYHSQYSRG GTGGGMTQDM [SEQ ID NO: 366]
V_L	SSNIGNNY [SEQ ID NO: 367]	DNN [SEQ ID NO: 368]	GTWDSSLRNWV [SEQ ID NO: 369]
Full V_H	QMQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPG QGLEWMGIINPSGGSTSYAQKFQGRVTMTRDTSTSTVYMELSSL RSEDTAVYYCARGQKYHSQYSRGGTGGGMTQDMWGQGTLVTV SS [SEQ ID NO:362]		
DNA	CAGATGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCT GGGGCCTCAGTGAAGGTTTCCTGCAAGGCATCTGGATACACCT TCACCAGCTACTATATGCACTGGGTGCGACAGGCCCCTGGACA AGGGCTTGAGTGGATGGGAATAATCAACCCTAGTGGTGGTAG CACAAGCTACGCACAAAAGTTCCAGGGCAGAGTCACCATGAC		

	CAGGGACACGTCCACGAGCACAGTCTACATGGAGCTGAGCAG CCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGCGCGGT CAGAAATACCATTCTCAGTACTCTCGTGGTGGTACTGGTGGTG GTATGACTCAGGATATGTGGGGTCAAGGTACTCTGGTGACCGT CTCCTCA [SEQ ID NO:370]
Full V_L	MKKTAIAIAVALAGFATVAQAAELQSVVTQPPSVSAAPGQRVTIS CSGGSSNIGNNYVSWFQQLPRTAPKLLIYDNNKRPSGIPDRFSGSK SGTSAALDITVLQTGDEADYYCGTWDSSLRNWVFGGGTKLTVL G [SEQ ID NO:363]
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGTCTGTCGTGA CGCAGCCGCCCTCTGTGTCTGCGGCCCCAGGACAGAGGGTCAC CATCTCCTGCTCTGGAGGTAGTTCCAACATTGGGAATAATTAT GTTTCCTGGTTCCAACAACTCCCACGAACAGCCCCCAAACTCC TCATTTATGACAATAATAAGCGACCCTCAGGGATTCCTGACCG ATTCTCTGGCTCCAAGTCTGGCACGTCAGCCGCCCTGGACATC ACCGTTCTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAA CTTGGGATAGCAGCCTGAGAAATTGGGTGTTCGGCGGAGGGA CCAAGCTGACCGTCCTAGGT [SEQ ID NO:371]
scFv	MKKTAIAIAVALAGFATVAQAAELQSVVTQPPSVSAAPGQRVTIS CSGGSSNIGNNYVSWFQQLPRTAPKLLIYDNNKRPSGIPDRFSGSK SGTSAALDITVLQTGDEADYYCGTWDSSLRNWVFGGGTKLTVL GSRGGGGSGGGGSGGGGSLEMAQMQLVQSGAEVKKPGASVKV SCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTSYAQKF QGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGQKYHSQYS RGGTGGGMTQDMWGQGTLVTVSS [SEQ ID NO:361]
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGTCTGTCGTGA CGCAGCCGCCCTCTGTGTCTGCGGCCCCAGGACAGAGGGTCAC CATCTCCTGCTCTGGAGGTAGTTCCAACATTGGGAATAATTAT GTTTCCTGGTTCCAACAACTCCCACGAACAGCCCCCAAACTCC TCATTTATGACAATAATAAGCGACCCTCAGGGATTCCTGACCG ATTCTCTGGCTCCAAGTCTGGCACGTCAGCCGCCCTGGACATC ACCGTTCTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAA CTTGGGATAGCAGCCTGAGAAATTGGGTGTTCGGCGGAGGGA CCAAGCTGACCGTCCTAGGTTCTAGAGGTGGTGGTGGTAGCGG CGGCGGCGGCTCTGGTGGTGGTGGATCCCTCGAGATGGCCCA GATGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GGCCTCAGTGAAGGTTTCCTGCAAGGCATCTGGATACACCTTC ACCAGCTACTATATGCACTGGGTGCGACAGGCCCCTGGACAA GGGCTTGAGTGGATGGGAATAATCAACCCTAGTGGTGGTAGC ACAAGCTACGCACAAAAGTTCCAGGGCAGAGTCACCATGACC AGGGACACGTCCACGAGCACAGTCTACATGGAGCTGAGCAGC CTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGCGCGGTC AGAAATACCATTCTCAGTACTCTCGTGGTGGTACTGGTGGTGG TATGACTCAGGATATGTGGGGTCAAGGTACTCTGGTGACCGTC TCCTCA [SEQ ID NO:372]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 373 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-032 scFv (also referred to as "ET150-182 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:374 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:375, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 31. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:374 as shown in Table 31. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:374, as shown in Table 31. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:375, as shown in Table 31. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:375, as shown in Table 31. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:374 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:375 as shown in Table 31. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the

sequence set forth in SEQ ID NO:376 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:377 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:378 or conservative modifications thereof, as shown in Table 31. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:379 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:380 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:381 or conservative modifications thereof, as shown in Table 31. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 376 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 377 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 378 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 379 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 380 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 381 or conservative modifications thereof, as shown in Table 31. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 376, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 377, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 378, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 379, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 380, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 381.

Table 31

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID NO:97		
CDRs	1	2	3
V_H	GYTFSRYY [SEQ ID NO: 376]	MNPNSGNT [SEQ ID NO: 377]	ARGRYHVIDY [SEQ ID NO: 378]
V_L	SSDVGGYNH [SEQ	EVT [SEQ ID NO:	SSYAGSAHWV

	ID NO: 379]	380]	[SEQ ID NO: 381]
Full V_H	EVQLVQSGAEVKKPGASVKVSCKASGYTFSRYYIHWVRQAPGQ GLEWMGWMNPNSGNTGYAQKFQGRVTMTRNTSISTAYMELSSL RSEDTAVYYCARGRYHVIDYWGQGTLVTVSS [SEQ ID NO:374]		
DNA	GAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCT GGGGCCTCAGTGAAGGTTTCCTGCAAGGCATCTGGATACACCT TCAGCAGGTACTATATACACTGGGTGCGACAGGCCCCTGGAC AAGGGCTTGAGTGGATGGGATGGATGAACCCTAACAGTGGTA ACACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCATGA CCAGGAACACCTCCATAAGCACAGCCTACATGGAGCTGAGCA GCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGCGCGG TCGTTACCATGTTATCGATTACTGGGGTCAAGGTACTCTGGTG ACCGTCTCCTCA [SEQ ID NO:382]		
Full V_L	MKKTAIAIAVALAGFATVAQAAELQSVLTQPPSASGSPGQSLTIS CTGTSSDVGGYNHVSWYQQYPGKAPKLMIYEVTKRPSGVPDRFS GSKSGNTASLTVSGLQAEDEADYYCSSYAGSAHWVFGGGTKLT VLG [SEQ ID NO:375]		
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGTCTGTGTTGA CTCAGCCACCCTCCGCGTCCGGGTCTCCTGGACAGTCACTCAC CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAAC CATGTCTCCTGGTACCAACAGTACCCAGGCAAAGCCCCCAAAC TCATGATTTATGAGGTCACTAAGCGGCCCTCAGGGGTCCCTGA TCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACC GTCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCA GCTCATATGCAGGCAGCGCCCATTGGGTGTTCGGCGGAGGGA CCAAGCTGACCGTCCTAGGT [SEQ ID NO:383]		
scFv	MKKTAIAIAVALAGFATVAQAAELQSVLTQPPSASGSPGQSLTIS CTGTSSDVGGYNHVSWYQQYPGKAPKLMIYEVTKRPSGVPDRFS GSKSGNTASLTVSGLQAEDEADYYCSSYAGSAHWVFGGGTKLT VLGSRGGGGSGGGGSGGGGSLEMAEVQLVQSGAEVKKPGASVK VSCKASGYTFSRYYIHWVRQAPGQGLEWMGWMNPNSGNTGYA QKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCARGRYHVID YWGQGTLVTVSS [SEQ ID NO:373]		
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGTCTGTGTTGA CTCAGCCACCCTCCGCGTCCGGGTCTCCTGGACAGTCACTCAC CATCTCCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAAC CATGTCTCCTGGTACCAACAGTACCCAGGCAAAGCCCCCAAAC TCATGATTTATGAGGTCACTAAGCGGCCCTCAGGGGTCCCTGA TCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACC GTCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCA GCTCATATGCAGGCAGCGCCCATTGGGTGTTCGGCGGAGGGA CCAAGCTGACCGTCCTAGGTTCTAGAGGTGGTGGTGGTAGCGG CGGCGGCGGCTCTGGTGGTGGTGGATCCCTCGAGATGGCCGA GGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGG GGCCTCAGTGAAGGTTTCCTGCAAGGCATCTGGATACACCTTC AGCAGGTACTATATACACTGGGTGCGACAGGCCCCTGGACAA GGGCTTGAGTGGATGGGATGGATGAACCCTAACAGTGGTAAC ACAGGCTATGCACAGAAGTTCCAGGGCAGAGTCACCATGACC		

	AGGAACACCTCCATAAGCACAGCCTACATGGAGCTGAGCAGC CTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGCGCGGTC GTTACCATGTTATCGATTACTGGGGTCAAGGTACTCTGGTGAC CGTCTCCTCA [SEQ ID NO:384]

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises the amino acid sequence of SEQ ID NO: 385 and specifically binds to a GPRC5D polypeptide (e.g., a GPRC5D polypeptide having the amino acid sequence SEQ ID NO:97, or fragments thereof), which scFv is designated as ET150-033 scFv (also referred to as "ET150-183 scFv").

In certain embodiments, the extracellular antigen-binding domain is a scFv, which comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:386 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:387, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 32. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:386 as shown in Table 32. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:386, as shown in Table 32. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:387, as shown in Table 32. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:387, as shown in Table 32. In certain embodiments, the extracellular antigen-

binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:386 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:387 as shown in Table 32. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:388 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:389 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:390 or conservative modifications thereof, as shown in Table 32. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:391 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO:392 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO:393 or conservative modifications thereof, as shown in Table 32. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 388 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 389 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 390 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 391 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 392 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 393 or conservative modifications thereof, as shown in Table 32. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 388, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 389, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 390, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 391, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 392, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 393.

Table 32

Antigen	A GPRC5D polypeptide having the amino acid sequence of SEQ ID

	NO:97		
CDRs	1	2	3
V_H	GYTFNTYY [SEQ ID NO: 388]	INPNNGGT [SEQ ID NO: 389]	ARSYDY [SEQ ID NO: 390]
V_L	SSNIGSNY [SEQ ID NO: 391]	RNN [SEQ ID NO: 392]	AAWDDSLSGRV [SEQ ID NO: 393]
Full V_H	QLQLVQSGAEVKKPGSSVKVSCKASGYTFNTYYLHWVRQAPGQ GLEWMGRINPNNGGTNYAQKFQGRVTMTRDTSINTAYMELSRL RSDDTAVYYCARSYDYWGQGTLVTVSS [SEQ ID NO:386]		
DNA	CAGCTGCAGCTGGTGCAATCTGGGGCTGAGGTGAAGAAGCCT GGGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCT TCAACACCTACTATCTGCACTGGGTACGACAGGCCCCTGGACA AGGGCTTGAGTGGATGGGACGGATCAACCCTAACAATGGTGG CACAAACTATGCACAGAAGTTTCAGGGCAGGGTCACCATGAC CAGGGACACGTCCATCAACACAGCCTACATGGAGCTGAGCAG GCTGAGATCTGACGACACGGCCGTGTATTACTGTGCGCGCTCT TACGATTACTGGGGTCAAGGTACTCTGGTGACCGTCTCCTCA [SEQ ID NO:394]		
Full V_L	MKKTAIAIAVALAGFATVAQAAELQAVLTQPPSASGTPGQRVTIS CSGSSSNIGSNYVYWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGS KSGTSASLAISGLRSEDEADYYCAAWDDSLSGRVFGTGTKVTVL G [SEQ ID NO:387]		
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGGCTGTGCTGA CTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCA CCATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATTA TGTATACTGGTACCAGCAGCTCCCAGGAACGGCCCCCAAACTC CTCATCTATAGGAATAATCAGCGGCCCTCAGGGGTCCCTGACC GATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCAT CAGTGGGCTCCGGTCCGAGGATGAGGCTGATTATTACTGTGCA GCATGGGATGACAGCCTGAGTGGTCGGGTCTTCGGAACTGGG ACCAAGGTCACCGTCCTAGGT [SEQ ID NO:395]		
scFv	MKKTAIAIAVALAGFATVAQAAELQAVLTQPPSASGTPGQRVTIS CSGSSSNIGSNYVYWYQQLPGTAPKLLIYRNNQRPSGVPDRFSGS KSGTSASLAISGLRSEDEADYYCAAWDDSLSGRVFGTGTKVTVL GSRGGGGSGGGGSGGGGSLEMAQLQLVQSGAEVKKPGSSVKVS CKASGYTFNTYYLHWVRQAPGQGLEWMGRINPNNGGTNYAQK FQGRVTMTRDTSINTAYMELSRLRSDDTAVYYCARSYDYWGQG TLVTVSS [SEQ ID NO:385]		
DNA	ATGAAAAAGACAGCTATCGCGATTGCAGTGGCACTGGCTGGT TTCGCTACCGTGGCCCAGGCGGCCGAGCTCCAGGCTGTGCTGA CTCAGCCACCCTCAGCGTCTGGGACCCCCGGGCAGAGGGTCA CCATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGTAATTA TGTATACTGGTACCAGCAGCTCCCAGGAACGGCCCCCAAACTC CTCATCTATAGGAATAATCAGCGGCCCTCAGGGGTCCCTGACC GATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCAT CAGTGGGCTCCGGTCCGAGGATGAGGCTGATTATTACTGTGCA GCATGGGATGACAGCCTGAGTGGTCGGGTCTTCGGAACTGGG ACCAAGGTCACCGTCCTAGGTTCTAGAGGTGGTGGTGGTAGCG GCGGCGGCGGCTCTGGTGGTGGTGGATCCCTCGAGATGGCCC		

	AGCTGCAGCTGGTGCAATCTGGGGCTGAGGTGAAGAAGCCTG GGTCCTCGGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTT CAACACCTACTATCTGCACTGGGTACGACAGGCCCCTGGACAA GGGCTTGAGTGGATGGGACGGATCAACCCTAACAATGGTGGC ACAAACTATGCACAGAAGTTTCAGGGCAGGGTCACCATGACC AGGGACACGTCCATCAACACAGCCTACATGGAGCTGAGCAGG CTGAGATCTGACGACACGGCCGTGTATTACTGTGCGCGCTCTT ACGATTACTGGGGTCAAGGTACTCTGGTGACCGTCTCCTCA [SEQ ID NO:396]

An extracellular antigen-binding domain (*e.g.*, scFv) comprising V_H and/or V_L regions having high (*i.e.*, 80% or greater) homology to the V_H and V_L regions of the sequences set forth above, can be obtained by mutagenesis (*e.g.*, site-directed or PCR-mediated mutagenesis), followed by testing of the encoded altered scFv for retained function (*i.e.*, the binding affinity) using the binding assays described herein. In certain embodiments, a V_H sequence having at least 9about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homology contains substitutions (*e.g.*, conservative substitutions to generate conservative modifications of a sequence), insertions or deletions relative to the reference sequence, but an extracellular antigen-binding domain (*e.g.*, scFv) comprising that sequence retains the ability to bind to a GPRC5D polypeptide. In certain embodiments, a V_L sequence having at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous contains substitutions (*e.g.*, conservative substitutions), insertions or deletions relative to the reference sequence, but an extracellular antigen-binding domain (*e.g.*, scFv) comprising that sequence retains the ability to bind to a GPRC5D polypeptide. In certain embodiments, a total of about 1 to about 10 amino acids have been substituted, inserted and/or deleted in the disclosed sequences. For example, and not by way of limitation, a V_H sequence or a V_L sequence, can have up to about one, up to about two, up to about three, up to about four, up to about five, up to about six, up to about seven, up to about eight, up to about nine or up to about ten amino acid residues that are modified and/or substituted. Non-limiting examples of conservative modifications are provided below, *e.g.*, within Table 33.

As used herein, the term “conservative sequence modifications” refers to

amino acid modifications that do not significantly affect or alter the binding characteristics of the presently disclosed CAR (e.g., the extracellular antigen-binding domain) comprising the amino acid sequence. Such conservative modifications include amino acid substitutions, additions and deletions. Modifications can be introduced into the human scFv of the presently disclosed subject matter by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Amino acids can be classified into groups according to their physicochemical properties such as charge and polarity. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid within the same group. For example, amino acids can be classified by charge: positively-charged amino acids include lysine, arginine, histidine, negatively-charged amino acids include aspartic acid, glutamic acid, neutral charge amino acids include alanine, asparagine, cysteine, glutamine, glycine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In addition, amino acids can be classified by polarity: polar amino acids include arginine (basic polar), asparagine, aspartic acid (acidic polar), glutamic acid (acidic polar), glutamine, histidine (basic polar), lysine (basic polar), serine, threonine, and tyrosine; non-polar amino acids include alanine, cysteine, glycine, isoleucine, leucine, methionine, phenylalanine, proline, tryptophan, and valine. Thus, one or more amino acid residues within a CDR region can be replaced with other amino acid residues from the same group and the altered antibody can be tested for retained function (*i.e.*, the functions set forth in (c) through (l) above) using the functional assays described herein. In certain embodiments, no more than one, no more than two, no more than three, no more than four, no more than five residues within a specified sequence or a CDR region are altered. Exemplary conservative amino acid substitutions are shown in Table 33.

Table 33

Original Residue	**Exemplary conservative amino acid Substitutions**
Ala (A)	Val; Leu; Ile
Arg (R)	Lys; Gln; Asn
Asn (N)	Gln; His; Asp, Lys; Arg
Asp (D)	Glu; Asn

Original Residue	Exemplary conservative amino acid Substitutions
Cys (C)	Ser; Ala
Gln (Q)	Asn; Glu
Glu (E)	Asp; Gln
Gly (G)	Ala
His (H)	Asn; Gln; Lys; Arg
Ile (I)	Leu; Val; Met; Ala; Phe
Leu (L)	Ile; Val; Met; Ala; Phe
Lys (K)	Arg; Gln; Asn
Met (M)	Leu; Phe; Ile
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr
Pro (P)	Ala
Ser (S)	Thr
Thr (T)	Val; Ser
Trp (W)	Tyr; Phe
Tyr (Y)	Trp; Phe; Thr; Ser
Val (V)	Ile; Leu; Met; Phe; Ala

In certain non-limiting embodiments, an extracellular antigen-binding domain of the CAR can comprise a linker connecting the heavy chain variable region and light chain variable region of the extracellular antigen-binding domain. As used herein, the term "linker" refers to a functional group (e.g., chemical or polypeptide) that covalently attaches two or more polypeptides or nucleic acids so that they are connected to one another. As used herein, a "peptide linker" refers to one or more amino acids used to couple two proteins together (*e.g.*, to couple V_H and V_L domains). Non-limiting examples of peptide linkers are disclosed in Shen et al., Anal. Chem. 80(6):1910-1917 (2008) and WO 2014/087010.

In one non-limiting example, the linker is a G4S linker that comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the nucleotide sequence encoding the amino acid sequence of SEQ ID NO:98 is set forth in SEQ ID NO:99. In one non-limiting example, the linker comprises amino acids having the sequence set forth in SEQ ID NO:284. In certain embodiments, the

nucleotide sequence encoding the amino acid sequence of SEQ ID NO:307 is set forth in SEQ ID NO:285.

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:286 as provided below.

GGGGS [SEQ ID NO:286].

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:287 as provided below.

SGGSGGS [SEQ ID NO:287].

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:288 as provided below.

GGGGSGGGS [SEQ ID NO:288].

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:289 as provided below.

GGGGSGGGGS [SEQ ID NO:289].

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:290 as provided below.

GGGGSGGGGSGGGGGGGS [SEQ ID NO:290].

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:291 as provided below.

GGGGSGGGGSGGGGSGGGGS [SEQ ID NO:291].

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:292 as provided below.

GGGGSGGGGSGGGGSGGGGSGGGGS [SEQ ID NO:292].

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:293 as provided below.

GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS [SEQ ID NO:293].

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:294 as provided below.

GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS [SEQ ID NO:294].

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:295 as provided below.

EPKSCDKTHTCPPCP [SEQ ID NO:295].

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:296 as provided below.

GGGGSGGGSEPKSCDKTHTCPPCP [SEQ ID NO:296].

In certain embodiments, the linker comprises amino acids having the sequence

set forth in SEQ ID NO:297 as provided below.

ELKTPLGDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCP [SEQ ID NO:297].

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:298 as provided below.

GSGSGS [SEQ ID NO:298].

In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:299 as provided below.

AAA [SEQ ID NO:299].

In addition, the extracellular antigen-binding domain can comprise a leader or a signal peptide that directs the nascent protein into the endoplasmic reticulum. Signal peptide or leader can be essential if the CAR is to be glycosylated and anchored in the cell membrane. The signal sequence or leader can be a peptide sequence (about 5, about 10, about 15, about 20, about 25, or about 30 amino acids long) present at the N-terminus of newly synthesized proteins that directs their entry to the secretory pathway. In non-limiting examples, the signal peptide is covalently joined to the 5' terminus of the extracellular antigen-binding domain. In certain embodiments, the signal peptide comprises a CD8 polypeptide comprising amino acids having the sequence set forth in SEQ ID NO:268 as provided below.

MALPVTALLLPLALLLHAAR [SEQ ID NO:268]

The nucleotide sequence encoding the amino acid sequence of SEQ ID NO:268 is set forth in SEQ ID NO:269, which is provided below:

ATGGCTCTCCCAGTGACTGCCCTACTGCTTCCCCTAGCGCTTCTCCTGCATGCAGCTCGT [SEQ ID NO:269]

In certain embodiments, the signal peptide comprises amino acids having the sequence set forth in SEQ ID NO:282 as provided below.

METDTLLLWVLLLWVPGSTG [SEQ ID NO:282]

The nucleotide sequence encoding the amino acid sequence of SEQ ID NO:282 is set forth in SEQ ID NO:283, which is provided below:

ATGGAAACCGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCAGGATCCACAGGA [SEQ ID NO:283]

In certain embodiments, the human scFv comprises a heavy chain variable region, a light chain variable region, a linker peptide between the heavy chain variable region and the light chain variable region, and an His-tag and an HA-tag. In certain

embodiments, the amino acid sequence of the His-tag and HA-tag comprises the amino acid sequence of SEQ ID NO:409,which is provided below:

TSGQAGQHHHHHHGAYPYDVPDYAS [SEQ ID NO: 409]

The nucloetide sequence encoding SEQ ID NO: 409 is SEQ ID NO: 410, which is provided below:

ACTAGTGGCCAGGCCGGCCAGCACCATCACCATCACCATGGCGCATACCCGTACGACGTTCCG GACTACGCTTCT [SEQ ID NO: 410]

In certain embodiments, the extracellular antigen-binding domain binds to a human GPRC5D polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 97. In certain embodiments, the extracellular antigen-binding domain binds to one, two, three or four of N-terminal region (amino acids 1-27 of SEQ ID NO:97), ECL1 region (amino acids 85-93 of SEQ ID NO:97), ECL2 region (amino acids 145-167 of SEQ ID NO:97), and ECL3 region (amino acids 226-239 of SEQ ID NO:97). In certain embodiments, the extracellular antigen-binding domain binds to an epitope region in the N-terminal region, including, but not limited to, an epitope region comprising amino acids 16-23 of SEQ ID NO:97, and an epitope region comprising amino acids 10-17 of SEQ ID NO:97. In certain embodiments, the epitope region in the N-terminal region comprises amino acids 15-23 of SEQ ID NO:97. In certain embodiments, the epitope region in the N-terminal region comprises amino acids 16-25 of SEQ ID NO:97. In certain embodiments, the epitope region in the N-terminal region comprises amino acids 10-17 of SEQ ID NO:97. In certain embodiments, the epitope region in the N-terminal region comprises amino acids 5-17 of SEQ ID NO:97.

In certain embodiments, the extracellular antigen-binding domain binds to an epitope region in the ECL1 region, including, but not limited to, an epitope region comprising amino acids 85-95 of SEQ ID NO:97.

In certain embodiments, the extracellular antigen-binding domain binds to an epitope region in the ECL2 region, including, but not limited to, an epitope region comprising amino acids 157-164 of SEQ ID NO:97. In certain embodiments, the epitope region in the ECL2 region comprises amino acids 157-164 of SEQ ID NO:97. In certain embodiments, the epitope region in the ECL2 region comprises amino acids 157-167 of SEQ ID NO:97.

In certain embodiments, the extracellular antigen-binding domain binds to an epitope region in the ECL3 region, including, but not limited to, an epitope region

comprising amino acids 230-237 of SEQ ID NO:97. In certain embodiments, the epitope region in the ECL3 region comprises amino acids 229-237 of SEQ ID NO:97. In certain embodiments, the epitope region in the ECL3 region comprises amino acids 230-243 of SEQ ID NO:97. In certain embodiments, the epitope region in the ECL3 region comprises amino acids 227-237 of SEQ ID NO:97.

In certain embodiments, the extracellular antigen-binding domain binds to one, two, or three epitope region selected from the group consisting of an epitope region comprising amino acids 16-25 of SEQ ID NO:97, an epitope region comprising amino acids 157-164 of SEQ ID NO:97, and an epitope region comprising amino acids 229-237 of SEQ ID NO:97. For example, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:57 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:58, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 15. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:57. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:57. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:58. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:58. In certain embodiments, the extracellular antigen-binding domain

comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:57 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:58. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:208 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 209 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 210 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 211 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 212 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 213 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 208 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 209 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 210 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 211 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 212 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 213 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 208, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 209, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 210, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 211, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 212, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 213. In certain embodiments, the extracellular antigen-binding domain is ET150-2 scFv (or ET150-152 scFv).

In certain embodiments, the extracellular antigen-binding domain binds to one, two, or three epitope region selected from the group consisting of an epitope

region comprising amino acids 5-17 of SEQ ID NO:97, an epitope region comprising amino acids 85-95 of SEQ ID NO:97, and an epitope region comprising amino acids 157-164 of SEQ ID NO:97. For example, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:61 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:62, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 16. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:61. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:61. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:62. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:62. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:61 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:62. Incertain embodiments certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:214 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 215 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ

ID NO: 216 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 217 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 218 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 219 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 214 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 215 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 216 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 217 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 218 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 219 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 214, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 215, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 216, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 217, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 218 and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 219. In certain embodiments, the extracellular antigen-binding domain is ET150-155 scFv (or ET150-5 scFv).

In certain embodiments, the extracellular antigen-binding domain binds to one or two epitope region selected from the group consisting of an epitope region comprising amino acids 15-23 of SEQ ID NO:97, and an epitope region comprising amino acids 230-243 of SEQ ID NO:97. For example, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:65 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:66, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker

comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 17. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:65. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:65. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:66, as shown in Table 17. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:66. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:65 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:66. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:220 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 221 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 222 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 223 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 224 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 225 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the

sequence set forth in SEQ ID NO: 220 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 221 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 222 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 223 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 224 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 225 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 220, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 221, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 222, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 223, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 224, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 225. In certain embodiments, the extracellular antigen-binding domain is ET150-8 scFv (or ET150-158 scFv).

In certain embodiments, the extracellular antigen-binding domain binds to one, two, or three epitope region selected from the group consisting of an epitope region comprising amino acids 10-17 of SEQ ID NO:97, an epitope region comprising amino acids 157-167 of SEQ ID NO:97, and an epitope region comprising amino acids 227-237 of SEQ ID NO:97. For example, the extracellular antigen-binding domain comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:69 and a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:70, optionally with (iii) a linker sequence, for example a linker peptide, between the heavy chain variable region and the light chain variable region. In certain embodiments, the linker comprises amino acids having the sequence set forth in SEQ ID NO:98. In certain embodiments, the extracellular antigen-binding domain is a scFv. In certain embodiments, the extracellular antigen-binding domain is a scFv-Fc fusion protein or full length human IgG with V_H and V_L regions or CDRs selected from Table 18. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising an amino acid sequence that is at least about 80%, about 81%, about 82%,

about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:69. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:69. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising an amino acid sequence that is at least about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98% or about 99% homologous to the amino acid sequence set forth in SEQ ID NO:70. In certain embodiments, the extracellular antigen-binding domain comprises a V_L comprising amino acids having the sequence set forth in SEQ ID NO:70. In certain embodiments, the extracellular antigen-binding domain comprises a V_H comprising amino acids having the sequence set forth in SEQ ID NO:69 and a V_L comprising amino acids having the sequence set forth in SEQ ID NO:70. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO:226 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 227 or conservative modifications thereof, and a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 228 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 229 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 230 or conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 231 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 226 or conservative modifications thereof, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 227 or conservative modifications thereof, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 228 or conservative modifications thereof, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 229 or conservative modifications thereof, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 230 or

conservativemodifications thereof, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 231 or conservative modifications thereof. In certain embodiments, the extracellular antigen-binding domain comprises a V_H CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 226, a V_H CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 227, a V_H CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 228, a V_L CDR1 comprising amino acids having the sequence set forth in SEQ ID NO: 229, a V_L CDR2 comprising amino acids having the sequence set forth in SEQ ID NO: 230, and a V_L CDR3 comprising amino acids having the sequence set forth in SEQ ID NO: 231. In certain embodiments, the extracellular antigen-binding domain is ET150-18 scFv (or ET150-168 scFv).

Transmembrane Domain of a CAR

In certain non-limiting embodiments, the transmembrane domain of the CAR comprises 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 is transmitted to the cell. In accordance with the presently disclosed subject matter, the transmembrane domain of the CAR can comprise a CD8 polypeptide, a CD28 polypeptide, a CD3ζ polypeptide, a CD4 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, a BTLA polypeptide, a synthetic peptide (not based on a protein associated with the immune response), or a combination thereof.

In certain embodiments, the transmembrane domain of a presently disclosed CAR comprises a CD28 polypeptide. The CD28 polypeptide can have an amino acid sequence that is at least about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or 100% homologous to the sequence having a NCBI Reference No: P10747 or NP_006130 (SEQ ID No: 270), or fragments thereof, and/or may optionally comprise up to one or up to two or up to three conservative amino acid substitutions. In non-limiting embodiments, the CD28 polypeptide can have an amino acid sequence that is a consecutive portion of SEQ ID NO:270 which is at least 20, or at least 30, or at least 40, or at least 50, and up to 220 amino acids in length. Alternatively or additionally, in non-limiting various embodiments, the CD28 polypeptide has an amino acid sequence of amino acids 1 to 220, 1 to 50, 50 to 100, 100 to 150, 150 to 200, or 200 to 220 of SEQ ID NO: 270. In certain embodiments,

the CAR of the presently disclosed comprises a transmembrane domain comprising a CD28 polypeptide, and an intracellular domain comprising a co-stimulatory signaling region that comprises a CD28 polypeptide. In certain embodiments, the CD28 polypeptide comprised in the transmembrane domain and the intracellular domain has an amino acid sequence of amino acids 114 to 220 of SEQ ID NO:270.

SEQ ID NO:270 is provided below:

1 MLRLLLALNL FPSIQVTGNK ILVKQSPMLV AYDNAVNLSC KYSYNLFSRE FRASLHKGLD
61 SAVEVCVVYG NYSQQLQVYS KTGFNCDGKL GNESVTFYLQ NLYVNQTDIY FCKIEVMYPP
121 PYLDNEKSNG TIIHVKGKHL CPSPLFPGPS KPFWVLVVVG GVLACYSLLV TVAFIIFWVR
181 SKRSRLLHSD YMNMTPRRPG PTRKHYQPYA PPRDFAAYRS [SEQ ID NO:270]

In accordance with the presently disclosed subject matter, a "CD28 nucleic acid molecule" refers to a polynucleotide encoding a CD28 polypeptide. In certain embodiments, the CD28 nucleic acid molecule encoding the CD28 polypeptide comprised in the transmembrane domain and the intracellular domain (*e.g.*, the co-stimulatory signaling region) of the presently disclosed CAR (amino acids 114 to 220 of SEQ ID NO:270) comprises nucleic acids having the sequence set forth in SEQ ID NO:271 as provided below.

ATTGAAGTTATGTATCCTCCTCCTTACCTAGACAATGAGAAGAGCAATGGAACCATTATCCAT
GTGAAAGGGAAACACCTTTGTCCAAGTCCCCTATTTCCCGGACCTTCTAAGCCCTTTTGGGTGCTGGTG
GTGGTTGGTGGAGTCCTGGCTTGCTATAGCTTGCTAGTAACAGTGGCCTTTATTATTTTCTGGGTGAGG
AGTAAGAGGAGCAGGCTCCTGCACAGTGACTACATGAACATGACTCCCCGCCGCCCCGGGCCCACCCGC
AAGCATTACCAGCCCTATGCCCCACCACGCGACTTCGCAGCCTATCGCTCC [SEQ ID NO:271]

In certain embodiments, the transmembrane domain of a presently disclosed CAR comprises a CD8 polypeptide. The CD8 polypeptide can have an amino acid sequence that is at least about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or 100% homologous to the sequence having a NCBI Reference No: AAH25715 (SEQ ID No: 404), or fragments thereof, and/or may optionally comprise up to one or up to two or up to three conservative amino acid substitutions. In non-limiting embodiments, the CD8 polypeptide can have an amino acid sequence that is a consecutive portion of SEQ ID NO: 404 which is at least 20, or at least 30, or at least 40, or at least 50, or at least 70, or at least 100, or at least 150, or at least 200 and up to 235 amino acids in length. Alternatively or additionally, in non-limiting various embodiments, the CD28 polypeptide has an amino acid sequence of amino acids 1 to 235, 1 to 50, 50 to 100, 100 to 150, 150 to 200, 130 to 210, or 200 to 235 of SEQ ID NO: 404. In certain embodiments, the CD8 polypeptide comprised in

the transmembrane domain has an amino acid sequence of amino acids 137 to 207 of SEQ ID NO: 404.

SEQ ID NO: 226 is provided below:

1 MALPVTALLL PLALLLHAAR PSQFRVSPLD RTWNLGETVE LKCQVLLSNP TSGCSWLFQP
61 RGAAASPTFL LYLSQNKPKA AEGLDTQRFS GKRLGDTFVL TLSDFRRENE GCYFCSALSN
121 SIMYFSHFVP VFLPAKPTTT PAPRPPTPAP TIASQPLSLR PEACRPAAGG AVHTRGLDFA
181 CDIYIWAPLA GTCGVLLLSL VITLYCNHRN RRRVCKCPRP VVKSGDKPSL SARYV [SEQ ID NO: 404].

In accordance with the presently disclosed subject matter, a "CD8 nucleic acid molecule" refers to a polynucleotide encoding a CD8 polypeptide. In certain embodiments, the CD8 nucleic acid molecule encoding the CD8 polypeptide comprised in the transmembrane domain of the presently disclosed CAR (amino acids 137 to 207 of SEQ ID NO: 404) comprises nucleic acids having the sequence set forth in SEQ ID NO: 405 as provided below.

CCCACCACGACGCCAGCGCCGCGACCACCAACCCCGGCGCCCACGATCGCGTCGCAGCCCCTG TCCCTGCGCCCAGAGGCGTGCCGGCCAGCGGCGGGGGGCGCAGTGCACACGAGGGGGCTGGACTTCGCC TGTGATATCTACATCTGGGCGCCCCTGGCCGGGACTTGTGGGGTCCTTCTCCTGTCACTGGTTATCACC CTTTACTGCAAC [SEQ ID NO:227]

In certain non-limiting embodiments, a CAR can also comprise a spacer region that links the extracellular antigen-binding domain to the transmembrane domain. The spacer region can be flexible enough to allow the antigen binding domain to orient in different directions to facilitate antigen recognition. The spacer region can be the hinge region from IgG1, or the CH_2CH_3 region of immunoglobulin and portions of CD3.

Intracellular Domain of a CAR

In certain non-limiting embodiments, an intracellular domain of the CAR can comprise a CD3ζ polypeptide, which can activate or stimulate a cell (*e.g.*, a cell of the lymphoid lineage, *e.g.*, a T cell). CD3ζ comprises three ITAMs, and transmits an activation signal to the cell (*e.g.*, a cell of the lymphoid lineage, *e.g.*, a T cell) after antigen is bound. The CD3ζ polypeptide can have an amino acid sequence that is at least about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or about 100% homologous to the sequence set forth in SEQ ID NO:272, or fragments thereof, and/or may optionally comprise up to one or up to two or up to three conservative amino acid substitutions. In non-limiting embodiments, the CD3ζ polypeptide can have an amino acid sequence that is a consecutive portion of SEQ ID NO:272 which is at least 20, or at least 30, or at least 40, or at least 50, and up to 163

amino acids in length. Alternatively or additionally, in non-limiting various embodiments, the CD3ζ polypeptide has an amino acid sequence of amino acids 1 to 163, 1 to 50, 50 to 100, 100 to 150, or 150 to 163 of SEQ ID NO: 272. In certain embodiments, the CD3ζ polypeptide comprised in the intracellular domain of a presently disclosed CAR has an amino acid sequence of amino acids 52 to 163 of SEQ ID NO: 272.

SEQ ID NO: 272 is provided below:

1 MKWKALFTAA ILQAQLPITE AQSFGLLDPK LCYLLDGILF IYGVILTALF LRVKFSRSAD
61 APAYQQGQNQ LYNELNLGRR EEYDVLDKRR GRDPEMGGKP RRKNPQEGLY NELQKDKMAE
121 AYSEIGMKGE RRRGKGHDGL YQGLSTATKD TYDALHMQAL PPR [SEQ ID NO: 272]

In accordance with the presently disclosed subject matter, a "CD3ζ nucleic acid molecule" refers to a polynucleotide encoding a CD3ζ polypeptide. In certain embodiments, the CD3ζ nucleic acid molecule encoding the CD3ζ polypeptide comprised in the intracellular domain of a presently disclosed CARs (amino acids 52 to 163 of SEQ ID NO: 272) comprises nucleic acids having the sequence set forth in SEQ ID NO: 273 as provided below.

AGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAGCAGGGCCAGAACCAGCTCTAT
AACGAGCTCAATCTAGGACGAAGAGAGGAGTACGATGTTTTGGACAAGAGACGTGGCCGGGACCCTGAG
ATGGGGGGAAAGCCGAGAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAAGATAAGATG
GCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGGGCACGATGGCCTTTAC
CAGGGTCTCAGTACAGCCACCAAGGACACCTACGACGCCCTTCACATGCAGGCCCTGCCCCCTCGCTAA
[SEQ ID NO: 273]

In certain non-limiting embodiments, an intracellular domain of the CAR further comprises at least one signaling region. The at least one signaling region can include a CD28 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a DAP-10 polypeptide, a PD-1 polypeptide, a CTLA-4 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, a BTLA polypeptide, a synthetic peptide (not based on a protein associated with the immune response), or a combination thereof.

In certain embodiments, the signaling region is a co-stimulatory signaling region. In certain embodiments, the co-stimulatory region comprises at least one co-stimulatory molecule, which can provide optimal lymphocyte activation. As used herein, "co-stimulatory molecules" refer to cell surface molecules other than antigen receptors or their ligands that are required for an efficient response of lymphocytes to antigen. The at least one co-stimulatory signaling region can include a CD28 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a

DAP-10 polypeptide, or a combination thereof. The co-stimulatory molecule can bind to a co-stimulatory ligand, which is a protein expressed on cell surface that upon binding to its receptor produces a co-stimulatory response, *i.e.*, an intracellular response that effects the stimulation provided when an antigen binds to its CAR molecule. Co-stimulatory ligands, include, but are not limited to CD80, CD86, CD70, OX40L, 4-1BBL, CD48, TNFRSF14, and PD-L1. As one example, a 4-1BB ligand (*i.e.*, 4-1BBL) may bind to 4-1BB (also known as "CD137") for providing an intracellular signal that in combination with a CAR signal induces an effector cell function of the CAR^+ T cell. CARs comprising an intracellular domain that comprises a co-stimulatory signaling region comprising 4-1BB, ICOS or DAP-10 are disclosed in U.S. 7,446,190 (*e.g.*, the nucleotide sequence encoding 4-1BB is set forth in SEQ ID NO:15, the nucleotide sequence encoding ICOS is set forth in SEQ ID NO:16, and the nucleotide sequence encoding DAP-10 is set forth in SEQ ID NO:17 in U.S.7,446,190), which is herein incorporated by reference in its entirety. In certain embodiments, the intracellular domain of the CAR comprises a co-stimulatory signaling region that comprises a CD28 polypeptide. In certain embodiments, the intracellular domain of the CAR comprises a co-stimulatory signaling region that comprises two co-stimulatory molecules:CD28 and 4-1BB or CD28 and OX40.

4-1BB can act as a tumor necrosis factor (TNF) ligand and have stimulatory activity. The 4-1BB polypeptide can have an amino acid sequence that is at least about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or 100% homologous to the sequence having a NCBI Reference No: P41273 or NP_001552 (SEQ ID NO: 274) or fragments thereof, and/or may optionally comprise up to one or up to two or up to three conservative amino acid substitutions. In certain embodiments, the 4-1BB polypeptide comprised in the intracellular domain of a presently disclosed CAR has an amino acid sequence of amino acids 214 to 255 of SEQ ID NO: 274. SEQ ID NO: 274 is provided below:

```
1   MGNSCYNIVA TLLLVLNFER TRSLQDPCSN CPAGTFCDNN RNQICSPCPP NSFSSAGGQR
61  TCDICRQCKG VFRTRKECSS TSNAECDCTP GFHCLGAGCS MCEQDCKQGQ ELTKKGCKDC
121 CFGTFNDQKR GICRPWTNCS LDGKSVLVNG TKERDVVCGP SPADLSPGAS SVTPPAPARE
181 PGHSPQIISF FLALTSTALL FLLFFLTLRF SVVKRGRKKL LYIFKQPFMR PVQTTQEEDG
241 CSCRFPEEEE GGCEL [SEQ ID NO: 274]
```

In accordance with the presently disclosed subject matter, a "4-1BB nucleic acid molecule" refers to a polynucleotide encoding a 4-1BB polypeptide. In certain

embodiments, the 4-1BB nucleic acid molecule encoding the 4-1BB polypeptide comprised in the intracellular domain of a presently disclosed CARs (amino acids 214 to 255 of SEQ ID NO: 274) comprises nucleic acids having the sequence set forth in SEQ ID NO: 300 as provided below.

aaacggggcagaaagaagctcctgtatatattcaaacaaccatttatgagaccagtacaaactactcaagagga agatggctgtagctgccgatttccagaagaagaagaaggaggatgtgaactg [SEQ ID NO: 300]

An OX40 polypeptide can have an amino acid sequence that is at least about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or 100% homologous to the sequence having a NCBI Reference No: P43489 or NP_003318 (SEQ ID NO: 275), or fragments thereof, and/or may optionally comprise up to one or up to two or up to three conservative amino acid substitutions.

SEQ ID NO: 275 is provided below:

1 MCVGARRLGR GPCAALLLLG LGLSTVTGLH CVGDTYPSND RCCHECRPGN GMVSRCSRSQ
61 NTVCRPCGPG FYNDVVSSKP CKPCTWCNLR SGSERKQLCT ATQDTVCRCR AGTQPLDSYK
121 PGVDCAPCPP GHFSPGDNQA CKPWTNCTLA GKHTLQPASN SSDAICEDRD PPATQPQETQ
181 GPPARPITVQ PTEAWPRTSQ GPSTRPVEVP GGRAVAAILG LGLVLGLLGP LAILLALYLL
241 RRDQRLPPDA HKPPGGGSFR TPIQEEQADA HSTLAKI [SEQ ID NO: 275]

In accordance with the presently disclosed subject matter, an "OX40 nucleic acid molecule" refers to a polynucleotide encoding an OX40 polypeptide.

An ICOS polypeptide can have an amino acid sequence that is at least about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or 100% homologous to the sequence having a NCBI Reference No: NP_036224 (SEQ ID NO: 276) or fragments thereof, and/or may optionally comprise up to one or up to two or up to three conservative amino acid substitutions.

SEQ ID NO: 276 is provided below:

1 MKSGLWYFFL FCLRIKVLTG EINGSANYEM FIFHNGGVQI LCKYPDIVQQ FKMQLLKGGQ
61 ILCDLTKTKG SGNTVSIKSL KFCHSQLSNN SVSFFLYNLD HSHANYYFCN LSIFDPPPFK
121 VTLTGGYLHI YESQLCCQLK FWLPIGCAAF VVVCILGCIL ICWLTKKKYS SSVHDPNGEY
181 MFMRAVNTAK KSRLTDVTL [SEQ ID NO: 276]

In accordance with the presently disclosed subject matter, an "ICOS nucleic acid molecule" refers to a polynucleotide encoding an ICOS polypeptide.

CTLA-4 is an inhibitory receptor expressed by activated T cells, which when engaged by its corresponding ligands (CD80 and CD86; B7-1 and B7-2, respectively), mediates activated T cell inhibition or anergy. In both preclinical and clinical studies,

CTLA-4 blockade by systemic antibody infusion, enhanced the endogenous anti-tumor response albeit, in the clinical setting, with significant unforeseen toxicities.

CTLA-4 contains an extracellular V domain, a transmembrane domain, and a cytoplasmic tail. Alternate splice variants, encoding different isoforms, have been characterized. The membrane-bound isoform functions as a homodimer interconnected by a disulfide bond, while the soluble isoform functions as a monomer. The intracellular domain is similar to that of CD28, in that it has no intrinsic catalytic activity and contains one YVKM motif able to bind PI3K, PP2A and SHP-2 and one proline-rich motif able to bind SH3 containing proteins. One role of CTLA-4 in inhibiting T cell responses seem to be directly via SHP-2 and PP2A dephosphorylation of TCR-proximal signaling proteins such as CD3 and LAT. CTLA-4 can also affect signaling indirectly via competing with CD28 for CD80/86 binding. CTLA-4 has also been shown to bind and/or interact with PI3K, CD80, AP2M1, and PPP2R5A.

In accordance with the presently disclosed subject matter, a CTLA-4 polypeptide can have an amino acid sequence that is at least about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or about 100% homologous to UniProtKB/Swiss-Prot Ref. No.: P16410.3 (SEQ ID NO: 277) (homology herein may be determined using standard software such as BLAST or FASTA) or fragments thereof, and/or may optionally comprise up to one or up to two or up to three conservative amino acid substitutions.

SEQ ID NO: 277 is provided below:

```
1   MACLGFQRHK AQLNLATRTW PCTLLFFLLF IPVFCKAMHV AQPAVVLASS RGIASFVCEY
61  ASPGKATEVR VTVLRQADSQ VTEVCAATYM MGNELTFLDD SICTGTSSGN QVNLTIQGLR
121 AMDTGLYICK VELMYPPPYY LGIGNGTQIY VIDPEPCPDS DFLLWILAAV SSGLFFYSFL
181  LTAVSLSKML KKRSPLTTGV YVKMPPTEPE CEKQFQPYFI PIN [SEQ ID NO: 277]
```

In accordance with the presently disclosed subject matter, a "CTLA-4 nucleic acid molecule" refers to a polynucleotide encoding a CTLA-4 polypeptide.

PD-1 is a negative immune regulator of activated T cells upon engagement with its corresponding ligands PD-L1 and PD-L2 expressed on endogenous macrophages and dendritic cells. PD-l is a type I membrane protein of 268 amino acids. PD-1 has two ligands, PD-L1 and PD-L2, which are members of the B7 family. The protein's structure comprises an extracellular IgV domain followed by a transmembrane region and an intracellular tail. The intracellular tail contains two phosphorylation sites located in an immunoreceptor tyrosine-based inhibitory motif

and an immunoreceptor tyrosine- based switch motif, that PD-1 negatively regulates TCR signals. SHP- I and SHP-2 phosphatases bind to the cytoplasmic tail of PD-1 upon ligand binding. Upregulation of PD-L1 is one mechanism tumor cells may evade the host immune system. In pre- clinical and clinical trials, PD-1 blockade by antagonistic antibodies induced anti-tumor responses mediated through the host endogenous immune system.

In accordance with the presently disclosed subject matter, a PD-1 polypeptide can have an amino acid sequence that is at least about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or about 100% homologous to NCBI Reference No: NP_005009.2 (SEQ ID NO: 278) or fragments thereof, and/or may optionally comprise up to one or up to two or up to three conservative amino acid substitutions.

SEQ ID NO: 278 is provided below:

1 MQIPQAPWPV VWAVLQLGWR PGWFLDSPDR PWNPPTFSPA LLVVTEGDNA TFTCSFSNTS
61 ESFVLNWYRM SPSNQTDKLA AFPEDRSQPG QDCRFRVTQL PNGRDFHMSV VRARRNDSGT
121 YLCGAISLAP KAQIKESLRA ELRVTERRAE VPTAHPSPSP RPAGQFQTLV VGVVGGLLGS
181 LVLLVWVLAV ICSRAARGTI GARRTGQPLK EDPSAVPVFS VDYGELDFQW REKTPEPPVP
241 CVPEQTEYAT IVFPSGMGTS SPARRGSADG PRSAQPLRPE DGHCSWPL [SEQ ID NO: 278]

In accordance with the presently disclosed subject matter, a "PD-1 nucleic acid molecule" refers to a polynucleotide encoding a PD-1 polypeptide.

Lymphocyte-activation protein 3 (LAG-3) is a negative immune regulator of immune cells. LAG-3 belongs to the immunoglobulin (lg) superfamily and contains 4 extracellular Ig-like domains. The LAG3 gene contains 8 exons. The sequence data, exon/intron organization, and chromosomal localization all indicate a close relationship of LAG3 to CD4. LAG3 has also been designated CD223 (cluster of differentiation 223).

In accordance with the the presently disclosed subject matter, a LAG-3 polypeptide can have an amino acid sequence that is at least about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or about 100% homologous to UniProtKB/Swiss-Prot Ref. No.: P18627.5 (SEQ ID NO: 279) or fragments thereof, and/or may optionally comprise up to one or up to two or up to three conservative amino acid substitutions.

SEQ ID NO: 279 is provided below:

1 MWEAQFLGLL FLQPLWVAPV KPLQPGAEVP VVWAQEGAPA QLPCSPTIPL QDLSLLRRAG

61 VTWQHQPDSG PPAAAPGHPL APGPHPAAPS SWGPRPRRYT VLSVGPGGLR SGRLPLQPRV
121 QLDERGRQRG DFSLWLRPAR RADAGEYRAA VHLRDRALSC RLRLRLGQAS MTASPPGSLR
181 ASDWVILNCS FSRPDRPASV HWFRNRGQGR VPVRESPHHH LAESFLFLPQ VSPMDSGPWG
241 CILTYRDGFN VSIMYNLTVL GLEPPTPLTV YAGAGSRVGL PCRLPAGVGT RSFLTAKWTP
301 PGGGPDLLVT GDNGDFTLRL EDVSQAQAGT YTCHIHLQEQ QLNATVTLAI ITVTPKSFGS
361 PGSLGKLLCE VTPVSGQERF VWSSLDTPSQ RSFSGPWLEA QEAQLLSQPW QCQLYQGERL
421 LGAAVYFTEL SSPGAQRSGR APGALPAGHL LLFLILGVLS LLLLVTGAFG FHLWRRQWRP
481 RRFSALEQGI HPPQAQSKIE ELEQEPEPEP EPEPEPEPEP EPEQL [SEQ ID NO: 279]

In accordance with the presently disclosed subject matter, a "LAG-3 nucleic acid molecule" refers to a polynucleotide encoding a LAG-3 polypeptide.

Natural Killer Cell Receptor 2B4 (2B4) mediates non-MHC restricted cell killing on NK cells and subsets of T cells. To date, the function of 2B4 is still under investigation, with the 2B4-S isoform believed to be an activating receptor, and the 2B4- L isoform believed to be a negative immune regulator of immune cells. 2B4 becomes engaged upon binding its high-affinity ligand, CD48. 2B4 contains a tyrosine-based switch motif, a molecular switch that allows the protein to associate with various phosphatases. 2B4 has also been designated CD244 (cluster of differentiation 244).

In accordance with the presently disclosed subject matter, a 2B4 polypeptide can have an amino acid sequence that is at least about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or about 100% homologous to UniProtKB/Swiss-Prot Ref. No.: Q9BZW8.2 (SEQ ID NO: 280) or fragments thereof, and/or may optionally comprise up to one or up to two or up to three conservative amino acid substitutions.

SEQ ID NO: 280 is provided below:

1 MLGQVVTLIL LLLLKVYQGK GCQGSADHVV SISGVPLQLQ PNSIQTKVDS IAWKKLLPSQ
61 NGFHHILKWE NGSLPSNTSN DRFSFIVKNL SLLIKAAQQQ DSGLYCLEVT SISGKVQTAT
121 FQVFVFESLL PDKVEKPRLQ GQGKILDRGR CQVALSCLVS RDGNVSYAWY RGSKLIQTAG
181 NLTYLDEEVD INGTHTYTCN VSNPVSWESH TLNLTQDCQN AHQEFRFWPF LVIIVILSAL
241 FLGTLACFCV WRRKRKEKQS ETSPKEFLTI YEDVKDLKTR RNHEQEQTFP GGGSTIYSMI
301 QSQSSAPTSQ EPAYTLYSLI QPSRKSGSRK RNHSPSFNST IYEVIGKSQP KAQNPARLSR
361 KELENFDVYS [SEQ ID NO: 280]

In accordance with the presently disclosed subject matter, a "2B4 nucleic acid molecule" refers to a polynucleotide encoding a 2B4 polypeptide.

B- and T-lymphocyte attenuator (BTLA) expression is induced during activation of T cells, and BTLA remains expressed on Th1 cells but not Th2 cells.

Like PD1 and CTLA4, BTLA interacts with a B7 homolog, B7H4. However, unlike PD-1 and CTLA-4, BTLA displays T-Cell inhibition via interaction with tumor necrosis family receptors (TNF-R), not just the B7 family of cell surface receptors. BTLA is a ligand for tumor necrosis factor (receptor) superfamily, member 14 (TNFRSF14), also known as herpes virus entry mediator (HVEM). BTLA-HVEM complexes negatively regulate T-cell immune responses. BTLA activation has been shown to inhibit the function of human $CD8^+$ cancer-specific T cells. BTLA has also been designated as CD272 (cluster of differentiation 272).

In accordance with the presently disclosed subject matter, a BTLA polypeptide can have an amino acid sequence that is at least about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% or about 100% homologous to UniProtKB/Swiss-Prot Ref. No.: Q7Z6A9.3 (SEQ ID NO: 281) or fragments thereof, and/or may optionally comprise up to one or up to two or up to three conservative amino acid substitutions.

SEQ ID NO: 281 is provided below:

1 MKTLPAMLGT GKLFWVFFLI PYLDIWNIHG KESCDVQLYI KRQSEHSILA GDPFELECPV
61 KYCANRPHVT WCKLNGTTCV KLEDRQTSWK EEKNISFFIL HFEPVLPNDN GSYRCSANFQ
121 SNLIESHSTT LYVTDVKSAS ERPSKDEMAS RPWLLYRLLP LGGLPLLITT CFCLFCCLRR
181 HQGKQNELSD TAGREINLVD AHLKSEQTEA STRQNSQVLL SETGIYDNDP DLCFRMQEGS
241 EVYSNPCLEE NKPGIVYASL NHSVIGPNSR LARNVKEAPT EYASICVRS [SEQ ID NO: 281]

In accordance with the presently disclosed subject matter, a "BTLA nucleic acid molecule" refers to a polynucleotide encoding a BTLA polypeptide.

In certain embodiments, the CAR comprises an extracellular antigen-binding region that specifically binds to a G-protein coupled receptor (*e.g.*, GPRC5D), a transmembrane domain comprising a CD28 polypeptide, and an intracellular domain comprising a CD3ζ polypeptide and a co-stimulatory signaling region that comprises a CD28 polypeptide, as shown in Figure 1. As shown in Figure 1, the CAR also comprises a signal peptide or a leader covalently joined to the 5' terminus of the extracellular antigen-binding domain. In certain embodiments, the signal peptide comprises amino acids having the sequence set forth in SEQ ID NO:282.

In certain embodiments, the CAR comprises an extracellular antigen-binding region that specifically binds to a G-protein coupled receptor (*e.g.*, GPRC5D), a transmembrane domain comprising a CD8 polypeptide, and an intracellular domain comprising a CD3ζ polypeptide and a co-stimulatory signaling region that comprises

a 4-1BB polypeptide, as shown in Figure 6. As shown in Figure 6, the CAR also comprises a signal peptide or a leader covalently joined to the 5' terminus of the extracellular antigen-binding domain. In certain embodiments, the signal peptide comprises amino acids having the sequence set forth in SEQ ID NO:282.

In some embodiments, the CAR of the presently disclosed subject matter can further comprise an inducible promoter, for expressing nucleic acid sequences in human cells. Promoters for use in expressing CAR genes can be a constitutive promoter, such as ubiquitin C (*UbiC*) promoter.

The presently disclosed subject matter also provides isolated nucleic acid molecule encoding the CAR targeting a G-protein coupled receptor (*e.g.*, GPRC5D) described herein or a functional portion thereof. In certain embodiments, the isolated nucleic acid molecule encodes a presently disclosed CAR targeting a G-protein coupled receptor (*e.g.*, GPRC5D) comprising an scFv that specifically binds to human GPRC5D, a transmembrane domain comprising a CD28 polypeptide, and an intracellular domain comprising a CD3ξ polypeptide and a co-stimulatory signaling region comprising a CD28 polypeptide. In certain embodiments, the scFv is a human scFv. In certain embodiments, the scFv is a murine scFv. In one specific non-limiting example, the isolated nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:397 provided below:

cagtctgtgttgacgcagcctgcctccgtgtctgggtctcctggacagtcgctcaccatctcctgcactggaacc
agcaatgacgttggtgcttataagtatgtctcctggtatcaacagtacccaggcaaagcccccaaactcatactttatgatgtc
tttaagcggccctcaggggtctctaatcgcttctctggctccaagtctgacaacacggcctccctgaccatctctgggctcca
ggctgaggacgaggctgattattactgcttctcacttacaagcagtaacacttatgtcttcggaactgggaccaaggtcaccg
tcctaggttctagaggtggtggtggtagcggcggcggcggctctggtggtggtggatccctcgagatggcccagatgcag
ctggtgcagtctggagctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaaca
gatatgctatcacctgggtgcgacaggcccctggacaaggccttgagtggatgggatggatcagcgcttacaatggtaatt
cacactatgcacagaagctccagggcagagtcaccatgaccacagacacatccacgggcacagcctatatggagctgag
gaggctgagatctgacgacacggccgtgtattactgtgcgcgcatggcttacgattcttggggtcaaggtactctggtgacc
gtctcctcagcggccgcaattgaagttatgtatcctcctccttacctagacaatgagaagagcaatggaaccattatccatgtg
aaagggaaacacctttgtccaagtcccctatttcccggaccttctaagccctttgggtgctggtggtggttggtggagtcctg
gcttgctatagcttgctagtaacagtggcctttattattttctgggtgaggagtaagaggagcaggctcctgcacagtgactac
atgaacatgactccccgccgccccgggcccacccgcaagcattaccagccctatgccccaccacgcgacttcgcagcct
atcgctccagagtgaagttcagcaggagcgcagacgcccccgcgtaccagcagggccagaaccagctctataacgagc
tcaatctaggacgaagagaggagtacgatgttttggacaagagacgtggccgggaccctgagatgggggggaaagccga

gaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggat gaaaggcgagcgccggaggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaaggacacctacg acgcccttcacatgcaggccctgcccccctcgc [SEQ ID NO:397]

In one specific non-limiting example, the isolated nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:398 provided below:

cagtctgtgttgactcagccaccctcagcgtctgggacccccggacagagggtcaccatctcttgttctggaagc aggtccaacgtaggaggtaattatgtattttggtaccagcaagtccccggagcgacccccaaactcctcatctataggagta atcagcggccctcgggggtccctgaccgattcgctggctccaagtctggctcctcagcctccctggccatcagtggactcc ggtccgaggatgaggctgattattactgtgcaacatgggatgacagcctgagtggttttgtcttcggaactgggaccaaggt caccgtcctaggttctagaggtggtggtggtagcggcggcggcggctctggtggtggtggatccctcgagatggccgag gtgcagctggtggagtctgggggaggcttggtcaagcctggagggtccctgagactctcctgtgcagcctctggattcacc ttcagtgactactacatgagctggatccgccaggctccagggaaggggctggagtgggtttcatacattagtagtagtggta gtaccatatactacgcagactctgtgaagggccgattcaccatctccagggacaacgccaagaactcactgtatctgcaaat gaacagcctgagagccgaggacacggccgtatattactgtgcgcgcggttacggtaaagcttacgatcagtggggtcaag gtactctggtgaccgtctcctcagcggccgcaattgaagttatgtatcctcctccttacctagacaatgagaagagcaatgga accattatccatgtgaaagggaaacacctttgtccaagtcccctatttcccggaccttctaagccctttgggtgctggtggtg gttggtggagtcctggcttgctatagcttgctagtaacagtggcctttattattttctgggtgaggagtaagaggagcaggctc ctgcacagtgactacatgaacatgactccccgccgccccgggcccacccgcaagcattaccagccctatgccccaccac gcgacttcgcagcctatcgctccagagtgaagttcagcaggagcgcagacgccccgcgtaccagcagggccagaacc agctctataacgagctcaatctaggacgaagagaggagtacgatgttttggacaagagacgtggccgggaccctgagatg gggggaaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggccta cagtgagattgggatgaaaggcgagcgccggaggggcaaggggcacgatggcctttaccagggtctcagtacagccac caaggacacctacgacgcccttcacatgcaggccctgcccccctcgc [SEQ ID NO:398]

In one specific non-limiting example, the isolated nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:399 provided below:

Tcttctgagctgactcaggaccctgctgtgtctgtggccttgggacagacagtcaggatcacatgccaaggaga cagcctcagaagctattatgcaagctggtaccagcagaagccaggacaggcccctgtacttgtcatctatggtaaaaacaa ccggccctcagggatcccagaccgattctctggctccagctcaggaaacacagcttccttgaccatcactggggctcaggc ggaagatgaggctgactattactgtaactcccgggacagcagtggtaacccccctgtggtattcggcggagggaccaagc tgaccgtcctaggttctagaggtggtggtggtagcggcggcggcggctctggtggtggtggatccctcgagatggccCa ggtgcagctggtggagtctgggggaggcctggtccaccctgggggtccctgagactctcctgtgcagcctctggattca ccttcagaagccatagcatgaactgggtccgccaggctccagggaaggggctggagtgggtctcatccattagtagtgata

gtacttacacatactacgcagactcagtgaagggccgattcaccatctccagagacaacgccaagaactcactgtatctgca
aatgaacagcctgagagccgaggacacggccgtatattactgtgcgcgctctggtggtcagtggaaatactacgattactg
gggtcaaggtactctggtgaccgtctcctcagcggccgcaattgaagttatgtatcctcctccttacctagacaatgagaaga
gcaatggaaccattatccatgtgaaagggaaacacctttgtccaagtcccctatttcccggaccttctaagccctttgggtgc
tggtggtggttggtggagtcctggcttgctatagcttgctagtaacagtggcctttattattttctgggtgaggagtaagagga
gcaggctcctgcacagtgactacatgaacatgactccccgccgccccgggcccacccgcaagcattaccagccctatgc
cccaccacgcgacttcgcagcctatcgctccagagtgaagttcagcaggagcgcagacgcccccgcgtaccagcaggg
ccagaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgttttggacaagagacgtggccgggac
cctgagatgggggaaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggc
ggaggcctacagtgagattgggatgaaaggcgagcgccggaggggcaaggggcacgatggcctttaccagggtctca
gtacagccaccaaggacacctacgacgcccttcacatgcaggccctgcccccctcgc [SEQ ID NO:399]

In one specific non-limiting example, the isolated nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:400 provided below:

cagtctgtcgtgacgcagccgccctcaatgtctgcggccccaggacagcaagtcaccatctcctgctctggag
gcaactccaacattgagagaaattatgtatcctggtacctccagctccctggaacagcccccaaactcgtcatttttgacaatg
ataggcgaccctcagggattcctgaccgattctctggctccaagtctggcacgtcagccaccctgggcatcaccggactcc
agactggggacgaggccgattattactgcggaacatgggatagcagcctgagaggttgggtgttcggcggagggaccaa
gctgaccgtcctaggttctagaggtggtggtggtagcggcggcggcggctctggtggtggtggatccctcgagatggccg
aggtgcagctggtggagtccgggggaggcttgatacagcctgggggtccctgagactctcctgtgcagcctctggattc
acctttagcaactatgccatgaactgggtccgccaggctccagggaaggggctggagtgggtctcaactattaatggtcgt
ggtagtagtacaatctacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtatctg
caaatgaacagcctgagagccgaggacacagccacgtattactgtgcgcgctacatctctcgtggtctgggtgattcttggg
gtcaaggtactctggtgaccgtctcctcagcggccgcaattgaagttatgtatcctcctccttacctagacaatgagaagagc
aatggaaccattatccatgtgaaagggaaacacctttgtccaagtcccctatttcccggaccttctaagccctttgggtgctg
gtggtggttggtggagtcctggcttgctatagcttgctagtaacagtggcctttattattttctgggtgaggagtaagaggagc
aggctcctgcacagtgactacatgaacatgactccccgccgccccgggcccacccgcaagcattaccagccctatgcccc
accacgcgacttcgcagcctatcgctccagagtgaagttcagcaggagcgcagacgcccccgcgtaccagcagggcca
gaaccagctctataacgagctcaatctaggacgaagagaggagtacgatgttttggacaagagacgtggccgggaccctg
agatgggggaaagccgagaaggaagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggag
gcctacagtgagattgggatgaaaggcgagcgccggaggggcaaggggcacgatggcctttaccagggtctcagtaca
gccaccaaggacacctacgacgcccttcacatgcaggccctgcccccctcgc [SEQ ID NO:400]

In one specific non-limiting example, the isolated nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:401 provided below:

CCGGTGCCGCCACCATGGAAACCGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCAGGATCCACAGGACAGTCT
GTCGTGACGCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGACGT
TGGTGGTTATAACTATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTATGATGTCAGTAAGC
GGCCCTCAGGGGTTTCTAATCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGGGCTCCAGGCT
GAGGACGAGGCTGATTATTACTGCAGCTCATATACAAGCAGCAGCACTTTGGTATTCGGCGGAGGGACCAAGCTGACCGT
CCTAGGTTCTAGAGGTGGTGGTGGTAGCGGCGGCGGCGGCTCTGGTGGTGGTGGATCCCTCGAGATGGCCGAGGTGCAGC
TGGTGGAGTCTGGGGGAGCCTTTGTACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGC
AGCTATGCCATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGCCTGGAATGGGTCTCGACTATTAGTGGTCGTGGTCGTAG
CACATTCTACGCAGACTCCGTGAAGGGCCGGTTTACCATCTCCAGAGACAATTCCAAGAACACGCTATATCTGCAAATGA
ACAGTCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGCGCTACTACCATGCTGGTGCTTTCGATCTGTGGGGTCAA
GGTACTCTGGTGACCGTCTCCTCAGAACAAAAACTCATCTCAGAAGAGGATCTGGCggccgcacccaccacgacgccagc
gccgcgaccaccaaccccggcgcccacgatcgcgtcgcagcccctgtccctgcgcccagaggcgtgccggccagcggcgg
ggggcgcagtgcacacgagggggctggacttcgcctgtgatatctacatctgggcgcccctggccgggacttgtggggtc
cttctcctgtcactggttatcacccttactgcaacaaacggggcagaaagaagctcctgtatatattcaaacaaccatt
tatgagaccagtacaaactactcaagaggaagatggctgtagctgccgatttccagaagaagaagaaggaggatgtgaac
tgagagtgaagttcagcaggagcgcagagccccccgcgtaccagcagggccagaaccagctctataacgagctcaatcta
ggacgaagagaggagtacgatgttttggacaagagacgtggccgggaccctgagatgggggaaagccgagaaggaagaa
ccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaaggcgagc
gccggaggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaaggacacctacgacgcccttcacatg
caggccctgcccccctcgctaacagccactcgaggatccggattagtccaatttgttaaagacaggatatcagtggtccag
gctctagttttgactcaacaatatcaccagctgaagcctatagagtacgagccatagataaaataaaagattttatttag
tctccagaaaaaggggggaatgaaagaccccacctgtaggtttggcaagctagcttaagtaacgccattttgcaaggcat
ggaaaaatacataactgagaatagagaagttcagatcaaggtcaggaacagatggaacagctgaatatgggccaaacagg
atatctgtggtaagcagttcctgccccggctcagggccaagaacagatggaacagctgaatatgggccaaacaggatatc
tgtggtaagcagttcctgccccggctcagggccaagaacagatggtccccagatgcggtccagccctcagcagtttctag
agaaccatcagatgtttccagggtgccccaaggacctgaaatgaccctgtgccttatttgaactaaccaatcagttcgct
tctcgcttctgttcgcgcgcttctgctccccgagctcaataaaagagcccacaaccctcactcggggcgccagtcctcc
gattgactgagtcgcccgggtacccgtgtatccaataaaccctcttgcagttgcatccgacttgtggtctcgctgttcct
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ttttttttcttaagtatttacattaaatggccatagtacttaaagttacattggcttccttgaaataaacatggagtatt
cagaatgtgtcataaatatttctaattttaagatagtatctccattggctttctacttttttcttttatttttttttgtcc
tctgtcttccatttgttgttgttgttgtttgtttgtttgtttgttggttggttggttaatttttttttaaagatcctaca
ctatagttcaagctagactattagctactctgtaacccagggtgaccttgaagtcatgggtagcctgctgttttagcctt
cccacatctaagattacaggtatgagctatcatttttggtatattgattgattgattgattgatgtgtgtgtgtgtgatt
gtgtttgtgtgtgtgactgtgaaaatgtgtgtatgggtgtgtgtgaatgtgtgtatgtatgtgtgtgtgtgagtgtgtgt
gtgtgtgtgtgcatgtgtgtgtgtgtgactgtgtctatgtgtatgactgtgtgtgtgtgtgtgtgtgtgtgtgtgtgt
gtgtgtgtgtgtgttgtgaaaaaatattctatggtagtgagagccaacgctccggctcaggtgtcaggttggtttttgag
acagagtctttcacttagcttggAATTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTACCCAA
CTTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACA
GTTGCGCAGCCTGAATGGCGAATGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATAT
GGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCC
TGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTC
ACCGTCATCACCGAAACGCGCGATGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATG
GTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAA
TATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATT
TCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAA
GATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCG

CCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGC
AAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACG
GATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAAC
GATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGG
AGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTA
ACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCT
GCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAG
CACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAAT
AGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGAT
TGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAAC
GTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTA
ATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCC
GAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGA
ACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTT
ACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAG
CTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCATTGAGAAAGCGCCACGCTTCCCGAAGGGAGAA
AGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTAT
CTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATG
GAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCCTGCGTTAT
CCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGC
GAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAG
CTGGCACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAGTTAGCTCACTCATTAGGCAC
CCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGC
TATGACCATGATTACGCCAAGCTTTGCTCTTAGGAGTTTCCTAATACATCCCAAACTCAAATATATAAAGCATTTGACTT
GTTCTATGCCCTAGGGGGCGGGGGGAAGCTAAGCCAGCTTTTTTTAACATTTAAAATGTTAATTCCATTTTAAATGCACA
GATGTTTTTATTTCATAAGGGTTTCAATGTGCATGAATGCTGCAATATTCCTGTTACCAAAGCTAGTATAAATAAAAATA
GATAAACGTGGAAATTACTTAGAGTTTCTGTCATTAACGTTTCCTTCCTCAGTTGACAACATAAATGCGCTGCTGAGCAA
GCCAGTTTGCATCTGTCAGGATCAATTTCCCATTATGCCAGTCATATTAATTACTAGTCAATTAGTTGATTTTTATTTTT
GACATATACATGTGAATGAAAGACCCCACCTGTAGGTTTGGCAAGCTAGCTTAAGTAACGCCATTTTGCAAGGCATGGAA
AAATACATAACTGAGAATAGAAAAGTTCAGATCAAGGTCAGGAACAGATGGAACAGCTGAATATGGGCCAAACAGGATAT
CTGTGGTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGAACAGCTGAATATGGGCCAAACAGGATATCTGTG
GTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGTCCCCAGATGCGGTCCAGCCCTCAGCAGTTTCTAGAGAA
CCATCAGATGTTTCCAGGGTGCCCCAAGGACCTGAAATGACCCTGTGCCTTATTTGAACTAACCAATCAGTTCGCTTCTC
GCTTCTGTTCGCGCGCTTATGCTCCCCGAGCTCAATAAAAGAGCCCACAACCCCTCACTCGGGGCGCCAGTCCTCCGATT
GACTGAGTCGCCCGGGTACCCGTGTATCCAATAAACCCTCTTGCAGTTGCATCCGACTTGTGGTCTCGCTGTTCCTTGGG
AGGGTCTCCTCTGAGTGATTGACTACCCGTCAGCGGGGGTCTTTCATTTGGGGGCTCGTCCGGGATCGGGAGACCCCTGC
CCAGGGACCACCGACCCACCACCGGGAGGTAAGCTGGCCAGCAACTTATCTGTGTCTGTCCGATTGTCTAGTGTCTATGA
CTGATTTTATGCGCCTGCGTCGGTACTAGTTAGCTAACTAGCTCTGTATCTGGCGGACCCGTGGTGGAACTGACGAGTTC
GGAACACCCGGCCGCAACCCTGGGAGACGTCCCAGGGACTTCGGGGGCCGTTTTTGTGGCCCGACCTGAGTCCTAAAATC
CCGATCGTTTAGGACTCTTTGGTGCACCCCCCTTAGAGGAGGGATATGTGGTTCTGGTAGGAGACGAGAACCTAAAACAG
TTCCCGCCTCCGTCTGAATTTTTGCTTTCGGTTTGGGACCGAAGCCGCGCCGCGCGTCTTGTCTGCTGCAGCATCGTTCT
GTGTTGTCTCTGTCTGACTGTGTTTCTGTATTTGTCTGAAAATATGGGCCCGGGCTAGACTGTTACCACTCCCTTAAGTT
TGACCTTAGGTCACTGGAAAGATGTCGAGCGGATCGCTCACAACCAGTCGGTAGATGTCAAGAAGAGACGTTGGGTTACC
TTCTGCTCTGCAGAATGGCCAACCTTTAACGTCGGATGGCCGCGAGACGGCACCTTTAACCGAGACCTCATCACCCAGGT
TAAGATCAAGGTCTTTTCACCTGGCCCGCATGGACACCCAGACCAGGTCCCCTACATCGTGACCTGGGAAGCCTTGGCTT
TTGACCCCCCTCCCTGGGTCAAGCCCTTTGTACACCCTAAGCCTCCGCCTCCTCTTCCTCCATCCGCCCCGTCTCTCCCC
CTTGAACCTCCTCGTTCGACCCCGCCTCGATCCTCCCTTTATCCAGCCCTCACTCCTTCTCTAGGCGCCCCCATATGGCC
ATATGAGATCTTATATGGGGCACCCCCGCCCCTTGTAAACTTCCCTGACCCTGACATGACAAGAGTTACTAACAGCCCCT
CTCTCCAAGCTCACTTACAGGCTCTCTACTTAGTCCAGCACGAAGTCTGGAGACCTCTGGCGGCAGCCTACCAAGAACAA
CTGGACCGA [SEQ ID NO: 401]

In one specific non-limiting example, the isolated nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:402 provided below:

CCGGTGCCGCCACCATGGAAACCGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCAGGATCCACAGGACAGTCT
GTGTTGACTCAGCCACCCTCAGCGTCTGGGACCCCCGGACAGAGGGTCACCATCTCTTGTTCTGGAAGCAGGTCCAACGT
AGGAGGTAATTATGTATTTTGGTACCAGCAAGTCCCCGGAGCGACCCCCAAACTCCTCATCTATAGGAGTAATCAGCGGC
CCTCGGGGGTCCCTGACCGATTCGCTGGCTCCAAGTCTGGCTCCTCAGCCTCCCTGGCCATCAGTGGACTCCGGTCCGAG
GATGAGGCTGATTATTACTGTGCAACATGGGATGACAGCCTGAGTGGTTTTGTCTTCGGAACTGGGACCAAGGTCACCGT
CCTAGGTTCTAGAGGTGGTGGTGGTAGCGGCGGCGGCGGCTCTGGTGGTGGTGGATCCCTCGAGATGGCCGAGGTGCAGC
TGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGT
GACTACTACATGAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACATTAGTAGTAGTGGTAGTAC
CATATACTACGCAGACTCTGTGAAGGGCCGATTCACCATCTCCCAGGGACAACGCCAAGAACTCACTGTATCTGCAAATG
AACAGCCTGAGAGCCGAGGACACGGCCGTATATTACTGTGCGCGCGGGTTACGGTAAAGCTTACGATCAGTGGGGTCAAG
GTACTCTGGTGACCGTCTCCTCAGAACAAAAACTCATCTCAGAAGAGGATCTGGCggccgcacccaccacgacgccagcg
ccgcgaccaccaaccccggcgcccacgatcgcgtcgcagcccctgtccctgcgcccagaggcgtgccggccagcggcggg
gggcgcagtgcacacgaggggggctggacttcgcctgtgatatctacatctgggcgcccctggccgggacttgtggggtcc
ttctcctgtcactggttatcacccttactgcaacaaacggggcagaaagaagctcctgtatatattcaaacaaccattt
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gagagtgaagttcagcaggagcgcagagccccccgcgtaccagcagggccagaaccagctctataacgagctcaatctag
gacgaagagaggagtacgatgttttggacaagagacgtggccgggaccctgagatgggggaaagccgagaaggaagaac
cctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaaggcgagcg
ccggaggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaaggacacctacgacgcccttcacatgc
aggccctgcccccctcgctaacagccactcgaggatccggattagtccaatttgttaaagacaggatatcagtggtccagg
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ctccagaaaaaggggggaatgaaagaccccacctgtaggtttggcaagctagcttaagtaacgccattttgcaaggcatg
gaaaaatacataactgagaatagagaagttcagatcaaggtcaggaacagatggaacagctgaatatgggccaaacagga
tatctgtggtaagcagttcctgccccggctcagggccaagaacagatggaacagctgaatatgggccaaacaggatatct
gtggtaagcagttcctgccccggctcagggccaagaacagatggtccccagatgcggtccagccctcagcagtttctaga
gaaccatcagatgtttccagggtgccccaaggacctgaaatgaccctgtgccttatttgaactaaccaatcagttcgctt
ctcgcttctgttcgcgcgcttctgctccccgagctcaataaaagagcccacaacccctcactcggggcgccagtcctccg
attgactgagtcgcccgggtacccgtgtatccaataaaccctcttgcagttgcatccgacttgtggtctcgctgttccttt
gggagggtctcctctgagtgattgactacccgtcagcgggggtctttcacacatgcagcatgtatcaaaattaatttggt
tttttttcttaagtatttacattaaatggccatagtacttaaagttacattggcttccttgaaataaacatggagtattc
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ctgtcttccatttgttgttgttgtttgtttgtttgtttgttggttggttggttaatttttttttaaagatcctacac
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ccacatctaagattacaggtatgagctatcatttttggtatattgattgattgattgattgatgtgtgtgtgtgtgattg
tgtttgtgtgtgtgactgtgaaaatgtgtgtatgggtgtgtgtgaatgtgtgtatgtatgtgtgtgtgtgagtgtgtgtg
tgtgtgtgtgcatgtgtgtgtgtgtgactgtgtctatgtgtatgactgtgtgtgtgtgtgtgtgtgtgtgtgtgtgtg
tgtgtgtgtgtgttgtgaaaaaatattctatggtagtgagagccaacgctccggctcaggtgtcaggttggtttttgaga
cagagtctttcacttagcttggAATTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTACCCAAC
TTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAG
TTGCGCAGCCTGAATGGCGAATGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATATG
GTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCT
GACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCA
CCGTCATCACCGAAACGCGCGATGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGG
TTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAAT
ATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTT
CCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAG
ATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGC

CCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCA
AGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGG
ATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACG
ATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGA
GCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAA
CTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTG
CGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGC
ACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATA
GACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATT
GATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACG
TGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAA
TCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCG
AAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAA
CTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTA
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TTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCATTGAGAAAGCGCCACGCTTCCCGAAGGGAGAAA
GGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATC
TTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGG
AAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCCTGCGTTATC
CCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCG
AGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGC
TGGCACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAGTTAGCTCACTCATTAGGCACC
CCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCT
ATGACCATGATTACGCCAAGCTTTGCTCTTAGGAGTTTCCTAATACATCCCAAACTCAAATATATAAAGCATTTGACTTG
TTCTATGCCCTAGGGGGCGGGGGGAAGCTAAGCCAGCTTTTTTTAACATTTAAAATGTTAATTCCATTTTAAATGCACAG
ATGTTTTTATTTCATAAGGGTTTCAATGTGCATGAATGCTGCAATATTCCTGTTACCAAAGCTAGTATAAATAAAAATAG
ATAAACGTGGAAATTACTTAGAGTTTCTGTCATTAACGTTTCCTTCCTCAGTTGACAACATAAATGCGCTGCTGAGCAAG
CCAGTTTGCATCTGTCAGGATCAATTTCCCATTATGCCAGTCATATTAATTACTAGTCAATTAGTTGATTTTTATTTTTG
ACATATACATGTGAATGAAAGACCCCACCTGTAGGTTTGGCAAGCTAGCTTAAGTAACGCCATTTTGCAAGGCATGGAAA
AATACATAACTGAGAATAGAAAAGTTCAGATCAAGGTCAGGAACAGATGGAACAGCTGAATATGGGCCAAACAGGATATC
TGTGGTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGAACAGCTGAATATGGGCCAAACAGGATATCTGTGG
TAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGTCCCCAGATGCGGTCCAGCCCTCAGCAGTTTCTAGAGAAC
CATCAGATGTTTCCAGGGTGCCCCAAGGACCTGAAATGACCCTGTGCCTTATTTGAACTAACCAATCAGTTCGCTTCTCG
CTTCTGTTCGCGCGCTTATGCTCCCCGAGCTCAATAAAAGAGCCCACAACCCCTCACTCGGGGCGCCAGTCCTCCGATTG
ACTGAGTCGCCCGGGTACCCGTGTATCCAATAAACCCTCTTGCAGTTGCATCCGACTTGTGGTCTCGCTGTTCCTTGGGA
GGGTCTCCTCTGAGTGATTGACTACCCGTCAGCGGGGGTCTTTCATTTGGGGGCTCGTCCGGGATCGGGAGACCCCTGCC
CAGGGACCACCGACCCACCACCGGGAGGTAAGCTGGCCAGCAACTTATCTGTGTCTGTCCGATTGTCTAGTGTCTATGAC
TGATTTTATGCGCCTGCGTCGGTACTAGTTAGCTAACTAGCTCTGTATCTGGCGGACCCGTGGTGGAACTGACGAGTTCG
GAACACCCGGCCGCAACCCTGGGAGACGTCCCAGGGACTTCGGGGGCCGTTTTTGTGGCCCGACCTGAGTCCTAAAATCC
CGATCGTTTAGGACTCTTTGGTGCACCCCCCTTAGAGGAGGGATATGTGGTTCTGGTAGGAGACGAGAACCTAAAACAGT
TCCCGCCTCCGTCTGAATTTTTGCTTTCGGTTTGGGACCGAAGCCGCGCCGCGCGTCTTGTCTGCTGCAGCATCGTTCTG
TGTTGTCTCTGTCTGACTGTGTTTCTGTATTTGTCTGAAAATATGGGCCCGGGCTAGACTGTTACCACTCCCTTAAGTTT
GACCTTAGGTCACTGGAAAGATGTCGAGCGGATCGCTCACAACCAGTCGGTAGATGTCAAGAAGAGACGTTGGGTTACCT
TCTGCTCTGCAGAATGGCCAACCTTTAACGTCGGATGGCCGCGAGACGGCACCTTTAACCGAGACCTCATCACCCAGGTT
AAGATCAAGGTCTTTTCACCTGGCCCGCATGGACACCCAGACCAGGTCCCCTACATCGTGACCTGGGAAGCCTTGGCTTT
TGACCCCCCTCCCTGGGTCAAGCCCTTTGTACACCCTAAGCCTCCGCCTCCTCTTCCTCCATCCGCCCCGTCTCTCCCCC
TTGAACCTCCTCGTTCGACCCCGCCTCGATCCTCCCTTTATCCAGCCCTCACTCCTTCTCTAGGCGCCCCCATATGGCCA
TATGAGATCTTATATGGGGCACCCCCGCCCCTTGTAAACTTCCCTGACCCTGACATGACAAGAGTTACTAACAGCCCCTC
TCTCCAAGCTCACTTACAGGCTCTCTACTTAGTCCAGCACGAAGTCTGGAGACCTCTGGCGGCAGCCTACCAAGAACAAC
TGGACCGA [SEQ ID NO: 402]

In one specific non-limiting example, the isolated nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:403 provided below:

CCGGTGCCGCCACCATGGAAACCGACACCCTGCTGCTGTGGGTGCTGCTGCTGTGGGTGCCAGGATCCACAGGACAGTCT
GTCGTGACGCAGCCGCCCTCAATGTCTGCGGCCCCAGGACAGCAAGTCACCATCTCCTGCTCTGGAGGCAACTCCAACAT
TGAGAGAAATTATGTATCCTGGTACCTCCAGCTCCCTGGAACAGCCCCCAAACTCGTCATTTTTGACAATGATAGGCGAC
CCTCAGGGATTCCTGACCGATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGGCATCACCGGACTCCAGACTGGG
GACGAGGCCGATTATTACTGCGGAACATGGGATAGCAGCCTGAGAGGTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGT
CCTAGGTTCTAGAGGTGGTGGTGGTAGCGGCGGCGGCGGCTCTGGTGGTGGTGGATCCCTCGAGATGGCCGAGGTGCAGC
TGGTGGAGTCCGGGGGAGGCTTGATACAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGC
AACTATGCCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAACTATTAATGGTCGTGGTAGTAG
TACAATCTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGA
ACAGCCTGAGAGCCGAGGACACAGCCACGTATTACTGTGCGCGCTACATCTCTCGTGGTCTGGGTGATTCTTGGGGTCAA
GGTACTCTGGTGACCGTCTCCTCAGAACAAAAACTCATCTCAGAGGAGGATCTGGCggccgcacccaccacgacgccagc
gccgcgaccaccaaccccggcgcccacgatcgcgtcgcagcccctgtccctgcgcccagaggcgtgccggccagcggcgg
ggggcgcagtgcacacgagggggctggacttcgcctgtgatatctacatctgggcgcccctggccgggacttgtggggtc
cttctcctgtcactggttatcacccttactgcaacaaacggggcagaaagaagctcctgtatatattcaaacaaccatt
tatgagaccagtacaaactactcaagaggaagatggctgtagctgccgatttccagaagaagaagaaggaggatgtgaac
tgagagtgaagttcagcaggagcgcagagcccccgcgtaccagcagggccagaaccagctctataacgagctcaatcta
ggacgaagagaggagtacgatgttttggacaagagacgtggccgggaccctgagatgggggaaagccgagaaggaagaa
ccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaaggcgagc
gccggaggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaaggacacctacgacgcccttcacatg
caggccctgccccctcgctaacagccactcgaggatccggattagtccaatttgttaaagacaggatatcagtggtccag
gctctagttttgactcaacaatatcaccagctgaagcctatagagtacgagccatagataaaataaaagattttatttag
tctccagaaaaaggggggaatgaaagaccccacctgtaggtttggcaagctagcttaagtaacgccattttgcaaggcat
ggaaaaatacataactgagaatagagaagttcagatcaaggtcaggaacagatggaacagctgaatatgggccaaacagg
atatctgtggtaagcagttcctgccccggctcagggccaagaacagatggaacagctgaatatgggccaaacaggatatc
tgtggtaagcagttcctgccccggctcagggccaagaacagatggtccccagatgcggtccagccctcagcagtttctag
agaaccatcagatgtttccagggtgccccaaggacctgaaatgaccctgtgccttatttgaactaaccaatcagttcgct
tctcgcttctgttcgcgcgcttctgctccccgagctcaataaaagagcccacaaccctcactcggggcgccagtcctcc
gattgactgagtcgcccgggtacccgtgtatccaataaaccctcttgcagttgcatccgacttgtggtctcgctgttcct
tgggagggtctcctctgagtgattgactacccgtcagcgggggtctttcacacatgcagcatgtatcaaaattaatttgg
ttttttttcttaagtatttacattaaatggccatagtacttaaagttacattggcttccttgaaataaacatggagtatt
cagaatgtgtcataaatatttctaattttaagatagtatctccattggctttctacttttttcttttatttttttttgtcc
tctgtcttccatttgttgttgttgttgtttgtttgtttgtttgttggttggttggttaatttttttttaaagatcctaca
ctatagttcaagctagactattagctactctgtaacccagggtgaccttgaagtcatgggtagcctgctgttttagcctt
cccacatctaagattacaggtatgagctatcatttttggtatattgattgattgattgattgatgtgtgtgtgtgtgatt
gtgtttgtgtgtgtgactgtgaaaatgtgtgtatgggtgtgtgtgaatgtgtgtatgtatgtgtgtgtgtgagtgtgtgt
gtgtgtgtgtgcatgtgtgtgtgtgtgactgtgtctatgtgtatgactgtgtgtgtgtgtgtgtgtgtgtgtgtgtgt
gtgtgtgtgtgtgttgtgaaaaaatattctatggtagtgagagccaacgctccggctcaggtgtcaggttggtttttgag
acagagtctttcacttagcttggAATTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTACCCAA
CTTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACA
GTTGCGCAGCCTGAATGGCGAATGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATAT
GGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCC
TGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTC
ACCGTCATCACCGAAACGCGCGATGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATG
GTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAA
TATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATT
TCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAA
GATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCG

CCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGC
AAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACG
GATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAAC
GATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGG
AGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTA
ACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCT
GCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAG
CACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAAT
AGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGAT
TGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAAC
GTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTA
ATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCC
GAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGA
ACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTT
ACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAG
CTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCATTGAGAAAGCGCCACGCTTCCCGAAGGGAGAA
AGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTAT
CTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATG
GAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCCTGCGTTAT
CCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGC
GAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAG
CTGGCACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAGTTAGCTCACTCATTAGGCAC
CCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGC
TATGACCATGATTACGCCAAGCTTTGCTCTTAGGAGTTTCCTAATACATCCCAAACTCAAATATATAAAGCATTTGACTT
GTTCTATGCCCTAGGGGGCGGGGGGAAGCTAAGCCAGCTTTTTTTAACATTTAAAATGTTAATTCCATTTTAAATGCACA
GATGTTTTTATTTCATAAGGGTTTCAATGTGCATGAATGCTGCAATATTCCTGTTACCAAAGCTAGTATAAATAAAAATA
GATAAACGTGGAAATTACTTAGAGTTTCTGTCATTAACGTTTCCTTCCTCAGTTGACAACATAAATGCGCTGCTGAGCAA
GCCAGTTTGCATCTGTCAGGATCAATTTCCCATTATGCCAGTCATATTAATTACTAGTCAATTAGTTGATTTTTATTTTT
GACATATACATGTGAATGAAAGACCCCACCTGTAGGTTTGGCAAGCTAGCTTAAGTAACGCCATTTTGCAAGGCATGGAA
AAATACATAACTGAGAATAGAAAAGTTCAGATCAAGGTCAGGAACAGATGGAACAGCTGAATATGGGCCAAACAGGATAT
CTGTGGTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGAACAGCTGAATATGGGCCAAACAGGATATCTGTG
GTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGTCCCCAGATGCGGTCCAGCCCTCAGCAGTTTCTAGAGAA
CCATCAGATGTTTCCAGGGTGCCCCAAGGACCTGAAATGACCCTGTGCCTTATTTGAACTAACCAATCAGTTCGCTTCTC
GCTTCTGTTCGCGCGCTTATGCTCCCCGAGCTCAATAAAAGAGCCCACAACCCCTCACTCGGGGCGCCAGTCCTCCGATT
GACTGAGTCGCCCGGGTACCCGTGTATCCAATAAACCCTCTTGCAGTTGCATCCGACTTGTGGTCTCGCTGTTCCTTGGG
AGGGTCTCCTCTGAGTGATTGACTACCCGTCAGCGGGGGTCTTTCATTTGGGGGCTCGTCCGGGATCGGGAGACCCCTGC
CCAGGGACCACCGACCCACCACCGGGAGGTAAGCTGGCCAGCAACTTATCTGTGTCTGTCCGATTGTCTAGTGTCTATGA
CTGATTTTATGCGCCTGCGTCGGTACTAGTTAGCTAACTAGCTCTGTATCTGGCGGACCCGTGGTGGAACTGACGAGTTC
GGAACACCCGGCCGCAACCCTGGGAGACGTCCCAGGGACTTCGGGGGCCGTTTTTGTGGCCCGACCTGAGTCCTAAAATC
CCGATCGTTTAGGACTCTTTGGTGCACCCCCCTTAGAGGAGGGATATGTGGTTCTGGTAGGAGACGAGAACCTAAAACAG
TTCCCGCCTCCGTCTGAATTTTTGCTTTCGGTTTGGGACCGAAGCCGCGCCGCGCGTCTTGTCTGCTGCAGCATCGTTCT
GTGTTGTCTCTGTCTGACTGTGTTTCTGTATTTGTCTGAAAATATGGGCCCGGGCTAGACTGTTACCACTCCCTTAAGTT
TGACCTTAGGTCACTGGAAAGATGTCGAGCGGATCGCTCACAACCAGTCGGTAGATGTCAAGAAGAGACGTTGGGTTACC
TTCTGCTCTGCAGAATGGCCAACCTTTAACGTCGGATGGCCGCGAGACGGCACCTTTAACCGAGACCTCATCACCCAGGT
TAAGATCAAGGTCTTTTCACCTGGCCCGCATGGACACCCAGACCAGGTCCCCTACATCGTGACCTGGGAAGCCTTGGCTT
TTGACCCCCCTCCCTGGGTCAAGCCCTTTGTACACCCTAAGCCTCCGCCTCCTCTTCCTCCATCCGCCCCGTCTCTCCCC
CTTGAACCTCCTCGTTCGACCCCGCCTCGATCCTCCCTTTATCCAGCCCTCACTCCTTCTCTAGGCGCCCCCATATGGCC
ATATGAGATCTTATATGGGGCACCCCCGCCCCTTGTAAACTTCCCTGACCCTGACATGACAAGAGTTACTAACAGCCCCT
CTCTCCAAGCTCACTTACAGGCTCTCTACTTAGTCCAGCACGAAGTCTGGAGACCTCTGGCGGCAGCCTACCAAGAACAA
CTGGACCGA [SEQ ID NO: 403]

In one specific non-limiting example, the isolated nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:406 provided below:

atggaaaccgacaccctgctgctgtgggtgctgctgctgtgggtgccaggatccacaggacag
tctgtcgtgacgcagcctgcctccgtgtctgggtctcctggacagtcgatcaccatctcctgc
actggaaccagcagtgacgttggtggttataactatgtctcctggtaccaacagcacccaggc
aaagcccccaaactcatgatttatgatgtcagtaagcggccctcaggggtttctaatcgcttc
tctggctccaagtctggcaacacggcctccctgaccatctctgggctccaggctgaggacgag
gctgattattactgcagctcatatacaagcagcagcactttggtattcggcggagggaccaag
ctgaccgtcctaggttctagaggtggtggtggtagcggcggcggcggctctggtggtggtgga
tccctcgagatggccgaggtgcagctggtggagtctgggggagcctttgtacagcctgggggg
tccctgagactctcctgtgcagcctctggattcacctttagcagctatgccatgacctgggtc
cgccaggctccagggaagggcctggaatgggtctcgactattagtggtcgtggtcgtagcaca
ttctacgcagactccgtgaagggccggtttaccatctccagagacaattccaagaacacgcta
tatctgcaaatgaacagtctgagagccgaggacacggccgtatattactgtgcgcgctactac
catgctggtgctttcgatctgtggggtcaaggtactctggtgaccgtctcctcagaacaaaaa
ctcatctcagaagaggatctggcggccgcaattgaagttatgtatcctcctccttacctagac
aatgagaagagcaatggaaccattatccatgtgaaagggaaacacctttgtccaagtccccta
tttcccggaccttctaagccctttgggtgctggtggtggttggtggagtcctggcttgctat
agcttgctagtaacagtggcctttattattttctgggtgaggagtaagaggagcaggctcctg
cacagtgactacatgaacatgactccccgccgccccgggcccacccgcaagcattaccagccc
tatgccccaccacgcgacttcgcagcctatcgctccagagtgaagttcagcaggagcgcagac
gcccccgcgtaccagcagggccagaaccagctctataacgagctcaatctaggacgaagagag
gagtacgatgttttggacaagagacgtggccgggaccctgagatgggggggaaagccgagaagg
aagaaccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctacagt
gagattgggatgaaaggcgagcgccggaggggcaaggggcacgatggcctttaccagggtctc
agtacagccaccaaggacacctacgacgcccttcacatgcaggccctgcccccctcgctaa
[SEQ ID NO: 406]

In one specific non-limiting example, the isolated nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:407 provided below:

CCGGTGCCGCCACcatggaaaccgacaccctgctgctgtgggtgctgctgctgtgggtgccaggatccacaggacagtct
gtgttgacgcagcctgcctccgtgtctgggtctcctggacagtcgctcaccatctcctgcactggaaccagcaatgacgt
tggtgcttataagtatgtctcctggtatcaacagtacccaggcaaagcccccaaactcatactttatgatgtctttaagc
ggccctcaggggtctctaatcgcttctctggctccaagtctgacaacacggcctccctgaccatctctgggctccaggct
gaggacgaggctgattattactgcttctcacttacaagcagtaacacttatgtcttcggaactgggaccaaggtcaccgt
cctaggttctagaggtggtggtggtagcggcggcggcggctctggtggtggtggatccctcgagatggcccagatgcagc
tggtgcagtctggagctgaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggttacacctttaac
agatatgctatcacctgggtgcgacaggcccctggacaaggccttgagtggatgggatggatcagcgcttacaatggtaa
ttcacactatgcacagaagctccagggcagagtcaccatgaccacagacacatccacgggcacagcctatatggagctga
ggaggctgagatctgacgacacggccgtgtattactgtgcgcgcatggcttacgattcttggggtcaaggtactctggtg
accgtctcctcagaacaaaaactcatctcagaagaggatctggcggccgcacccaccacgacgccagcgccgcgaccacc

aaccccggcgcccacgatcgcgtcgcagcccctgtccctgcgcccagaggcgtgccggccagcggcgggggggcgcagtgc
acacgagggggctggacttcgcctgtgatatctacatctgggcgcccctggccgggacttgtggggtccttctcctgtca
ctggttatcacccttactgcaacaaacggggcagaaagaagctcctgtatatattcaaacaaccatttatgagaccagt
acaaactactcaagaggaagatggctgtagctgccgatttccagaagaagaagaaggaggatgtgaactgagagtgaagt
tcagcaggagcgcagaCGcccccgcgtaccagcagggccagaaccagctctataacgagctcaatctaggacgaagagag
gagtacgatgttttggacaagagacgtggccgggaccctgagatgggggaaagccgagaaggaagaaccctcaggaagg
cctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaaggcgagcgccggaggggca
aggggcacgatggcctttaccagggtctcagtacagccaccaaggacacctacgacgcccttcacatgcaggccctgccc
cctcgctaacagccactcgaggatccggattagtccaatttgttaaagacaggatatcagtggtccaggctctagttttg
actcaacaatatcaccagctgaagcctatagagtacgagccatagataaaataaaagattttatttagtctccagaaaaa
gggggaatgaaagaccccacctgtaggtttggcaagctagcttaagtaacgccattttgcaaggcatggaaaaatacat
aactgagaatagagaagttcagatcaaggtcaggaacagatggaacagctgaatatgggccaaacaggatatctgtggta
agcagttcctgccccggctcagggccaagaacagatggaacagctgaatatgggccaaacaggatatctgtggtaagcag
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tgtttccagggtgccccaaggacctgaaatgaccctgtgccttatttgaactaaccaatcagttcgcttctcgcttctgt
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cgcccgggtacccgtgtatccaataaaccctcttgcagttgcatccgacttgtggtctcgctgttccttgggagggtctc
ctctgagtgattgactacccgtcagcgggggtctttcacacatgcagcatgtatcaaaattaatttggtttttttttctta
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taaatatttctaattttaagatagtatctccattggctttctacttttttcttttatttttttttgtcctctgtcttccat
ttgttgttgttgttgtttgtttgtttgtttgttggttggttggttaatttttttttaaagatcctacactatagttcaag
ctagactattagctactctgtaacccagggtgaccttgaagtcatgggtagcctgctgttttagccttcccacatctaag
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GCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACAGTTGCGCAGCCT
GAATGGCGAATGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATATGGTGCACTCTCA
GTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCCTGACGGGCTTGT
CTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTCACCGTCATCACC
GAAACGCGCGATGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATGGTTTCTTAGACG
TCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCT
CATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCGCCC
TTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAGAT
CAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCGCCCCGAAGAACG
TTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTCG
GTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACA
GTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACC
GAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAG
CCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTA
CTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCT
TCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAG
ATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCT
GAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTTAAAACT
TCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGT
TCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGCTTG
CAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAACTGG
CTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCAC
CGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGAC
TCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAAC

GACCTACACCGAACTGAGATACCTACAGCGTGAGCATTGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGT
ATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCT
GTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAG
CAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCCTGCGTTATCCCCTGATTCTG
TGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGC
GAGGAAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAGCTGGCACGACAG
GTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTAC
ACTTTATGCTTCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCTATGACCATGAT
TACGCCAAGCTTTGCTCTTAGGAGTTTCCTAATACATCCCAAACTCAAATATATAAAGCATTTGACTTGTTCTATGCCCT
AGGGGGCGGGGGGAAGCTAAGCCAGCTTTTTTTAACATTTAAAATGTTAATTCCATTTTAAATGCACAGATGTTTTTATT
TCATAAGGGTTTCAATGTGCATGAATGCTGCAATATTCCTGTTACCAAAGCTAGTATAAATAAAAATAGATAAACGTGGA
AATTACTTAGAGTTTCTGTCATTAACGTTTCCTTCCTCAGTTGACAACATAAATGCGCTGCTGAGCAAGCCAGTTTGCAT
CTGTCAGGATCAATTTCCCATTATGCCAGTCATATTAATTACTAGTCAATTAGTTGATTTTTATTTTTGACATATACATG
TGAATGAAAGACCCCACCTGTAGGTTTGGCAAGCTAGCTTAAGTAACGCCATTTTGCAAGGCATGGAAAAATACATAACT
GAGAATAGAAAAGTTCAGATCAAGGTCAGGAACAGATGGAACAGCTGAATATGGGCCAAACAGGATATCTGTGGTAAGCA
GTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGAACAGCTGAATATGGGCCAAACAGGATATCTGTGGTAAGCAGTTCC
TGCCCCGGCTCAGGGCCAAGAACAGATGGTCCCCAGATGCGGTCCAGCCCTCAGCAGTTTCTAGAGAACCATCAGATGTT
TCCAGGGTGCCCCAAGGACCTGAAATGACCCTGTGCCTTATTTGAACTAACCAATCAGTTCGCTTCTCGCTTCTGTTCGC
GCGCTTATGCTCCCCGAGCTCAATAAAAGAGCCCACAACCCCTCACTCGGGGCGCCAGTCCTCCGATTGACTGAGTCGCC
CGGGTACCCGTGTATCCAATAAACCCTCTTGCAGTTGCATCCGACTTGTGGTCTCGCTGTTCCTTGGGAGGGTCTCCTCT
GAGTGATTGACTACCCGTCAGCGGGGGTCTTTCATTTGGGGGCTCGTCCGGGATCGGGAGACCCCTGCCCAGGGACCACC
GACCCACCACCGGGAGGTAAGCTGGCCAGCAACTTATCTGTGTCTGTCCGATTGTCTAGTGTCTATGACTGATTTTATGC
GCCTGCGTCGGTACTAGTTAGCTAACTAGCTCTGTATCTGGCGGACCCGTGGTGGAACTGACGAGTTCGGAACACCCGGC
CGCAACCCTGGGAGACGTCCCAGGGACTTCGGGGGCCGTTTTTGTGGCCCGACCTGAGTCCTAAAATCCCGATCGTTTAG
GACTCTTTGGTGCACCCCCCTTAGAGGAGGGATATGTGGTTCTGGTAGGAGACGAGAACCTAAAACAGTTCCCGCCTCCG
TCTGAATTTTTGCTTTCGGTTTGGGACCGAAGCCGCGCCGCGCGTCTTGTCTGCTGCAGCATCGTTCTGTGTTGTCTCTG
TCTGACTGTGTTTCTGTATTTGTCTGAAAATATGGGCCCGGGCTAGACTGTTACCACTCCCTTAAGTTTGACCTTAGGTC
ACTGGAAAGATGTCGAGCGGATCGCTCACAACCAGTCGGTAGATGTCAAGAAGAGACGTTGGGTTACCTTCTGCTCTGCA
GAATGGCCAACCTTTAACGTCGGATGGCCGCGAGACGGCACCTTTAACCGAGACCTCATCACCCAGGTTAAGATCAAGGT
CTTTTCACCTGGCCCGCATGGACACCCAGACCAGGTCCCCTACATCGTGACCTGGGAAGCCTTGGCTTTTGACCCCCCTC
CCTGGGTCAAGCCCTTTGTACACCCTAAGCCTCCGCCTCCTCTTCCTCCATCCGCCCCGTCTCTCCCCCTTGAACCTCCT
CGTTCGACCCCGCCTCGATCCTCCCTTTATCCAGCCCTCACTCCTTCTCTAGGCGCCCCCATATGGCCATATGAGATCTT
ATATGGGGCACCCCCGCCCCTTGTAAACTTCCCTGACCCTGACATGACAAGAGTTACTAACAGCCCCTCTCTCCAAGCTC
ACTTACAGGCTCTCTACTTAGTCCAGCACGAAGTCTGGAGACCTCTGGCGGCAGCCTACCAAGAACAACTGGACCGA [SEQ
ID NO: 407]

In one specific non-limiting example, the isolated nucleic acid molecule comprises nucleic acids having the sequence set forth in SEQ ID NO:408 provided below:

CCGGTGCCGCCACcatggaaaccgacaccctgctgctgtgggtgctgctgctgtgggtgccaggatccacaggatcttct
gagctgactcaggaccctgctgtgtctgtggccttgggacagacagtcaggatcacatgccaaggagacagcctcagaag
ctattatgcaagctggtaccagcagaagccaggacaggcccctgtacttgtcatctatggtaaaaacaaccggccctcag
ggatcccagaccgattctctggctccagctcaggaaacacagcttccttgaccatcactggggctcaggcggaagatgag
gctgactattactgtaactcccgggacagcagtggtaacccccctgtggtattcggcggagggaccaagctgaccgtcct
aggttctagaggtggtggtggtagcggcggcggcggctctggtggtggtggatccctcgagatggcccaggtgcagctgg
tggagtctgggggaggcctggtccaccctgggggtccctgagactctcctgtgcagcctctggattcaccttcagaagc
catagcatgaactgggtccgccaggctccagggaaggggctggagtgggtctcatccattagtagtgatagtacttacac
atactacgcagactcagtgaagggccgattcaccatctccagagacaacgccaagaactcactgtatctgcaaatgaaca
gcctgagagccgaggacacggccgtatattactgtgcgcgctctggtggtcagtggaaatactacgattactggggtcaa
ggtactctggtgaccgtctcctcagaacaaaaactcatctcagaagaggatctggcggccgcacccaccacgacgccagc

gccgcgaccaccaaccccggcgcccacgatcgcgtcgcagcccctgtccctgcgcccagaggcgtgccggccagcggcgg
ggggcgcagtgcacacgaggggctggacttcgcctgtgatatctacatctgggcgcccctggccgggacttgtggggtc
cttctcctgtcactggttatcacccttactgcaacaaacggggcagaaagaagctcctgtatatattcaaacaaccatt
tatgagaccagtacaaactactcaagaggaagatggctgtagctgccgatttccagaagaagaagaaggaggatgtgaac
tgagagtgaagttcagcaggagcgcagaCGcccccgcgtaccagcagggccagaaccagctctataacgagctcaatcta
ggacgaagagaggagtacgatgttttggacaagagacgtggccgggaccctgagatgggggggaaagccgagaaggaagaa
ccctcaggaaggcctgtacaatgaactgcagaaagataagatggcggaggcctacagtgagattgggatgaaaggcgagc
gccggaggggcaaggggcacgatggcctttaccagggtctcagtacagccaccaaggacacctacgacgcccttcacatg
caggccctgccccctcgctaacagccactcgaggatccggattagtccaatttgttaaagacaggatatcagtggtccag
gctctagttttgactcaacaatatcaccagctgaagcctatagagtacgagccatagataaaataaaagattttatttag
tctccagaaaaaggggggaatgaaagaccccacctgtaggtttggcaagctagcttaagtaacgccattttgcaaggcat
ggaaaaatacataactgagaatagagaagttcagatcaaggtcaggaacagatggaacagctgaatatgggccaaacagg
atatctgtggtaagcagttcctgccccggctcagggccaagaacagatggaacagctgaatatgggccaaacaggatatc
tgtggtaagcagttcctgccccggctcagggccaagaacagatggtccccagatgcggtccagccctcagcagtttctag
agaaccatcagatgtttccagggtgccccaaggacctgaaatgaccctgtgccttatttgaactaaccaatcagttcgct
tctcgcttctgttcgcgcgcttctgctccccgagctcaataaaagagcccacaacccctcactcggggcgccagtcctcc
gattgactgagtcgcccgggtacccgtgtatccaataaaccctcttgcagttgcatccgacttgtggtctcgctgttcct
tgggagggtctcctctgagtgattgactacccgtcagcgggggtctttcacacatgcagcatgtatcaaaattaatttgg
ttttttttcttaagtatttacattaaatggccatagtacttaaagttacattggcttccttgaaataaacatggagtatt
cagaatgtgtcataaatatttctaatttaagatagtatctccattggctttctacttttttcttttatttttttttgtcc
tctgtcttccatttgttgttgttgtttgtttgtttgtttgttggttggttggttaatttttttttaaagatcctaca
ctatagttcaagctagactattagctactctgtaacccagggtgaccttgaagtcatgggtagcctgctgttttagcctt
cccacatctaagattacaggtatgagctatcatttttggtatattgattgattgattgattgatgtgtgtgtgtgtgatt
gtgtttgtgtgtgtgactgtgaaaatgtgtgtatgggtgtgtgtgaatgtgtgtatgtatgtgtgtgtgtgagtgtgtgt
gtgtgtgtgtgcatgtgtgtgtgtgtgactgtgtctatgtgtatgactgtgtgtgtgtgtgtgtgtgtgtgtgtgtgt
gtgtgtgtgtgtgttgtgaaaaaatattctatggtagtgagagccaacgctccggctcaggtgtcaggttggtttttgag
acagagtctttcacttagcttggAATTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGCGTTACCCAA
CTTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAAGAGGCCCGCACCGATCGCCCTTCCCAACA
GTTGCGCAGCCTGAATGGCGAATGGCGCCTGATGCGGTATTTTCTCCTTACGCATCTGTGCGGTATTTCACACCGCATAT
GGTGCACTCTCAGTACAATCTGCTCTGATGCCGCATAGTTAAGCCAGCCCCGACACCCGCCAACACCCGCTGACGCGCCC
TGACGGGCTTGTCTGCTCCCGGCATCCGCTTACAGACAAGCTGTGACCGTCTCCGGGAGCTGCATGTGTCAGAGGTTTTC
ACCGTCATCACCGAAACGCGCGATGACGAAAGGGCCTCGTGATACGCCTATTTTTATAGGTTAATGTCATGATAATAATG
GTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAA
TATGTATCCGCTCATGAGACAATAACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATT
TCCGTGTCGCCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAAGTAAAA
GATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTCG
CCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGC
AAGAGCAACTCGGTCGCCGCATACACTATTCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACG
GATGGCATGACAGTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAAC
GATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTTGATCGTTGGGAACCGG
AGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTA
ACTGGCGAACTACTTACTCTAGCTTCCCGGCAACAATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCT
GCGCTCGGCCCTTCCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAG
CACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAAT
AGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGAT
TGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAAC
GTGAGTTTTCGTTCCACTGAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTA
ATCTGCTGCTTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCTTTTTCC
GAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGA
ACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTT
ACCGGGTTGGACTCAAGACGATAGTTACCGGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAG

CTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCATTGAGAAAGCGCCACGCTTCCCGAAGGGAGAA
AGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTAT
CTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTCGTCAGGGGGGCGGAGCCTATG
GAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCCTGCGTTAT
CCCCTGATTCTGTGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGC
GAGTCAGTGAGCGAGGAAGCGGAAGAGCGCCCAATACGCAAACCGCCTCTCCCCGCGCGTTGGCCGATTCATTAATGCAG
CTGGCACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCAACGCAATTAATGTGAGTTAGCTCACTCATTAGGCAC
CCCAGGCTTTACACTTTATGCTTCCGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGC
TATGACCATGATTACGCCAAGCTTTGCTCTTAGGAGTTTCCTAATACATCCCAAACTCAAATATATAAAGCATTTGACTT
GTTCTATGCCCTAGGGGGCGGGGGGAAGCTAAGCCAGCTTTTTTTAACATTTAAAATGTTAATTCCATTTTAAATGCACA
GATGTTTTTATTTCATAAGGGTTTCAATGTGCATGAATGCTGCAATATTCCTGTTACCAAAGCTAGTATAAATAAAAATA
GATAAACGTGGAAATTACTTAGAGTTTCTGTCATTAACGTTTCCTTCCTCAGTTGACAACATAAATGCGCTGCTGAGCAA
GCCAGTTTGCATCTGTCAGGATCAATTTCCCATTATGCCAGTCATATTAATTACTAGTCAATTAGTTGATTTTTATTTTT
GACATATACATGTGAATGAAAGACCCCACCTGTAGGTTTGGCAAGCTAGCTTAAGTAACGCCATTTTGCAAGGCATGGAA
AAATACATAACTGAGAATAGAAAAGTTCAGATCAAGGTCAGGAACAGATGGAACAGCTGAATATGGGCCAAACAGGATAT
CTGTGGTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGAACAGCTGAATATGGGCCAAACAGGATATCTGTG
GTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGATGGTCCCCAGATGCGGTCCAGCCCTCAGCAGTTTCTAGAGAA
CCATCAGATGTTTCCAGGGTGCCCCAAGGACCTGAAATGACCCTGTGCCTTATTTGAACTAACCAATCAGTTCGCTTCTC
GCTTCTGTTCGCGCGCTTATGCTCCCCGAGCTCAATAAAAGAGCCCACAACCCCTCACTCGGGGCGCCAGTCCTCCGATT
GACTGAGTCGCCCGGGTACCCGTGTATCCAATAAACCCTCTTGCAGTTGCATCCGACTTGTGGTCTCGCTGTTCCTTGGG
AGGGTCTCCTCTGAGTGATTGACTACCCGTCAGCGGGGGTCTTTCATTTGGGGGCTCGTCCGGGATCGGGAGACCCCTGC
CCAGGGACCACCGACCCACCACCGGGAGGTAAGCTGGCCAGCAACTTATCTGTGTCTGTCCGATTGTCTAGTGTCTATGA
CTGATTTTATGCGCCTGCGTCGGTACTAGTTAGCTAACTAGCTCTGTATCTGGCGGACCCGTGGTGGAACTGACGAGTTC
GGAACACCCGGCCGCAACCCTGGGAGACGTCCCAGGGACTTCGGGGGCCGTTTTTGTGGCCCGACCTGAGTCCTAAAATC
CCGATCGTTTAGGACTCTTTGGTGCACCCCCCTTAGAGGAGGGATATGTGGTTCTGGTAGGAGACGAGAACCTAAAACAG
TTCCCGCCTCCGTCTGAATTTTTGCTTTCGGTTTGGGACCGAAGCCGCGCCGCGCGTCTTGTCTGCTGCAGCATCGTTCT
GTGTTGTCTCTGTCTGACTGTGTTTCTGTATTTGTCTGAAAATATGGGCCCGGGCTAGACTGTTACCACTCCCTTAAGTT
TGACCTTAGGTCACTGGAAAGATGTCGAGCGGATCGCTCACAACCAGTCGGTAGATGTCAAGAAGAGACGTTGGGTTACC
TTCTGCTCTGCAGAATGGCCAACCTTTAACGTCGGATGGCCGCGAGACGGCACCTTTAACCGAGACCTCATCACCCAGGT
TAAGATCAAGGTCTTTTCACCTGGCCCGCATGGACACCCAGACCAGGTCCCCTACATCGTGACCTGGGAAGCCTTGGCTT
TTGACCCCCCTCCCTGGGTCAAGCCCTTTGTACACCCTAAGCCTCCGCCTCCTCTTCCTCCATCCGCCCCGTCTCTCCCC
CTTGAACCTCCTCGTTCGACCCCGCCTCGATCCTCCCTTTATCCAGCCCTCACTCCTTCTCTAGGCGCCCCCATATGGCC
ATATGAGATCTTATATGGGGCACCCCCGCCCCTTGTAAACTTCCCTGACCCTGACATGACAAGAGTTACTAACAGCCCCT
CTCTCCAAGCTCACTTACAGGCTCTCTACTTAGTCCAGCACGAAGTCTGGAGACCTCTGGCGGCAGCCTACCAAGAACAA
CTGGACCGA [SEQ ID NO: 408]

The isolated nucleic acid molecule having the nucleotide sequence of SEQ ID NO:406 encodes a GPRC5D-targeted CAR (designated as GRPC5D 28z CAR1) comprising a human scFv that comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:53, a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:54, and a linker having an amino acid sequence of SEQ ID NO:98 positioned between the heavy chain variable region and the light chain variable region, a transmembrane domain comprising a CD28 polypeptide, and an intracellular domain comprising a CD3ξ polypeptide comprising amino acids 52 to 163 of SEQ ID NO: 272, and a co-stimulatory signaling region comprising a CD28 polypeptide, wherein the CD28

region comprising the transmembrane domain and the co-stimulatory signaling region comprises amino acids 114 to 220 of SEQ ID NO:270.

The isolated nucleic acid molecule having the nucleotide sequence of SEQ ID NO:397 encodes a GPRC5D-targeted CAR (designated as GRPC5D 28z CAR2) comprising a human scFv that comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:57, a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:58, and a linker having an amino acid sequence of SEQ ID NO:98 positioned between the heavy chain variable region and the light chain variable region, a transmembrane domain comprising a CD28 polypeptide, and an intracellular domain comprising a CD3ξ polypeptide comprising amino acids 52 to 163 of SEQ ID NO: 272, and a co-stimulatory signaling region comprising a CD28 polypeptide, wherein the CD28 region comprising the transmembrane domain and the co-stimulatory signaling region comprises amino acids 114 to 220 of SEQ ID NO:270.

The isolated nucleic acid molecule having the nucleotide sequence of SEQ ID NO:398 encodes a GPRC5D-targeted CAR (designated as GRPC5D 28z CAR5) comprising a human scFv that comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:61, a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:62, and a linker having an amino acid sequence of SEQ ID NO:98 positioned between the heavy chain variable region and the light chain variable region, a transmembrane domain comprising a CD28 polypeptide, and an intracellular domain comprising a CD3ξ polypeptide comprising amino acids 52 to 163 of SEQ ID NO: 272, and a co-stimulatory signaling region comprising a CD28 polypeptide, wherein the CD28 region comprising the transmembrane domain and the co-stimulatory signaling region comprises amino acids 114 to 220 of SEQ ID NO:270.

The isolated nucleic acid molecule having the nucleotide sequence of SEQ ID NO:399 encodes a GPRC5D-targeted CAR (designated as GRPC5D 28z CAR8) comprising a human scFv that comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:65, a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:66, and a linker having an amino acid sequence of SEQ ID NO:98 positioned between the heavy chain variable region and the light chain variable region, a transmembrane domain comprising a CD28 polypeptide, and an intracellular domain comprising a

CD3ξ polypeptide comprising amino acids 52 to 163 of SEQ ID NO: 272 and a co-stimulatory signaling region comprising a CD28 polypeptide, wherein the CD28 region comprising the transmembrane domain and the co-stimulatory signaling region comprises amino acids 114 to 220 of SEQ ID NO:270.

The isolated nucleic acid molecule having the nucleotide sequence of SEQ ID NO:400 encodes a GPRC5D-targeted CAR (designated as GRPC5D 28z CAR18) comprising a human scFv that comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:69, a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:70, and a linker having an amino acid sequence of SEQ ID NO:98 positioned between the heavy chain variable region and the light chain variable region, a transmembrane domain comprising a CD28 polypeptide, and an intracellular domain comprising a CD3ξ polypeptide comprising amino acids 52 to 163 of SEQ ID NO: 272, and a co-stimulatory signaling region comprising a CD28 polypeptide, wherein the CD28 region comprising the transmembrane domain and the co-stimulatory signaling region comprises amino acids 114 to 220 of SEQ ID NO:270.

The isolated nucleic acid molecule having the nucleotide sequence of SEQ ID NO:401 encodes a GPRC5D-targeted CAR (designated as GRPC5D BBz CAR1) comprising a human scFv that comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 53, a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 54, and a linker having an amino acid sequence of SEQ ID NO:98 positioned between the heavy chain variable region and the light chain variable region, a transmembrane domain comprising a CD8 polypeptide having 137 to 207 of SEQ ID NO: 404, and an intracellular domain comprising a CD3ξ polypeptide comprising amino acids 52 to 163 of SEQ ID NO: 272, and a co-stimulatory signaling region comprising a 4-1BB polypeptide having amino acids 214-255 of SEQ ID NO: 274. Nucleotide sequences 6-856 of SEQ ID NO: 401 encodes the human scFv. Nucleotide sequences 864-1076 of SEQ ID NO: 401 encodes the CD8 polypeptide comprised in the transmembrane domain. Nucleotide sequences 1077-1202 of SEQ ID NO: 401 encodes the 4-1BB polypeptide comprised in the intracellular domain. Nucleotide sequences 1203-1541 of SEQ ID NO: 401 encodes the CD3ξ polypeptide comprised in the intracellular domain. Other portions of SEQ ID NO: 401 are shown in Table 34.

Table 34

Portions	nucleotide Sequence positions of SEQ ID NO: 401	number of nucleotides
LTR	1821..2290	470
M13 fwd	2989..3005	17
AmpR promoter	3480..3584	105
AmpR	3585..4445	861
ori	4616..5204	589
CAP binding site	5492..5513	22
lac promoter	5528..5558	31
lac operator	5566..5582	17
M13 rev	5590..5606	17
LTR	6015..6608	594
MMLV Psi	6671..7028	358
gag (truncated)	7093..7509	417

The isolated nucleic acid molecule having the nucleotide sequence of SEQ ID NO:407 encodes a GPRC5D-targeted CAR (designated as GRPC5D BBz CAR2) comprising a human scFv that comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 57, a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:58, and a linker having an amino acid sequence of SEQ ID NO:98 positioned between the heavy chain variable region and the light chain variable region, a transmembrane domain comprising a CD8 polypeptide having 137 to 207 of SEQ ID NO: 404, and an intracellular domain comprising a CD3ξ polypeptide comprising amino acids 52 to 163 of SEQ ID NO: 272, and a co-stimulatory signaling region comprising a 4-1BB polypeptide having amino acids 214-255 of SEQ ID NO: 274. Nucleotide sequences 5-855 of SEQ ID NO: 402 encodes the human scFv. Nucleotide sequences 15-812 of SEQ ID NO: 407 encodes the human scFv. Nucleotide sequences 852-1064 of SEQ ID NO: 407 encodes the CD8 polypeptide comprised in the transmembrane domain. Nucleotide sequences 1065-1190 of SEQ ID NO: 407 encodes the 4-1BB polypeptide comprised in the intracellular domain. Nucleotide sequences 1191-1529 of SEQ ID NO: 407 encodes the CD3ξ polypeptide comprised in the intracellular domain. Other portions of SEQ ID NO: 407 are shown in Table 41.

Table 41

Portions	nucleotide Sequence positions of SEQ ID NO: 407	number of nucleotides
Myc	813..842	30
LTR	1809..2278	470
M13 fwd	2977..2993	17
AmpR promoter	3468..3572	105
AmpR	3573..4433	861
ori	4604..5192	589

CAP binding site	5480..5501	22
lac promoter	5516..5546	31
lac operator	5554..5570	17
M13 rev	5578..5594	17
LTR	6003..6596	594
MMLV Psi	6659..7016	358
gag (truncated)	7081..7497	417

The isolated nucleic acid molecule having the nucleotide sequence of SEQ ID NO:402 encodes a GPRC5D-targeted CAR (designated as GRPC5D BBz CAR5) comprising a human scFv that comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 61, a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO:62, and a linker having an amino acid sequence of SEQ ID NO:98 positioned between the heavy chain variable region and the light chain variable region, a transmembrane domain comprising a CD8 polypeptide having 137 to 207 of SEQ ID NO: 404, and an intracellular domain comprising a CD3ξ polypeptide comprising amino acids 52 to 163 of SEQ ID NO: 272, and a co-stimulatory signaling region comprising a 4-1BB polypeptide having amino acids 214-255 of SEQ ID NO: 274. Nucleotide sequences 5-855 of SEQ ID NO: 402 encodes the human scFv. Nucleotide sequences 863-1075 of SEQ ID NO: 402 encodes the CD8 polypeptide comprised in the transmembrane domain. Nucleotide sequences 1076-1201 of SEQ ID NO: 402 encodes the 4-1BB polypeptide comprised in the intracellular domain. Nucleotide sequences 1202-1540 of SEQ ID NO: 402 encodes the CD3ξ polypeptide comprised in the intracellular domain. Other portions of SEQ ID NO: 402 are shown in Table 35.

Table 35

Portions	nucleotide Sequence positions of SEQ ID NO: 402	number of nucleotides
LTR	1820..2289	470
M13 fwd	2988..3004	17
AmpR promoter	3479..3583	105
AmpR	3584..4444	861
ori	4615..5203	589
CAP binding site	5491..5512	22
lac promoter	5527..5557	31
lac operator	5565..5581	17
M13 rev	5589..5605	17
LTR	6014..6607	594
MMLV Psi	6670..7027	358
gag (truncated)	7092..7508	417

The isolated nucleic acid molecule having the nucleotide sequence of SEQ ID NO:408 encodes a GPRC5D-targeted CAR (designated as GRPC5D BBz CAR8) comprising a human scFv that comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 65, a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 66, and a linker having an amino acid sequence of SEQ ID NO:98 positioned between the heavy chain variable region and the light chain variable region, a transmembrane domain comprising a CD8 polypeptide having 137 to 207 of SEQ ID NO: 404, and an intracellular domain comprising a CD3ξ polypeptide comprising amino acids 52 to 163 of SEQ ID NO: 272, and a co-stimulatory signaling region comprising a 4-1BB polypeptide having amino acids 214-255 of SEQ ID NO: 274. Nucleotide sequences 15-824 of SEQ ID NO: 408 encodes the human scFv. Nucleotide sequences 864-1076 of SEQ ID NO: 408 encodes the CD8 polypeptide comprised in the transmembrane domain. Nucleotide sequences 1077-1202 of SEQ ID NO: 408 encodes the 4-1BB polypeptide comprised in the intracellular domain. Nucleotide sequences 1203-1541 of SEQ ID NO: 408 encodes the CD3ξ polypeptide comprised in the intracellular domain. Other portions of SEQ ID NO: 408 are shown in Table 42.

Table 42

Portions	nucleotide Sequence positions of SEQ ID NO: 408	number of nucleotides
Myc	825..854	30
LTR	1821..2290	470
M13 fwd	2989..3005	17
AmpR promoter	3480..3584	105
AmpR	3585..4445	861
ori	4616..5204	589
CAP binding site	5492..5513	22
lac promoter	5528..5558	31
lac operator	5566..5582	17
M13 rev	5590..5606	17
LTR	6015..6608	594
MMLV Psi	6671..7028	358
gag (truncated)	7093..7509	417

The isolated nucleic acid molecule having the nucleotide sequence of SEQ ID NO:403 encodes a GPRC5D-targeted CAR (designated as GRPC5D BBz CAR18) comprising a human scFv that comprises a heavy chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 69, a light chain variable region comprising amino acids having the sequence set forth in SEQ ID NO: 70, and a

linker having an amino acid sequence of SEQ ID NO:98 positioned between the heavy chain variable region and the light chain variable region, a transmembrane domain comprising a CD8 polypeptide having 137 to 207 of SEQ ID NO: 404, and an intracellular domain comprising a CD3ξ polypeptide comprising amino acids 52 to 163 of SEQ ID NO: 272, and a co-stimulatory signaling region comprising a 4-1BB polypeptide having amino acids 214-255 of SEQ ID NO: 274. Nucleotide sequences 6-856 of SEQ ID NO: 403 encodes the human scFv. Nucleotide sequences 864-1076 of SEQ ID NO: 403 encodes the CD8 polypeptide comprised in the transmembrane domain. Nucleotide sequences 1077-1202 of SEQ ID NO: 403 encodes the 4-1BB polypeptide comprised in the intracellular domain. Nucleotide sequences 1203-1541 of SEQ ID NO: 403 encodes the CD3ξ polypeptide comprised in the intracellular domain. Other portions of SEQ ID NO: 403 are shown in Table 36.

Table 36

Portions	nucleotide Sequence positions of SEQ ID NO: 403	number of nucleotides
LTR	1821..2290	470
M13 fwd	2989..3005	17
AmpR promoter	3480..3584	105
AmpR	3585..4445	861
ori	4616..5204	589
CAP binding site	5492..5513	22
lac promoter	5528..5558	31
lac operator	566..5582	17
M13 rev	5590..5606	17
LTR	6015..6608	594
MMLV Psi	6671..7028	358
gag (truncated)	7093..7509	417

In certain embodiments, the isolated nucleic acid molecule encodes a functional portion of a presently disclosed CAR targeting a G-protein coupled receptor (*e.g.*, GPRC5D). As used herein, the term "functional portion" refers to any portion, part or fragment of a presently disclosed CAR targeting a G-protein coupled receptor (*e.g.*, GPRC5D), which portion, part or fragment retains the biological activity of the CAR targeting a G-protein coupled receptor (*e.g.*, GPRC5D) (the parent CAR). For example, functional portions encompass the portions, parts or fragments of a presently disclosed CAR targeting a G-protein coupled receptor (*e.g.*, GPRC5D) that retains the ability to recognize a target cell, to treat a disease, *e.g.*, multiple myeloma, to a similar, same, or even a higher extent as the parent CAR. In certain embodiments, an isolated nucleic acid molecule encoding a functional portion

of a presently disclosed CAR targeting a G-protein coupled receptor (*e.g.*, GPRC5D) can encode a protein comprising, *e.g.*, about 10%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, and 95%, or more of the parent CAR.

III. Immunoresponsive Cells

The presently disclosed subject matter provides immunoresponsive cells expressing a CAR that comprises an extracellular antigen-binding domain, a transmembrane domain and an intracellular domain, where the extracellular antigen-binding domain specifically binds to a G-protein coupled receptor (*e.g.*, GPRC5D), as described above. The immunoresponsive cells can be transduced with a presently disclosed CAR such that the cells express the CAR. The presently disclosed subject matter also provides methods of using such cells for the treatment of a tumor, e.g., multiple myeloma (MM). The immunoresponsive cells of the presently disclosed subject matter can be cells of the lymphoid lineage. The lymphoid lineage, comprising B, T and natural killer (NK) cells, provides for the production of antibodies, regulation of the cellular immune system, detection of foreign agents in the blood, detection of cells foreign to the host, and the like. Non-limiting examples of immunoresponsive cells of the lymphoid lineage include T cells, Natural Killer (NK) cells, cytotoxic T lymphocytes (CTLs), regulatory T cells, embryonic stem cells, and pluripotent stem cells (e.g., those from which lymphoid cells may be differentiated). T cells can be lymphocytes that mature in the thymus and are chiefly responsible for cell-mediated immunity. T cells are involved in the adaptive immune system. The T cells of the presently disclosed subject matter can be any type of T cells, including, but not limited to, T helper cells, cytotoxic T cells, memory T cells (including central memory T cells, stem-cell-like memory T cells (or stem-like memory T cells), and two types of effector memory T cells: *e.g.*, T_{EM} cells and T_{EMRA} cells), Regulatory T cells (also known as suppressor T cells), Natural killer T cells, Mucosal associated invariant T cells, and γδ T cells. In certain embodiments, the CAR-expressing T cells express Foxp3 to achieve and maintain a T regulatory phenotype. Natural killer (NK) cells can be lymphocytes that are part of cell-mediated immunity and act during the innate immune response. NK cells do not require prior activation in order to perform their cytotoxic effect on target cells. Cytotoxic T cells (CTL or killer T cells) are a subset of T lymphocytes capable of inducing the death of infected somatic or tumor cells.

The immunoresponsive cells of the presently disclosed subject matter can express an extracellular antigen-binding domain (*e.g.*, an scFV, a Fab that is optionally crosslinked, or a $F(ab)_2$) that specifically binds to a G-protein coupled receptor (*e.g.*, GPRC5D), for the treatment of multiple myeloma. Such immunoresponsive cells can be administered to a subject (*e.g.*, a human subject) in need thereof for the treatment of multiple myeloma. In certain embodiments, the immunoresponsive cell is a T cell. The T cell can be a $CD4^+$ T cell or a $CD8^+$ T cell. In certain embodiments, the T cell is a $CD4^+$ T cell. In certain embodiments, the T cell is a $CD8^+$ T cell.

A presently disclosed immunoresponsive cell can be further transduced with at least one co-stimulatory ligand, such that the immunoresponsive cell co-expresses or is induced to co-express the CAR targeting a G-protein coupled receptor (*e.g.*, GPRC5D) and the at least one co-stimulatory ligand. The interaction between the CAR targeting a G-protein coupled receptor (*e.g.*, GPRC5D) and at least one co-stimulatory ligand provides a non-antigen-specific signal important for full activation of an immunoresponsive cell (*e.g.*, T cell). Co-stimulatory ligands include, but are not limited to, members of the tumor necrosis factor (TNF) superfamily, and immunoglobulin (Ig) superfamily ligands. TNF is a cytokine involved in systemic inflammation and stimulates the acute phase reaction. Its primary role is in the regulation of immune cells. Members of TNF superfamily share a number of common features. The majority of TNF superfamily members are synthesized as type II transmembrane proteins (extracellular C-terminus) containing a short cytoplasmic segment and a relatively long extracellular region. TNF superfamily members include, without limitation, nerve growth factor (NGF), CD40L (CD40L)/CD154, CD137L/4-1BBL, TNF-α, CD134L/OX40L/CD252, CD27L/CD70, Fas ligand (FasL), CD30L/CD153, tumor necrosis factor beta (TNFβ)/lymphotoxin-alpha (LTα), lymphotoxin-beta (LTβ), CD257/B cell-activating factor (BAFF)/Blys/THANK/Tall-1, glucocorticoid-induced TNF Receptor ligand (GITRL), and TNF-related apoptosis-inducing ligand (TRAIL), LIGHT (TNFSF14). The immunoglobulin (Ig) superfamily is a large group of cell surface and soluble proteins that are involved in the recognition, binding, or adhesion processes of cells. These proteins share structural features with immunoglobulins -- they possess an immunoglobulin domain (fold). Immunoglobulin superfamily ligands include, but are not limited to, CD80 and CD86,

both ligands for CD28, PD-L1/(B7-H1) that ligands for PD-1. In some embodiments, the at least one co-stimulatory ligand is selected from the group consisting of 4-1BBL, CD80, CD86, CD70, OX40L, CD48, TNFRSF14, PD-L1, and combinations thereof. In certain embodiments, the immunoresponsive cell is transduced with one co-stimulatory ligand that is 4-1BBL. In certain embodiments, the immunoresponsive cell is transduced with two co-stimulatory ligands that are 4-1BBL and CD80. CARs transduced with at least one co-stimulatory ligand are described in U.S. Patent No. 8,389,282, which is incorporated by reference in its entirety.

Furthermore, a presently disclosed immunoresponsive cell can be further transduced with at least one cytokine, such that the immunoresponsive cell secretes the at least one cytokine as well as expresses the CAR targeting a G-protein coupled receptor (*e.g.*, GPRC5D). In certain embodiments, the at least one cytokine is selected from the group consisting of IL-2, IL-3, IL-6, IL-7, IL-11, IL-12, IL-15, IL-17, and IL-21. In certain embodiments, the cytokine is IL-12.

The G-protein coupled receptor (*e.g.*, GPRC5D)-specific or -targeted human lymphocytes that can be used in peripheral donor lymphocytes, *e.g.*, those disclosed in Sadelain, M., *et al.* 2003 *Nat Rev Cancer* 3:35-45 (disclosing peripheral donor lymphocytes genetically modified to express CARs), in Morgan, R.A., *et al.* 2006 *Science* 314:126-129 (disclosing peripheral donor lymphocytes genetically modified to express a full-length tumor antigen-recognizing T cell receptor complex comprising the α and β heterodimer), in Panelli, M.C., *et al.* 2000 *J Immunol* 164:495-504; Panelli, M.C., *et al.* 2000 *J Immunol* 164:4382-4392 (disclosing lymphocyte cultures derived from tumor infiltrating lymphocytes (TILs) in tumor biopsies), and in Dupont, J., *et al.* 2005 *Cancer Res* 65:5417-5427; Papanicolaou, G.A., *et al.* 2003 *Blood* 102:2498-2505 (disclosing selectively *in vitro*-expanded antigen-specific peripheral blood leukocytes employing artificial antigen-presenting cells (AAPCs) or pulsed dendritic cells). The immunoresponsive cells (*e.g.*, T cells) can be autologous, non-autologous (*e.g.*, allogeneic), or derived *in vitro* from engineered progenitor or stem cells.

In certain embodiments, a presently disclosed immunoresponsive cell (*e.g.*, T cell) expresses from about 1 to about 4, from about 2 to about 4, from about 3 to about 4, from about 1 to about 2, from about 1 to about 3, or from about 2 to about 3 vector

copy numbers/cell of a presently disclosed CAR targeting a G-protein coupled receptor (*e.g.*, GPRC5D).

The unpurified source of CTLs may be any known in the art, such as the bone marrow, fetal, neonate or adult or other hematopoietic cell source, *e.g.*, fetal liver, peripheral blood or umbilical cord blood. Various techniques can be employed to separate the cells. For instance, negative selection methods can remove non-CTLs initially. Monoclonal antibodies are particularly useful for identifying markers associated with particular cell lineages and/or stages of differentiation for both positive and negative selections.

A large proportion of terminally differentiated cells can be initially removed by a relatively crude separation. For example, magnetic bead separations can be used initially to remove large numbers of irrelevant cells. Preferably, at least about 80%, usually at least 70% of the total hematopoietic cells will be removed prior to cell isolation.

Procedures for separation include, but are not limited to, density gradient centrifugation; resetting; coupling to particles that modify cell density; magnetic separation with antibody-coated magnetic beads; affinity chromatography; cytotoxic agents joined to or used in conjunction with a mAb, including, but not limited to, complement and cytotoxins; and panning with antibody attached to a solid matrix, e.g. plate, chip, elutriation or any other convenient technique.

Techniques for separation and analysis include, but are not limited to, flow cytometry, which can have varying degrees of sophistication, *e.g.*, a plurality of color channels, low angle and obtuse light scattering detecting channels, impedance channels.

The cells can be selected against dead cells, by employing dyes associated with dead cells such as propidium iodide (PI). Preferably, the cells are collected in a medium comprising 2% fetal calf serum (FCS) or 0.2% bovine serum albumin (BSA) or any other suitable, preferably sterile, isotonic medium.

IV. Vectors

Genetic modification of immunoresponsive cells (*e.g.*, T cells, CTL cells, NK cells) can be accomplished by transducing a substantially homogeneous cell composition with a recombinant DNA or RNA construct. The vector can be a retroviral vector (*e.g.*, gamma retroviral), which is employed for the introduction of the DNA or RNA construct into the host cell genome. For example, a polynucleotide

encoding the G-protein coupled receptor (*e.g.*, GPRC5D-specific CAR can be cloned into a retroviral vector and expression can be driven from its endogenous promoter, from the retroviral long terminal repeat, or from an alternative internal promoter.

Non-viral vectors or RNA may be used as well. Random chromosomal integration, or targeted integration (e.g., using a nuclease, transcription activator-like effector nucleases (TALENs), Zinc-finger nucleases (ZFNs), and/or clustered regularly interspaced short palindromic repeats (CRISPRs), or transgene expression (*e.g.*, using a natural or chemically modified RNA) can be used.

For initial genetic modification of the cells to provide G-protein coupled receptor (*e.g.*, GPRC5D-specific CAR expressing cells, a retroviral vector is generally employed for transduction, however any other suitable viral vector or non-viral delivery system can be used. For subsequent genetic modification of the cells to provide cells comprising an antigen presenting complex comprising at least two co-stimulatory ligands, retroviral gene transfer (transduction) likewise proves effective. Combinations of retroviral vector and an appropriate packaging line are also suitable, where the capsid proteins will be functional for infecting human cells. Various amphotropic virus-producing cell lines are known, including, but not limited to, PA12 (Miller, *et al.* (1985) *Mol. Cell. Biol.* 5:431-437); PA317 (Miller, *et al.* (1986) *Mol. Cell. Biol.* 6:2895-2902); and CRIP (Danos, *et al.* (1988) *Proc. Natl. Acad. Sci.* USA 85:6460-6464). Non -amphotropic particles are suitable too, e.g., particles pseudotyped with VSVG, RD114 or GALV envelope and any other known in the art.

Possible methods of transduction also include direct co-culture of the cells with producer cells, *e.g.*, by the method of Bregni, *et al.* (1992) *Blood* 80:1418-1422, or culturing with viral supernatant alone or concentrated vector stocks with or without appropriate growth factors and polycations, e.g., by the method of Xu, *et al.* (1994) *Exp. Hemat.* 22:223-230; and Hughes, *et al.* (1992) *J. Clin. Invest.* 89:1817.

Transducing viral vectors can be used to express a co-stimulatory ligand (*e.g.*, 4-1BBL and IL-12) in an immunoresponsive cell. Preferably, the chosen vector exhibits high efficiency of infection and stable integration and expression (*see, e.g.*, Cayouette et al., Human Gene Therapy 8:423-430, 1997; Kido *et al.*, Current Eye Research 15:833-844, 1996; Bloomer *et al.*, Journal of Virology 71:6641-6649, 1997; Naldini *et al.*, Science 272:263 267, 1996; and Miyoshi *et al.*, Proc. Natl. Acad. Sci. U.S.A. 94:10319, 1997). Other viral vectors that can be used include, for example, adenoviral, lentiviral, and adeno-associated viral vectors, vaccinia virus, a bovine

papilloma virus, or a herpes virus, such as Epstein-Barr Virus (also see, for example, the vectors of Miller, Human Gene Therapy 15-14, 1990; Friedman, Science 244:1275-1281, 1989; Eglitis et al., BioTechniques 6:608-614, 1988; Tolstoshev et al., Current Opinion in Biotechnology 1:55-61, 1990; Sharp, The Lancet 337:1277-1278, 1991; Cornetta et al., Nucleic Acid Research and Molecular Biology 36:311-322, 1987; Anderson, Science 226:401-409, 1984; Moen, Blood Cells 17:407-416, 1991; Miller et al., Biotechnology 7:980-990, 1989; Le Gal La Salle et al., Science 259:988-990, 1993; and Johnson, Chest 107:77S- 83S, 1995). Retroviral vectors are particularly well developed and have been used in clinical settings (Rosenberg et al., N. Engl. J. Med 323:370, 1990; Anderson et al., U.S. Pat. No. 5,399,346).

In certain non-limiting embodiments, the vector expressing a presently disclosed G-protein coupled receptor (*e.g.*, GPRC5D)-targeted CAR is a retroviral vector, *e.g.*, a 293galv9 retroviral vector.

Non-viral approaches can also be employed for the expression of a protein in cell. For example, a nucleic acid molecule can be introduced into a cell by administering the nucleic acid in the presence of lipofection (Feigner et al., Proc. Nat'l. Acad. Sci. U.S.A. 84:7413, 1987; Ono et al., Neuroscience Letters 17:259, 1990; Brigham et al., Am. J. Med. Sci. 298:278, 1989; Staubinger et al., Methods in Enzymology 101:512, 1983), asialoorosomucoid-polylysine conjugation (Wu et al., Journal of Biological Chemistry 263:14621 , 1988; Wu et al., Journal of Biological Chemistry 264:16985, 1989), or by micro-injection under surgical conditions (Wolff et al., Science 247:1465, 1990). Other non-viral means for gene transfer include transfection in vitro using calcium phosphate, DEAE dextran, electroporation, and protoplast fusion. Liposomes can also be potentially beneficial for delivery of DNA into a cell. Transplantation of normal genes into the affected tissues of a subject can also be accomplished by transferring a normal nucleic acid into a cultivatable cell type *ex vivo* (e.g., an autologous or heterologous primary cell or progeny thereof), after which the cell (or its descendants) are injected into a targeted tissue or are injected systemically. Recombinant receptors can also be derived or obtained using transposases or targeted nucleases (e.g. Zinc finger nucleases, meganucleases, or TALE nucleases). Transient expression may be obtained by RNA electroporation.

cDNA expression for use in polynucleotide therapy methods can be directed from any suitable promoter (e.g., the human cytomegalovirus (CMV), simian virus 40 (SV40), or metallothionein promoters), and regulated by any appropriate mammalian

regulatory element or intron (e.g. the elongation factor 1 α enhancer/promoter/intron structure). For example, if desired, enhancers known to preferentially direct gene expression in specific cell types can be used to direct the expression of a nucleic acid. The enhancers used can include, without limitation, those that are characterized as tissue- or cell-specific enhancers. Alternatively, if a genomic clone is used as a therapeutic construct, regulation can be mediated by the cognate regulatory sequences or, if desired, by regulatory sequences derived from a heterologous source, including any of the promoters or regulatory elements described above.

The resulting cells can be grown under conditions similar to those for unmodified cells, whereby the modified cells can be expanded and used for a variety of purposes.

V. Polypeptides and Analogs and Polynucleotides

Also included in the presently disclosed subject matter are extracellular antigen-binding domains that specifically binds to a G-protein coupled receptor (*e.g.*, GPRC5D) (*e.g.*, an scFv, a Fab, or a $(Fab)_2$), CD3ζ, CD8, CD28, *etc.* polypeptides or fragments thereof, and polynucleotides encoding thereof that are modified in ways that enhance their anti-tumor activity when expressed in an immunoresponsive cell. The presently disclosed subject matter provides methods for optimizing an amino acid sequence or a nucleic acid sequence by producing an alteration in the sequence. Such alterations may comprise certain mutations, deletions, insertions, or post-translational modifications. The presently disclosed subject matter further comprises analogs of any naturally-occurring polypeptide of the presently disclosed subject matter. Analogs can differ from a naturally-occurring polypeptide of the presently disclosed subject matter by amino acid sequence differences, by post-translational modifications, or by both. Analogs of the presently disclosed subject matter can generally exhibit at least about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or more identity with all or part of a naturally-occurring amino, acid sequence of the presently disclosed subject matter. The length of sequence comparison is at least 5, 10, 15, 20, 25, 50, 75, 100 or more amino acid residues. Again, in an exemplary approach to determining the degree of identity, a BLAST program may be used, with a probability score between e^{-3} and e^{-100} indicating a closely related sequence. Modifications comprise *in vivo* and *in vitro* chemical derivatization of polypeptides, e.g., acetylation,

carboxylation, phosphorylation, or glycosylation; such modifications may occur during polypeptide synthesis or processing or following treatment with isolated modifying enzymes. Analogs can also differ from the naturally-occurring polypeptides of the presently disclosed subject matter by alterations in primary sequence. These include genetic variants, both natural and induced (for example, resulting from random mutagenesis by irradiation or exposure to ethanemethylsulfate or by site-specific mutagenesis as described in Sambrook, Fritsch and Maniatis, Molecular Cloning: A Laboratory Manual (2d ed.), CSH Press, 1989, or Ausubel et al., supra). Also included are cyclized peptides, molecules, and analogs which contain residues other than L-amina acids, e.g., D-amino acids or non-naturally occurring or synthetic amino acids, e.g., beta (β) or gamma (γ) amino acids.

In addition to full-length polypeptides, the presently disclosed subject matter also provides fragments of any one of the polypeptides or peptide domains of the presently disclosed subject matter. A fragment can be at least 5, 10, 13, or 15 amino acids. In certain embodiments, a fragment is at least 20 contiguous amino acids, at least 30 contiguous amino acids, or at least 50 contiguous amino acids. In certain embodiments, a fragment is at least 60 to 80, 100, 200, 300 or more contiguous amino acids. Fragments of the presently disclosed subject matter can be generated by methods known to those of ordinary skill in the art or may result from normal protein processing (e.g., removal of amino acids from the nascent polypeptide that are not required for biological activity or removal of amino acids by alternative mRNA splicing or alternative protein processing events).

Non-protein analogs have a chemical structure designed to mimic the functional activity of a protein of the invention. Such analogs are administered according to methods of the presently disclosed subject matter. Such analogs may exceed the physiological activity of the original polypeptide. Methods of analog design are well known in the art, and synthesis of analogs can be carried out according to such methods by modifying the chemical structures such that the resultant analogs increase the anti-neoplastic activity of the original polypeptide when expressed in an immunoresponsive cell. These chemical modifications include, but are not limited to, substituting alternative R groups and varying the degree of saturation at specific carbon atoms of a reference polypeptide. The protein analogs can be relatively resistant to *in vivo* degradation, resulting in a more prolonged

therapeutic effect upon administration. Assays for measuring functional activity include, but are not limited to, those described in the Examples below.

In accordance with the presently disclosed subject matter, the polynucleotides encoding an extracellular antigen-binding domain that specifically binds to a G-protein coupled receptor (*e.g.*, GPRC5D) (*e.g.*, an scFV, a Fab, or a $(Fab)_2$), CD3ζ, CD8, CD28) can be modified by codon optimization. Codon optimization can alter both naturally occurring and recombinant gene sequences to achieve the highest possible levels of productivity in any given expression system. Factors that are involved in different stages of protein expression include codon adaptability, mRNA structure, and various *cis*-elements in transcription and translation. Any suitable codon optimization methods or technologies that are known to ones skilled in the art can be used to modify the polynucleotids of the presently disclosed subject matter, including, but not limited to, OPTIMUMGENE™, Encor optimization, and Blue Heron.

VI. Administration

G-protein coupled receptor (e.g., GPRC5D)-specific CARs and immunoresponsive cells expressing thereof of the presently disclosed subject matter can be provided systemically or directly to a subject for treating or preventing a neoplasia. In certain embodiments, the G-protein coupled receptor (*e.g.*, GPRC5D)-specific CARs and immunoresponsive cells expressing thereof are directly injected into an organ of interest (*e.g.*, an organ affected by a neoplasia). Alternatively or additionally, the G-protein coupled receptor (*e.g.*, GPRC5D)-specific CARs and immunoresponsive cells expressing thereof are provided indirectly to the organ of interest, for example, by administration into the circulatory system (*e.g.*, the tumor vasculature). Expansion and differentiation agents can be provided prior to, during or after administration of cells and compositions to increase production of T cells *in vitro or in vivo*.

G-protein coupled receptor (*e.g.*, GPRC5D)-specific CARs and immunoresponsive cells expressing thereof of the presently disclosed subject matter can be administered in any physiologically acceptable vehicle, normally intravascularly, although they may also be introduced into bone or other convenient site where the cells may find an appropriate site for regeneration and differentiation (*e.g.*, thymus). Usually, at least 1 x 10^5 cells can be administered, eventually reaching

1×10^{10} or more. A cell population comprising immunoresponsive cells expressing a G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR can comprise a purified population of cells. Those skilled in the art can readily determine the percentage of immunoresponsive cells in a cell population using various well-known methods, such as fluorescence activated cell sorting (FACS). The ranges of purity in cell populations comprising genetically modified immunoresponsive cells expressing a G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR can be from about 50% to about 55%, from about 55% to about 60%, from about 65% to about 70%, from about 70% to about 75%, from about 75% to about 80%, from about 80% to about 85%; from about 85% to about 90%, from about 90% to about 95%, or from about 95 to about 100%. Dosages can be readily adjusted by those skilled in the art (*e.g.*, a decrease in purity may require an increase in dosage). The immunoresponsive cells can be introduced by injection, catheter, or the like. If desired, factors can also be included, including, but not limited to, interleukins, e.g. IL-2, IL-3, IL 6, IL-11, IL-7, IL-12, IL-15, IL-21, as well as the other interleukins, the colony stimulating factors, such as G-, M- and GM-CSF, interferons, e.g., γ-interferon.

Compositions of the presently disclosed subject matter comprise pharmaceutical compositions comprising immunoresponsive cells expressing a G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR and a pharmaceutically acceptable carrier. Administration can be autologous or non-autologous. For example, immunoresponsive cells expressing a G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR and compositions comprising thereof can be obtained from one subject, and administered to the same subject or a different, compatible subject. Peripheral blood derived T cells of the presently disclosed subject matter or their progeny (e.g., *in vivo, ex vivo or in vitro* derived) can be administered via localized injection, including catheter administration, systemic injection, localized injection, intravenous injection, or parenteral administration. When administering a pharmaceutical composition of the presently disclosed subject matter (*e.g.*, a pharmaceutical composition comprising immunoresponsive cells expressing a G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR), it can be formulated in a unit dosage injectable form (solution, suspension, emulsion).

VII. Formulations

Immunoresponsive cells expressing a generally G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR and compositions comprising thereof of the presently

disclosed subject matter can be conveniently provided as sterile liquid preparations, *e.g.*, isotonic aqueous solutions, suspensions, emulsions, dispersions, or viscous compositions, which may be buffered to a selected pH. Liquid preparations are normally easier to prepare than gels, other viscous compositions, and solid compositions. Additionally, liquid compositions are somewhat more convenient to administer, especially by injection. Viscous compositions, on the other hand, can be formulated within the appropriate viscosity range to provide longer contact periods with specific tissues. Liquid or viscous compositions can comprise carriers, which can be a solvent or dispersing medium containing, for example, water, saline, phosphate buffered saline, polyol (for example, glycerol, propylene glycol, liquid polyethylene glycol, and the like) and suitable mixtures thereof.

Sterile injectable solutions can be prepared by incorporating the compositions comprising immunoresponsive cells expressing a generally G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR of the presently disclosed subject matter in the required amount of the appropriate solvent with various amounts of the other ingredients, as desired. Such compositions may be in admixture with a suitable carrier, diluent, or excipient such as sterile water, physiological saline, glucose, dextrose, or the like. The compositions can also be lyophilized. The compositions can contain auxiliary substances such as wetting, dispersing, or emulsifying agents (e.g., methylcellulose), pH buffering agents, gelling or viscosity enhancing additives, preservatives, flavoring agents, colors, and the like, depending upon the route of administration and the preparation desired. Standard texts, such as "REMINGTON'S PHARMACEUTICAL SCIENCE", 17th edition, 1985, incorporated herein by reference, may be consulted to prepare suitable preparations, without undue experimentation.

Various additives which enhance the stability and sterility of the compositions, including antimicrobial preservatives, antioxidants, chelating agents, and buffers, can be added. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, alum inurn monostearate and gelatin. According to the present invention, however, any vehicle, diluent, or additive used would have to be compatible with the

immunoresponsive cells expressing a generally G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR of the presently disclosed subject matter.

The compositions can be isotonic, i.e., they can have the same osmotic pressure as blood and lacrimal fluid. T he desired isotonicity of the compositions of the presently disclosed subject matter may be accomplished using sodium chloride, or other pharmaceutically acceptable agents such as dextrose, boric acid, sodium tartrate, propylene glycol or other inorganic or organic solutes. Sodium chloride is preferred particularly for buffers containing sodium ions.

Viscosity of the compositions, if desired, can be maintained at the selected level using a pharmaceutically acceptable thickening agent. Methylcellulose can be used because it is readily and economically available and is easy to work with. Other suitable thickening agents include, for example, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, and the like. The concentration of the thickener can depend upon the agent selected. The important point is to use an amount that will achieve the selected viscosity. Obviously, the choice of suitable carriers and other additives will depend on the exact route of administration and the nature of the particular dosage form, e.g., liquid dosage form (e.g., whether the composition is to be formulated into a solution, a suspension, gel or another liquid form, such as a time release form or liquid-filled form).

Those skilled in the art will recognize that the components of the compositions should be selected to be chemically inert and will not affect the viability or efficacy of the immunoresponsive cells as describe in the presently disclosed subject matter. This will present no problem to those skilled in chemical and pharmaceutical principles, or problems can be readily avoided by reference to standard texts or by simple experiments (not involving undue experimentation), from this disclosure and the documents cited herein.

One consideration concerning the therapeutic use of the immunoresponsive cells of the presently disclosed subject matter is the quantity of cells necessary to achieve an optimal effect. The quantity of cells to be administered will vary for the subject being treated. In certain embodiments, from about 10^4 to about 10^{10} , from about 10^5 to about 10^9, or from about 10^6 to about 10^8 immunoresponsive cells of the presently disclosed subject matter are administered to a subject. More effective cells may be administered in even smaller numbers. In some embodiments, at least about 1 x 10^8, about 2 x 10^8, about 3 x 10^8, about 4 x 10^8, and about 5 x 10^8

immunoresponsive cells of the presently disclosed subject matter are administered to a human subject. The precise determination of what would be considered an effective dose may be based on factors individual to each subject, including their size, age, sex, weight, and condition of the particular subject. Dosages can be readily ascertained by those skilled in the art from this disclosure and the knowledge in the art.

The skilled artisan can readily determine the amount of cells and optional additives, vehicles, and/or carrier in compositions and to be administered in methods of the presently disclosed subject matter. Typically, any additives (in addition to the active cell(s) and/or agent(s)) are present in an amount of from about 0.001% to about 50% by weight) solution in phosphate buffered saline, and the active ingredient is present in the order of micrograms to milligrams, such as from about 0.0001 wt% to about 5 wt %, from about 0.0001 wt% to about 1 wt %, from about 0.0001 wt% to about 0.05 wt%, from about 0.001 wt% to about 20 wt %, from about 0.01 wt% to about 10 wt %, or from about 0.05 wt% to about 5 wt %. For any composition to be administered to an animal or human, and for any particular method of administration, toxicity should be determined, such as by determining the lethal dose (LD) and LD50 in a suitable animal model e.g., rodent such as mouse; and, the dosage of the composition(s), concentration of components therein and timing of administering the composition(s), which elicit a suitable response. Such determinations do not require undue experimentation from the knowledge of the skilled artisan, this disclosure and the documents cited herein. And, the time for sequential administrations can be ascertained without undue experimentation.

VIII. Methods of Treatment

Tumor Microenvironment. Tumors have a microenvironment that is hostile to the host immune response involving a series of mechanisms by malignant cells to protect themselves from immune recognition and elimination. This "hostile tumor microenvironment" comprises a variety of immune suppressive factors including infiltrating regulatory $CD4^+$ T cells (Tregs), myeloid derived suppressor cells (MDSCs), tumor associated macrophages (TAMs), immune suppressive cytokines including IL-10 and TGF-β, and expression of ligands targeted to immune suppressive receptors expressed by activated T cells (CTLA-4 and PD-1). These mechanisms of immune suppression play a role in the maintenance of tolerance and suppressing inappropriate immune responses, however within the tumor microenvironment these mechanisms prevent an effective anti-tumor immune

response. Collectively these immune suppressive factors can induce either marked anergy or apoptosis of adoptively transferred CAR modified T cells upon encounter with targeted tumor cells.

Challenges in tumor immunology. Effective tumor immunity requires recognition of tumor antigens and unopposed tumor elimination by immune effector cells. Tumor antigens must contain peptide epitopes that are presented by the tumor and can be recognized by specific cytotoxic T lymphocytes (CTLs). The primed CTLs must expand to a sufficient number and migrate to tumor sites, wherein they mature into effectors to perform their functions, which are enhanced by helper T cells and dampened by Tregs and inhibitory macrophages.

Targeted T cell therapy with engineered T lymphocytes. T cell engineering is a groundbreaking strategy to potentially resolve many previously observed shortcomings of earlier immunotherapeutic approaches. Within the past year, researchers have reported dramatic complete remissions in relapsed[17,18], chemorefractory leukemia and metastatic melanoma[19-21], obtained with autologous peripheral blood T cells targeted to a defined antigen (CD19 and NY-ESO-1, respectively).

Rationale for a genetic approach: Cell engineering can be used to redirect T cells toward tumor antigens and to enhance T cell function. One impetus for genetic T cell modification is the potential to enhance T cell survival and expansion and to offset T cell death, anergy, and immune suppression. The genetic targeting of T cells can also be refined to prevent undesired destruction of normal tissues.

Chimeric antigen receptors (CARs): Tumor-specific T cells can be generated by the transfer of genes that encode CARs[22-27]. Second-generation CARs comprise a tumor antigen-binding domain fused to an intracellular signaling domain capable of activating T cells and a co-stimulatory domain designed to augment T cell potency and persistence[28]. CAR design can therefore reconcile antigen recognition with signal transduction, two functions that are physiologically borne by two separate complexes, the TCR heterodimer and the CD3 complex. The CAR's extracellular antigen-binding domain is usually derived from a murine monoclonal antibody (mAb) or from receptors or their ligands. Antigen recognition is therefore not MHC-restricted[29,30] and is therefore applicable to any patient expressing the target antigen, using the same CAR. Antigen binding by the CARs triggers phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) in the intracellular domain, initiating a

signaling cascade required for cytolysis induction, cytokine secretion, and proliferation. Because MHC restriction of antigen recognition is bypassed, the function of CAR-targeted T cells is not affected by HLA downregulation or defects in the antigen-processing machinery.

T cell requirements for expansion and survival: Proliferation of tumor-specific T cells is needed *ex vivo* and is arguably desirable *in vivo*. T cell proliferation must be accompanied by T cell survival to permit absolute T cell expansion and persistence. To proliferate in response to antigen, T cells must receive two signals. One is provided by TCR recognition of antigenic peptide/MHC complexes displayed on the surface of antigen-presenting cells (APCs)[26]. The other is provided by a T cell co-stimulatory receptor, such as the CD28 or 4-1BB receptors. Whereas the cytolytic activity of T cells does not require concomitant co-stimulation, there is a critical need for the provision of co-stimulatory signals to sustain the antitumor functions of adoptively transferred T cells, as previously demonstrated[24,28,31-33].

Immune monitoring: Lymphocytes are multifunctional "drugs" that exhibit dynamically evolving effects after infusion. Upon antigen encounter, tumor-specific T cells activate and/or release a variety of proteins that can trigger tumor killing, T cell proliferation, and recruitment or immunomodulation of other immune cells. Thus, measuring which proteins are secreted from which cells, in what quantity, and at what time point yields profound insights into why a particular patient is or is not responding and provides critical feedback for designing more-effective trials. These assay systems will permit direct and meaningful comparisons of clinical approaches and thus help design rational, next-generation therapeutic strategies.

For treatment, the amount administered is an amount effective in producing the desired effect. An effective amount can be provided in one or a series of administrations. An effective amount can be provided in a bolus or by continuous perfusion.

An "effective amount" (or, "therapeutically effective amount") is an amount sufficient to affect a beneficial or desired clinical result upon treatment. An effective amount can be administered to a subject in one or more doses. In terms of treatment, an effective amount is an amount that is sufficient to palliate, ameliorate, stabilize, reverse or slow the progression of the disease, or otherwise reduce the pathological consequences of the disease. The effective amount is generally determined by the physician on a case-by-case basis and is within the skill of one in the art. Several

factors are typically taken into account when determining an appropriate dosage to achieve an effective amount. These factors include age, sex and weight of the subject, the condition being treated, the severity of the condition and the form and effective concentration of the immunoresponsive cells administered.

For adoptive immunotherapy using antigen-specific T cells, cell doses in the range of about 10^6 to about 10^{10} (e.g., about 10^9) are typically infused. Upon administration of the immunoresponsive cells into the subject and subsequent differentiation, the immunoresponsive cells are induced that are specifically directed against one specific antigen (*e.g.*, a G-protein coupled receptor (*e.g.*, GPRC5D)). "Induction" of T cells can include inactivation of antigen-specific T cells such as by deletion or anergy. Inactivation is particularly useful to establish or reestablish tolerance such as in autoimmune disorders. The immunoresponsive cells of the presently disclosed subject matter can be administered by any methods known in the art, including, but not limited to, pleural administration, intravenous administration, subcutaneous administration, intranodal administration, intratumoral administration, intrathecal administration, intrapleural administration, intraperitoneal administration, and direct administration to the thymus. In certain embodiments, the immunoresponsive cells and the compositions comprising thereof are intravenously administered to the subject in need.

The presently disclosed subject matter provides various methods of using the immunoresponsive cells (*e.g.*, T cells) expressing a G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR. For example, the presently disclosed subject matter provides methods of reducing tumor burden in a subject. In one non-limiting example, the method of reducing tumor burden comprises administering an effective amount of the presently disclosed immunoresponsive cell to the subject, thereby inducing tumor cell death in the subject. The presently disclosed immunoresponsive cell can reduce the number of tumor cells, reduce tumor size, and/or eradicate the tumor in the subject. Non-limiting examples of suitable tumor include multiple myeloma Waldenstrom's Macroglobulinemia. In certain embodiments, the tumor is multiple myeloma.

The presently disclosed subject matter also provides methods of increasing or lengthening survival of a subject having a neoplasia. In one non-limiting example, the method of increasing or lengthening survival of a subject having neoplasia comprises administering an effective amount of the presently disclosed

immunoresponsive cell to the subject, thereby increasing or lengthening survival of the subject. The method can reduce or eradicate tumor burden in the subject. The presently disclosed subject matter further provides methods for treating or preventing a neoplasia in a subject, comprising administering the presently disclosed immunoresponsive cell to the subject.

As used herein, the term "neoplasia" refers to a disease characterized by the pathological proliferation of a cell or tissue and its subsequent migration to or invasion of other tissues or organs. Neoplasia growth is typically uncontrolled and progressive, and occurs under conditions that would not elicit, or would cause cessation of, multiplication of normal cells. Neoplasias can affect a variety of cell types, tissues, or organs, including but not limited to an organ selected from the group consisting of bladder, colon, bone, brain, breast, cartilage, glia, esophagus, fallopian tube, gallbladder, heart, intestines, kidney, liver, lung, lymph node, nervous tissue, ovaries, pleura, pancreas, prostate, skeletal muscle, skin, spinal cord, spleen, stomach, testes, thymus, thyroid, trachea, urogenital tract, ureter, urethra, uterus, and vagina, or a tissue or cell type thereof. Neoplasias include cancers, such as sarcomas, carcinomas, or plasmacytomas (malignant tumor of the plasma cells).

Cancers whose growth may be inhibited using the immunoresponsive cells of the presently disclosed subject matter comprise cancers typically responsive to immunotherapy. Non-limiting examples of cancers for treatment include multiple myeloma and Waldenstrom's Macroglobulinemia. In certain embodiments, the cancer is multiple myeloma.

Additionally, the presently disclosed subject matter provides methods of increasing immune-activating cytokine production in response to a cancer cell in a subject. In one non-limiting example, the method comprises administering the presently disclosed immunoresponsive cell to the subject. The immune-activating cytokine can be granulocyte macrophage colony stimulating factor (GM-CSF), IFN-α, IFN-β, IFN-γ, TNF-α, IL-2, IL-3, IL-6, IL-11, IL-7, IL-12, IL-15, IL-21, interferon regulatory factor 7 (IRF7), and combinations thereof. In certain embodiments, the immunoresponsive cells including a G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR of the presently disclosed subject matter increase the production of GM-CSF, IFN-γ, and/or TNF-α.

Suitable human subjects for therapy typically comprise two treatment groups that can be distinguished by clinical criteria. Subjects with "advanced disease" or

"high tumor burden" are those who bear a clinically measurable tumor (*e.g.*, multiple myeloma). A clinically measurable tumor is one that can be detected on the basis of tumor mass (*e.g.*, by palpation, CAT scan, sonogram, mammogram or X-ray; positive biochemical or histopathologic markers on their own are insufficient to identify this population). A pharmaceutical composition embodied in the presently disclosed subject matter is administered to these subjects to elicit an anti-tumor response, with the objective of palliating their condition. Ideally, reduction in tumor mass occurs as a result, but any clinical improvement constitutes a benefit. Clinical improvement comprises decreased risk or rate of progression or reduction in pathological consequences of the tumor (*e.g.*, multiple myeloma).

A second group of suitable subjects is known in the art as the "adjuvant group." These are individuals who have had a history of neoplasia (*e.g.*, multiple myeloma), but have been responsive to another mode of therapy. The prior therapy can have included, but is not restricted to, surgical resection, radiotherapy, and traditional chemotherapy. As a result, these individuals have no clinically measurable tumor. However, they are suspected of being at risk for progression of the disease, either near the original tumor site, or by metastases. This group can be further subdivided into high-risk and low-risk individuals. The subdivision is made on the basis of features observed before or after the initial treatment. These features are known in the clinical arts, and are suitably defined for each different neoplasia. Features typical of high-risk subgroups are those in which the tumor (*e.g.*, multiple myeloma) has invaded neighboring tissues, or who show involvement of lymph nodes. Another group has a genetic predisposition to neoplasia (*e.g.*, multiple myeloma) but has not yet evidenced clinical signs of neoplasia (*e.g.*, multiple myeloma). For instance, women testing positive for a genetic mutation associated with breast cancer, but still of childbearing age, can wish to receive one or more of the antigen-binding fragments described herein in treatment prophylactically to prevent the occurrence of neoplasia until it is suitable to perform preventive surgery.

The subjects can have an advanced form of disease (*e.g.*, multiple myeloma), in which case the treatment objective can include mitigation or reversal of disease progression, and /or amelioration of side effects. The subjects can have a history of the condition, for which they have already been treated, in which case the therapeutic objective will typically include a decrease or delay in the risk of recurrence.

Further modification can be introduced to the G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR-expressing immunoresponsive cells (*e.g.*, T cells) to avert or minimize the risks of immunological complications (known as "malignant T-cell transformation"), *e.g.*, graft versus-host disease (GvHD), or when healthy tissues express the same target antigens as the tumor cells, leading to outcomes similar to GvHD. A potential solution to this problem is engineering a suicide gene into the CAR-expressing T cells. Suitable suicide genes include, but are not limited to, Herpes simplex virus thymidine kinase (hsv-tk), inducible Caspase 9 Suicide gene (iCasp-9), and a truncated human epidermal growth factor receptor (EGFRt) polypeptide. In certain embodiments, the suicide gene is an EGFRt polypeptide. The EGFRt polypeptide can enable T cell elimination by administering anti-EGFR monoclonal antibody (*e.g.*, cetuximab). EGFRt can be covalently joined to the 3' terminus of the intracellular domain of the G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR. The suicide gene can be included within the vector comprising nucleic acids encoding the presently disclosed G-protein coupled receptor (*e.g.*, GPRC5D)-specific CARs. In this way, administration of a prodrug designed to activate the suicide gene (e.g., a prodrug (e.g., AP1903 that can activates iCasp-9) during malignant T-cell transformation (*e.g.*, GVHD) triggers apoptosis in the suicide gene-activated CAR-expressing T cells.

IX. Kits

The presently disclosed subject matter provides kits for the treatment or prevention of a neoplasia (*e.g.*, multiple myeloma). In certain embodiment, the kit comprises a therapeutic or prophylactic composition containing an effective amount of an immunoresponsive cell comprising a G-protein coupled receptor (*e.g.*, GPRC5D)-specific CAR in unit dosage form. In particular embodiments, the cells further expresses at least one co-stimulatory ligand. In certain embodiments, the kit comprises a sterile container which contains a therapeutic or prophylactic vaccine; such containers can be boxes, ampules, bottles, vials, tubes, bags, pouches, blister-packs, or other suitable container forms known in the art. Such containers can be made of plastic, glass, laminated paper, metal foil, or other materials suitable for holding medicaments.

If desired, the immunoresponsive cell is provided together with instructions for administering the cell to a subject having or at risk of developing a neoplasia (*e.g.*,

multiple myeloma). The instructions will generally include information about the use of the composition for the treatment or prevention of a neoplasia (*e.g.*, multiple myeloma). In other embodiments, the instructions include at least one of the following: description of the therapeutic agent; dosage schedule and administration for treatment or prevention of a neoplasia (*e.g.*, multiple myeloma) or symptoms thereof; precautions; warnings; indications; counter-indications; overdosage information; adverse reactions; animal pharmacology; clinical studies; and/or references. The instructions may be printed directly on the container (when present), or as a label applied to the container, or as a separate sheet, pamphlet, card, or folder supplied in or with the container.

EXAMPLES

The practice of the present invention employs, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are well within the purview of the skilled artisan. Such techniques are explained fully in the literature, such as, "Molecular Cloning: A Laboratory Manual", second edition (Sambrook, 1989); "Oligonucleotide Synthesis" (Gait, 1984); "Animal Cell Culture" (Freshney, 1987); "Methods in Enzymology" "Handbook of Experimental Immunology" (Weir, 1996); "Gene Transfer Vectors for Mammalian Cells" (Miller and Calos, 1987); "Current Protocols in Molecular Biology" (Ausubel, 1987); "PCR: The Polymerase Chain Reaction", (Mullis, 1994); "Current Protocols in Immunology" (Coligan, 1991). These techniques are applicable to the production of the polynucleotides and polypeptides of the invention, and, as such, may be considered in making and practicing the invention. Particularly useful techniques for particular embodiments will be discussed in the sections that follow.

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the assay, screening, and therapeutic methods of the invention, and are not intended to limit the scope of what the inventors regard as their invention.

Example 1 – GPRC5D Expression in various tissues

The Expression of human GPRC5D was evaluated in various malignant and normal tissues by investigating gene expression profiles in databases such as the cancer cell line encyclopedia and BioGPS. As shown in Figure 2, human GPRC5D

was highly expressed in multiple myeloma, but not in other malignant tissues. Normal expression appeared limited to plasma cells. Potential GPRC5D targeted CAR T cell eradication of this normal cell type may not have significant adverse effects based on inventors' patient experience with CD19 targeted CAR T cells. Any lack of physiologic antibody production can be addressed with intravenous immunoglobulin treatment.

Example 2 – Construct of GPRC5D-specific 28z CARs

Multiple unique fully human scFv's to GPRC5D were generated, and CARs based on these scFv's were generated. Multiple scFv's were identified by screening a fully human scFv phage library (> 6 x 10^{10} scFv's) with 3T3 cells expressing GPRC5D. Four independent pannings with 12 different phage libraries were carried out against GPRC5D overexpressing 3T3 cells identifying 80 positive clones. 72 positive clones were identified out of 80 clones screened FACS; the positive clone rate was 90%. After sequencing, 32 unique and GPRC5D-3T3 positive binding clones were found out of 72 sequenced positive clones; the unique clone rate was 45%.

ET150-151 scFv (or "ET150-1 scFv"), ET150-152 scFv (or "ET150-2 scFv"), ET150-155 scFv (or "ET150-5 scFv"), ET150-158 (or "ET150-8 scFv")scFv, and ET150-168 scFv (or "ET150-18 scFv") were used to generate GPRC5D-targeted 28z CARs 2, 5, 8, and 18, respectively. These GPRC5D-targeted 28z CARs have similar structure, *e.g.*, each has a transmembrane domain comprising a CD28 polypeptide, and an intracellular domain comprising a CD3ξ polypeptide and a co-stimulatory signaling region that comprises a CD28 polypeptide, as shown in Figure 1. Each of these GPRC5D-targeted CARs were cloned into a retroviral vector. These viral vectors were then transduced into HEK 293galv9 viral packaging cells in order to generate a stable packaging line for generation of CAR^+ T cells.

Human T cells (unselected (CD4 and CD8) human T cells from a healthy donor) were transduced with each of these GPRC5D-targeted 28z CARs such that the T cells expressed these GPRC5D-targeted CARs.

The cell surface expression of GPRC5D-targeted 28z CAR18 on human T cells via binding human GPRC5D was assessed, and cell surface detection was validated by flow cytometry, as shown in Figure 3.

Example 3 – Activity of GPRC5D-specific 28z CARs

The anti-tumor activity of the presently disclosed GPRC5D-specific 28z CARs was evaluated. The *in vitro* data showed that the GPRC5D-specific CARs specifically killed GPRC5D presenting cells, including MM cell lines. For example, as shown in Figure 4, the T cells expressing the GPRC5D-specific 28z CAR18 killed 3T3 cells overexpressing GPRC5D (but not control 3T3s overexpressing another antigen). As shown in Figure 5, the T cells expressing the GPRC5D-specific 28z CARs 2, 5, 8, and 18 killed human MM cell lines.

Example 4 – Screening Data for Anti-GPRC5D Antibodies

FACS Screening: Figure 24 shows FACS analysis of GPRC5D-specific phage antibody clones (ET150-1, ET150-2, ET150-5, ET150-8, ET150-18). Phage clones were incubated with 3T3-GPRC5D cell line, then with anti-M13 mouse antibody. Finally APC-labeled anti-mouse IgG 2nd antibody was added to the reaction after washing again. The binding was measured by FACS and expressed as mean fluorescence intensity (MFI). Cells incubated with M13 K07 helper phage and cells only were used as negative controls.

Example 5 – Construct of GPRC5D-specific BBz CARs

Multiple unique fully human scFv's to GPRC5D were generated, and CARs based on these scFv's were generated as described in Example 2. ET150-151 scFv (or "ET150-1 scFv"), ET150-152 scFv (or "ET150-2 scFv"), ET150-155 scFv (or "ET150-5 scFv"), ET150-158 scFv (or "ET150-8 scFv"), and ET150-168 scFv (or "ET150-18 scFv") were used to generate GPRC5D-targeted BBz CARs 1, 2, 5, 8, and 18, respectively. These GPRC5D-targeted BBz CARs have similar structure, *e.g.*, each has a transmembrane domain comprising a CD8a polypeptide, and an intracellular domain comprising a CD3ξ polypeptide and a co-stimulatory signaling region that comprises a 4-1BB polypeptide, as shown in Figure 6. Each of these GPRC5D-targeted BBz CARs were cloned into an SFG retroviral vector, as shown in Figures 7-9, 26 and 27.

Example 6 – Activity of GPRC5D-targeted CAR T cells

As shown in Figure 10, GPRC5D 28z CAR8 lysed human MM cell lines L363, NCL-H929, and U266, compared to irrelevantly targeted 4h11-28z MUC16 targeted CAR T cells. The cytotoxicity exhibited by observed GPRC5D 28z CAR8 was specific to GPRC5D, as it did not lyse GPRC5D negative CD19 positive Raji Burkett lymphoma cell line, as shown in Figure 10.

Example 7 – Induction of Cytokine Secretion by GPRC5D-targeted CAR T cells

Co-culture of GPRC5D 28z CAR8 T cells specifically with MM cell line induced cytokine secretion profile consistent with T cell activation. Figure 11 shows the IL-2 secretion after 24h co-culture of CAR T cells with human tumor cell lines (E:T ratio 1:1). Only the lymphoplasmacytic lymphoma ($CD19^+$ $GPRC5D^-$) with CD19 targeted CAR T cells (positive control) and the MM cell line with the GPRC5D targeted 28z CAR8 T cells displayed increased cytokine production. IFNg, IL-6, TNFa, sCD40L, GM-CSF all had similar secretion profiles (data not shown).

Example 8 – Anti-tumor activity of GPRC5D-targeted CAR T cells

GPRC5D targeted 28z CAR18 T cells mediated an anti-myeloma immune response. $1x10^7$ U266 human myeloma cell line cells were injected IV into NSG mice on day 0. On day 4 $1x10^6$ GPRC5D targeted or CD19 targeted second generation CAR T cells were injected IV. Imaging on day 11 (day 7 s/p CAR T cell injection) shows that, unlike irrelevant (CD19) targeted CAR T cells; GPRC5D A targeted 28z CAR18 T cells can mediate an anti-tumor response. *See* Figure 12.

Example 9 – Activity of GPRC5D-targeted CAR T cells

The ability of GPRC5D targeted CAR T cells to specifically lyse human myeloma cell line (HMCL) was tested. CD19 targeted CAR T cells or GPRC5D targeted 28z CAR8 T cells were incubated with GFP expressing tumor cell lines SET2 (Acute myeloid leukemia (AML), CD19-GPRC5D-); BCWM1 (Lymphoplasmacytic Lymphoma (LPL), CD19-GPRC5D-); L363 (Multiple Myeloma (MM), CD19-GPRC5D+). At time 0, the percent of GFP^+ tumor line is shown in Figure 13A. At 36h the positive control CD19 targeted CAR T cells have specifically killed the GFP^+ LPL line, and similarly the GPRC5D targeted 28z CAR8 T cells have specifically killed the GFP^+ MM line. *See* Figure 13B.

Example 10 -- Epitope Mapping of Anti-GPRC5D Antibodies

Four anti-GPRC5D antibodies: ET150-2, ET150-5, ET150-8, and ET150-18 mIgG1. "mIgG1" used in all Examples represents that the variable region is fully human and the Fc part is mouse IgG1. *See* Table 37.

Table 37

Name	Species	Concentration	Temperature	Stored
ET150-18 mIgG1	mouse Fc	1,1 mg/ml	+4°C/22	ok
ET150-2 mIgG1	mouse Fc	0,56 mg/ml	+4°C/22	ok
ET150-5 mIgG1	mouse Fc	1,9 mg/ml	+4°C/22	ok
ET150-8 mIgG1	mouse Fc	2,9 mg/ml	+4°C/22	ok

The target protein is human GPRC5D having the amino acid sequence set forth in SEQ ID NO: 97. The N-terminal region of human GPRC5D has amino acids 1-27 of SEQ ID NO:97. The extracellular loop 1 (ECL1) region of human GPRC5D has amino acids 85-93 of SEQ ID NO:97. The extracellular loop 2 (ECL2) region of human GPRC5D has amino acids 145-167 of SEQ ID NO:97. The extracellular loop 3 (ECL3) region of human GPRC5D has amino acids 226-239 of SEQ ID NO:97.

Methods

The principles of clips technology -- CLIPS technology structurally fixes peptides into defined three-dimensional structures. This results in functional mimics of even the most complex binding sites. CLIPS technology is now routinely used to shape peptide libraries into single, double or triple looped structures as well as sheet- and helix-like folds (Figure 14).

Combinatorial clips library screening in detail -- CLIPS library screening starts with the conversion of the target protein into a library of up to 10,000 overlapping peptide constructs, using a combinatorial matrix design. On a solid carrier, a matrix of linear peptides is synthesized, which are subsequently shaped into spatially defined CLIPS constructs (Figure 15). Constructs representing both parts of the discontinuous epitope in the correct conformation bind the antibody with high affinity, which is detected and quantified. Constructs presenting the incomplete epitope bind the antibody with lower affinity, whereas constructs not containing the epitope do not bind at all. Affinity information is used in iterative screens to define the sequence and conformation of epitopes in detail.

Heat map analysis -- A heat map is a graphical representation of data where the values taken by a variable in a two-dimensional map are represented as colors. For double-looped CLIPS peptides, such a two-dimensional map can be derived from the independent sequences of the first and second loops. For example, the sequences of the 16 CLIPS peptides depicted in Figure 17 are effectively permutations of 4 unique sub-sequences in loop 1 (colored in blue in Figure 16) and 4 unique sub-sequences in loop 2 (colored in green in Figure 16). Thus, the observed ELISA data (colored in red in Figure 17A) can be plotted in a 4x4 matrix, where each X coordinate corresponds to the sequence of the first loop, and each Y coordinate corresponds to the sequence of the second loop. For instance, the ELISA value observed for CLIPS peptide CLSSERERVEDLFEYECELLTSEPIFHCRQEDC (indicated with an arrow in Figure 4A) can be found at the third row, third column of

Figure 17B (indicated with an arrow and a red square). To further facilitate the visualization, ELISA values can be replaced with colors from a continuous gradient. In this case, extremely low values are colored in green, extremely high values are colored in red, and average values are colored in black (see Figure 17C). For the aforementioned example, the average value is 0.71. When this color map is applied to the data matrix depicted in Figure 17B, a color heat map is obtained (see Figure 17D, the original data is still indicated for extra clarity).

Synthesis of peptides -- To reconstruct epitopes of the target molecule a library of peptides was synthesized. An amino functionalized polypropylene support was obtained by grafting with a proprietary hydrophilic polymer formulation, followed by reaction with t-butyloxycarbonyl-hexamethylenediamine (BocHMDA) using dicyclohexylcarbodiimide (DCC) with Nhydroxybenzotriazole (HOBt) and subsequent cleavage of the Boc-groups using trifluoroacetic acid (TFA). Standard Fmoc-peptide synthesis was used to synthesize peptides on the amino-functionalized solid support by custom modified JANUS liquid handling stations (Perkin Elmer). Synthesis of structural mimics was done using Pepscan's proprietary Chemically Linked Peptides on Scaffolds (CLIPS) technology. CLIPS technology allows to structure peptides into single loops, doubleloops, triple loops, sheet-like folds, helix-like folds and combinations thereof. CLIPS templates are coupled to cysteine residues. The side-chains of multiple cysteines in the peptides were coupled to one or two CLIPS templates. For example, a 0.5 mM solution of the P2 CLIPS (2,6-bis(bromomethyl)pyridine) was dissolved in ammonium bicarbonate (20 mM, pH 7.8)/acetonitrile (1:3(v/v)). This solution was added onto the peptide arrays. The CLIPS template bound to side-chains of two cysteines as present in the solid-phase bound peptides of the peptide-arrays (455 wells plate with 3 µl wells). The peptide arrays were gently shaken in the solution for 30 to 60 minutes while completely covered in solution. Finally, the peptide arrays were washed extensively with excess of H_2O and sonicated in disrupt-buffer containing 1 % SDS/0.1 % beta-mercaptoethanol in PBS (pH 7.2) at 70°C for 30 minutes, followed by sonication in H_2O for another 45 minutes. The T3 CLIPS carrying peptides were made in a similar way but now with three cysteines.

ELISA Screening -- The binding of antibody to each of the synthesized peptides was tested in a PEPSCAN-based ELISA. The peptide arrays were incubated with primary antibody solution (overnight at 4°C). After washing, the peptide arrays

were incubated with a 1/1000 dilution of an appropriate antibody peroxidase conjugate (SBA) for one hour at 25°C. After washing, the peroxidase substrate 2,2'-azino-di-3-ethylbenzthiazoline sulfonate (ABTS) and 2 µl/ml of 3 percent H_2O_2 were added. After one hour, the color development was measured. The color development was quantified with a charge coupled device (CCD) - camera and an image processing system.

Data processing -- the values obtained from the CCD camera ranged from 0 to 3000 mAU, similar to a standard 96-well plate ELISA-reader. The results were quantified and stored into the Peplab database. Occasionally a well contained an air-bubble resulting in a false-positive value, the cards were manually inspected and any values caused by an air-bubble were scored as 0.

Synthesis quality control -- To verify the quality of the synthesized peptides, a separate set of positive and negative control peptides was synthesized in parallel. These were screened with antibody 57.9 (ref. Posthumus et al., J. Virology, 1990, 64:3304-3309).

Results

Screening

Antibody binding depends on a combination of factors, including concentration of the antibody and the amounts and nature of competing proteins in the ELISA buffer. Also, the pre-coat conditions (the specific treatment of the peptide arrays prior to incubation with the experimental sample) affected binding. These details are summed up in Table 38. For the Pepscan Buffer and Preconditioning (SQ), the numbers indicate the relative amount of competing protein (a combination of horse serum and ovalbumin).

Table 38 -- screening condition

Label	Dilution	Sample buffer	Pre-conditioning
ET150-18 mIgG1	1 µg/ml	1% SQ	1% SQ
ET150-2 mIgG1	1 µg/ml	10% SQ	10% SQ
ET150-5 mIgG1	1 µg/ml	10% SQ	10% SQ
ET150-8 mIgG1	3 µg/ml	10% SQ	10% SQ

Antibody ET150-2

When tested under moderate stringency conditions antibody ET150-2 avidly bound peptides from all sets (Figure 18). Cumulative data analysis shows that the antibody recognize a discontinuous epitope composed of peptides stretches

$_{16}$CDAEGPWGII$_{25}$ (N-term), $_{157}$MFVNMTPC$_{164}$ (ECL2) and $_{229}$PQFQRQPQW$_{237}$ (ECL3), where peptide stretches $_{16}$CDAEGPWGII$_{25}$ and $_{229}$PQFQRQPQW$_{237}$ alone suffice for binding.

Antibody ET150-5

When tested under high stringency conditions antibody ET150-5 avidly bound peptides from all sets (Figure 19). Cumulative data analysis shows that the antibody recognizes a discontinuous epitope composed of peptide stretches $_{5}$CIESTGDYFLLCD$_{17}$ (N-term), $_{85}$NQQTAPVRYFL$_{95}$ (ECL1) and $_{157}$MFVNMTPC$_{164}$ (ECL2), where peptide stretch $_{5}$CIESTGDYFLCD$_{17}$ alone suffices for binding.

Antibody ET150-18

When tested under high stringency conditions antibody ET150-18 bound peptides from set 4 and set 7, containing structurally constrained peptides. No significant binding was recorded on sets containing linear peptides (Figure 20). Cumulative data analysis shows that the antibody recognizes a discontinuous epitope composed of stretches $_{10}$GDYFLLCD$_{17}$ (N-term), $_{157}$MFVNMTPCQLN$_{167}$ (ECL2) and $_{227}$GNPQFQRQPQW$_{237}$ (ECL3). Peptide stretches $_{10}$GDYFLLCD$_{17}$ and $_{227}$GNPQFQRQPQW$_{237}$ represent the epitope's core, as both peptide stretches separately suffice for binding.

Antibody ET150-8

When tested under high stringency conditions antibody ET150-8 bound peptides from all sets, except for set 2 (Figure 21). Cumulative data analysis shows that the antibody recognizes a discontinuous epitope composed of peptides stretches $_{15}$LCDAEGPWG$_{23}$ (N-term) and $_{230}$QFQRQPQWDDPVVC$_{243}$ (ECL3) where peptide stretch $_{15}$LCDAEGPWG$_{23}$ is the dominant part of the epitope, as it alone suffices for binding. Moreover, comparison of the results obtained on set 1 (linear) and set 4 (loop) shows that introduction of structural constrains to epitope mimics enhances binding of peptides, especially in case of peptides containing sequence $_{230}$QFQRQPQWDDPVVC$_{243}$.

Conclusions

All antibodies investigated recognized discontinuous epitopes, which were mapped using Pepscan arrays. Core tentative epitopes are listed in Table 39. All antibodies commonly recognized overlapping regions at the N-terminus of the protein in combination with regions from one or two ECLs. Two antibodies ET150-18 and

ET150-8 showed a requirement for structural constraints to support antibody binding, suggesting that these two antibodies recognize not only discontinuous, but also conformational epitopes. Antibodies ET150-2 and ET150-5 did not show notable discrepancies in peptide binding between linear and looped peptides.

Table 39 - list of epitopes

Antibody	N-terminus	ECL1	ECL2	ECL3
ET150-2	$_{12}$CDAEGPWGI$_{22}$*	-	$_{157}$MFVNMTPC$_{164}$	$_{232}$PQFQRQPQW$_{241}$*
ET150-5	$_{1}$CIESTGDYFLLCD$_{13}$*	$_{86}$NQQTAPVRYFL$_{96}$	$_{157}$MFVNMTPC$_{164}$	-
ET150-8	$_{12}$LCDAEGPWG$_{22}$*	-	-	$_{230}$QFQRQPQWDDPVVC$_{243}$
ET150-18	$_{10}$GDYFLLCD$_{17}$*	-	$_{157}$MFVNMTPCQLN$_{167}$	$_{227}$GNPQFQRQPQW$_{237}$*

*dominant part

Figure 22 is an illustration of the results of the study with respect to overall organization of GPCRs. As the N-terminus is highly flexible and unstructured, it likely transiently interacts with ECLs forming discontinuous immunodominant regions.

Differences and commonalities in peptide binding can be illustrated with a scatter plot analysis in Figure 23. Data points in the top left and bottom right corners point to the differences in the binding. Despite significant epitope overlap, the fine specificities of epitopes of the individual antibodies differ to a large extent.

Example 11 -- Binding Affinity of Anti-GPRC5D Antibodies

Figure 25 shows FACS analysis of GPRC5D-specific phage antibody clones (ET150-2, ET150-5, ET150-8, ET150-18). Each antibodies (ET150-2, ET150-5, ET150-8, ET150-18) were incubated with 3T3 or 3T3-GPRC5D cells at 10 or 1 ug/mL, then with anti-M13 mouse antibody. Finally PE-labeled anti-mouse IgG 2nd antibody was added to the reaction. The binding was measured by FACS and expressed as mean fluorescence intensity (MFI). Cells incubated with 2nd antibody alone, ET901 mIgG1 isotype control and cells only were used as negative controls.

Although the foregoing presently disclosed subject matter has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the presently disclosed subject matter. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.

References

1. Atamaniuk, J., *et al.* Overexpression of G protein-coupled receptor 5D in the bone marrow is associated with poor prognosis in patients with multiple myeloma. *European journal of clinical investigation* **42**, 953-960 (2012).

2. Frigyesi, I., *et al.* Robust isolation of malignant plasma cells in multiple myeloma. *Blood* **123**, 1336-1340 (2014).

3. Cohen, Y., Gutwein, O., Garach-Jehoshua, O., Bar-Haim, A. & Kornberg, A. GPRC5D is a promising marker for monitoring the tumor load and to target multiple myeloma cells. *Hematology (Amsterdam, Netherlands)* **18**, 348-351 (2013).

4. Bam, R., *et al.* GPRC5D Is a Cell Surface Plasma Cell Marker Whose Expression Is High In Myeloma Cells and Reduced Following Coculture With Osteoclasts. *Blood* **122**, 3099 (2013).

5. Brentjens, R.J., *et al.* Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. *Blood* **118**, 4817-4828 (2011).

6. Brentjens, R.J., *et al.* Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15. *Nature medicine* **9**, 279-286 (2003).

7. Brentjens, R.J., *et al.* CD19-Targeted T Cells Rapidly Induce Molecular Remissions in Adults with Chemotherapy-Refractory Acute Lymphoblastic Leukemia. *Science translational medicine* **5**, 177ra138 (2013).

8. Davila, M.L., *et al.* Efficacy and Toxicity Management of 19-28z CAR T Cell Therapy in B Cell Acute Lymphoblastic Leukemia. *Science translational medicine* **6**, 224ra225 (2014).

9. Siegel, R., Naishadham, D. & Jemal, A. Cancer statistics, 2013. *CA: a cancer journal for clinicians* **63**, 11-30 (2013).

10. Boyd, K.D., *et al.* The clinical impact and molecular biology of del(17p) in multiple myeloma treated with conventional or thalidomide-based therapy. *Genes, chromosomes & cancer* **50**, 765-774 (2011).

11. Shaughnessy, J.D., Jr., *et al.* A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. *Blood* **109**, 2276-2284 (2007).

12. Gahrton, G., *et al.* Allogeneic bone marrow transplantation in multiple myeloma. European Group for Bone Marrow Transplantation. *The New England journal of medicine* **325**, 1267-1273 (1991).

13. Pegram, H.J., *et al.* Tumor-targeted T cells modified to secrete IL-12 eradicate systemic tumors without need for prior conditioning. *Blood* **119**, 4133-4141 (2012).

14. Sabrina Bertilaccio, M.T., *et al.* Low-Dose Lenalidomide Improves CAR-Based Immunotherapy In CLL By Reverting T-Cell Defects In Vivo. *Blood* **122**, 4171 (2013).

15. Bataille, R., *et al.* The phenotype of normal, reactive and malignant plasma cells. Identification of "many and multiple myelomas" and of new targets for myeloma therapy. *Haematologica* **91**, 1234-1240 (2006).

16. Morgan, R.A., *et al.* Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. *Molecular therapy : the journal of the American Society of Gene Therapy* **18**, 843-851 (2010).

17. Brentjens, R.J., *et al.* Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. *Blood* **118**, 4817-4828 (2011).

18. Brentjens, R.J., *et al.* CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Science translational medicine* **5**, 177ra138 (2013).

19. Hunder, N.N., *et al.* Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. *N.Engl.J.Med.* **358**, 2698-2703 (2008).

20. Rosenberg, S.A., Restifo, N.P., Yang, J.C., Morgan, R.A. & Dudley, M.E. Adoptive cell transfer: a clinical path to effective cancer immunotherapy. *Nat.Rev.Cancer* **8**, 299-308 (2008).

21. Dudley, M.E., *et al.* Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. *J Clin Oncol* **26**, 5233-5239 (2008).

22. Brentjens, R.J., *et al.* Genetically targeted T cells eradicate systemic acute lymphoblastic leukemia xenografts. *Clin.Cancer Res.* **13**, 5426-5435 (2007).

23. Gade, T.P., *et al.* Targeted elimination of prostate cancer by genetically directed human T lymphocytes. *Cancer Res.* **65**, 9080-9088 (2005).

24. Maher, J., Brentjens, R.J., Gunset, G., Riviere, I. & Sadelain, M. Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRzeta /CD28 receptor. *Nat.Biotechnol.* **20**, 70-75 (2002).

25. Kershaw, M.H., *et al.* Gene-engineered T cells as a superior adjuvant therapy for metastatic cancer. *J Immunol* **173**, 2143-2150 (2004).

26. Sadelain, M., Brentjens, R. & Riviere, I. The promise and potential pitfalls of chimeric antigen receptors. *Curr Opin Immunol* (2009).

27. Hollyman, D., *et al.* Manufacturing validation of biologically functional T cells targeted to CD19 antigen for autologous adoptive cell therapy. *J Immunother* **32**, 169-180 (2009).

28. Sadelain, M., Brentjens, R. & Riviere, I. The basic principles of chimeric antigen receptor design. *Cancer discovery* **3**, 388-398 (2013).

29. Riviere, I., Sadelain, M. & Brentjens, R.J. Novel strategies for cancer therapy: the potential of genetically modified T lymphocytes. *Curr Hematol Rep* **3**, 290-297 (2004).

30. Stephan, M.T., *et al.* T cell-encoded CD80 and 4-1BBL induce auto- and transco-stimulation, resulting in potent tumor rejection. *Nat.Med.* **13**, 1440-1449 (2007).

31. Krause, A., *et al.* Antigen-dependent CD28 signaling selectively enhances survival and proliferation in genetically modified activated human primary T lymphocytes. *J Exp Med* **188**, 619-626 (1998).

32. Gong, M.C., *et al.* Cancer patient T cells genetically targeted to prostate-specific membrane antigen specifically lyse prostate cancer cells and release cytokines in response to prostate-specific membrane antigen. *Neoplasia.* **1**, 123-127 (1999).

33. Lyddane, C., *et al.* Cutting Edge: CD28 controls dominant regulatory T cell activity during active immunization. *J.Immunol.* **176**, 3306-3310 (2006).

From the foregoing description, it will be apparent that variations and modifications may be made to the invention described herein to adopt it to various usages and conditions. Such embodiments are also within the scope of the following claims.

All patents and publications and sequences referred to by accession or reference number mentioned in this specification are herein incorporated by reference

to the same extent as if each independent patent and publication and sequence was specifically and individually indicated to be incorporated by reference.

What is claimed is:

1. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain that binds to a G-protein coupled receptor family C group 5 member D (GPRC5D), a transmembrane domain and an intracellular domain, wherein the extracellular antigen-binding domain comprises:

(a) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 124, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 125 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 126; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 127, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 128 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 129;

(b) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 130, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 131 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 132; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 133, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 134 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 135;

(c) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 136, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 137 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 138; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 139, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 140 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 141;

(d) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 142, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 143 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 144; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 145, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 146 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 147;

(e) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 148, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 149 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 150; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 151, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 152 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 153;

(f) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 154, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 155 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 156; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 157, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 158 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 159;

(g) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 160, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 161 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 162; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 163, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 164 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 165;

(h) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 166, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 167 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 168; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 169, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 170 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 171;

(i) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 172, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 173 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 174; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 175, a CDR2 comprising the amino acid sequence set forth

in SEQ ID NO: 176 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 177;

(j) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 178, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 179 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 180; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 181, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 182 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 183;

(k) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 184, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 185 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 186; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 187, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 188 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 189;

(l) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 190, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 191 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 192; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 193, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 194 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 195;

(m) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 196, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 197 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 198; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 199, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 200 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 201;

(n) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 202, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 203 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 204; and a light chain variable region comprising a CDR1 comprising the amino acid

sequence set forth in SEQ ID NO: 205, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 206 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 207;

(o) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 208, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 209 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 210; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 211, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 212 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 213;

(p) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 214, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 215 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 216; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 217, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 218 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 219;

(q) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 220, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 221 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 222; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 223, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 224 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 225;

(r) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 226, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 227 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 228; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 229, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 230 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 231;

(s) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 232, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 233 and a CDR3 comprising the amino acid sequence set forth in SEQ ID

NO: 234; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 235, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 236 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 237;

(t) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 238, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 239 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 240; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 241, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 242 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 243;

(u) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 244, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 245 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 246; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 247, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 248 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 249;

(v) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 250, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 251 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 252; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 253, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 254 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 255;

(w) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 256, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 257 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 258; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 259, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 260 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 261;

(x) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 262, a CDR2 comprising the amino acid sequence set forth

in SEQ ID NO: 263 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 264; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 265, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 266 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 267;

(y) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 304, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 305 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 306; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 307, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 308 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 309;

(z) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 316, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 317 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 318; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 319, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 320 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 321;

(aa) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 328, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 329 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 330; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 331, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 332 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 333;

(ab) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO:340, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 341 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 342; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 343, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 344 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 345;

(ac) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 352, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 353 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 354; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 355, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 356 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 357;

(ad) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 364, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 365 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 366; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 367, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 368 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 369;

(ae) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 376, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 377 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 378; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 379, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 380 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 381;or

(af) a heavy chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 388, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 389 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 390; and a light chain variable region comprising a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 391, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 393 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 393.

2. A chimeric antigen receptor (CAR), comprising an extracellular antigen-binding domain that binds to a G-protein coupled receptor family C group 5 member D (GPRC5D), a transmembrane domain and an intracellular domain, wherein the extracellular antigen-binding domain comprises:

(a) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:1, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:2;

(b) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:5, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:6;

(c) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:9, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:10;

(d) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:13, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:14;

(e) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:17, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:18;

(f) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:21, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:22;

(g) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:25, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:26;

(h) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:29, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:30;

(i) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:33, and a light chain variable

region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:34;

(j) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:37, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:38;

(k) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:41, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:42;

(l) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:45, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:46;

(m) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:49, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:50;

(n) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:53, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:54;

(o) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:57, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:58;

(p) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:61, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:62;

(q) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:65, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:66;

(r) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:69, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:70;

(s) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:73, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:74;

(t) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:77, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:78;

(u) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:81, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:82;

(v) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:85, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:86;

(w) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:89, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:90;

(x) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:93, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:94;

(y) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:302, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:303;

(z) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:314, and a light chain variable

region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:315;

(aa) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:326, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:327;

(ab) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:338, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:339;

(ac) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:350, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:351;

(ad) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:362, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:363;

(ae) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:374, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:375; or

(af) a heavy chain variable region comprising a CDR1, a CDR2, and a CDR3 of the heavy chain variable region sequence set forth in SEQ ID NO:386, and a light chain variable region comprising a CDR1, a CDR2, and a CDR3 of the light chain variable region sequence set forth in SEQ ID NO:387.

3. The CAR of claim 1 or claim 2, wherein the extracellular antigen-binding domain binds to GPRC5D with a binding affinity (K_d) of from 1×10^{-9} M to 3×10^{-6} M.

4. The CAR of any one of claims 1-3, wherein the extracellular antigen-binding domain is a single-chain variable fragment (scFv).

5. The CAR of any one of claims 1-4, wherein the extracellular antigen-binding domain is a single-chain variable fragment (scFv) comprising the amino acid sequence set forth in

any one of SEQ ID NOS: 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 301, 313, 325, 337, 349, 361, 373, and 385.

6. The CAR of any one of claims 1-4, wherein the extracellular antigen-binding domain is a murine scFv.

7. The CAR of any one of claims 1-5, wherein the extracellular antigen-binding domain is a human scFv.

8. The CAR of any one of claims 1-3, wherein the extracellular antigen-binding domain is a Fab, which is optionally crosslinked.

9. The CAR of any one of claims 1-3, wherein the extracellular antigen-binding domain is a $F(ab)_2$.

10. The CAR of any one of claims 4-9, wherein one or more of the scFv, the Fab and the $F(ab)_2$ is comprised in a fusion protein with a heterologous sequence to form the extracellular antigen-binding domain.

11. The CAR of any one of claims 1-10, wherein the heavy chain variable region comprises an amino acid sequence that is at least 90% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOS:1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386.

12. The CAR of any one of claims 1-11, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386, and conservative modifications thereof.

13. The CAR of any one of claims 1-12, wherein the heavy chain variable region comprises the amino acid sequence selected from the group consisting of SEQ ID NOS:1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386.

14. The CAR of any one of claims 1-13, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:53.

15. The CAR of any one of claims 1-13, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:57.

16. The CAR of any one of claims 1-13, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:61.

17. The CAR of any one of claims 1-13, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:65.

18. The CAR of any one of claims 1-13, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:69.

19. The CAR of any one of claims 1-18, wherein the light chain variable region comprises an amino acid sequence that is at least 90% homologous to an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387.

20. The CAR of any one of claims 1-19, wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387, and conservative modifications thereof.

21. The CAR of any one of claims 1-20, wherein the light chain variable region comprises the amino acid sequence selected from the group consisting of SEQ ID NOS:2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387.

22. The CAR of any one of claims 1-21, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:54.

23. The CAR of any one of claims 1-21, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:58.

24. The CAR of any one of claims 1-21, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:62.

25. The CAR of any one of claims 1-21, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:66.

26. The CAR of any one of claims 1-21, wherein the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:70.

27. The CAR of any one of claims 1-26, wherein (a) the heavy chain variable region comprises an amino acid sequence that is at least 90% homologous to an amino acid sequence selected from the group consisting of SEQ ID NO: 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386; and (b) the light chain variable region comprises an amino acid sequence that is at least 90% to an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387.

28. The CAR of any one of claims 1-27, wherein (a) the heavy chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOS:1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386, and conservative modifications thereof, and (b) the light chain variable region comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387, and conservative modifications thereof.

29. The CAR of any one of claims 1-28, wherein (a) the heavy chain variable region comprises the amino acid sequence selected from the group consisting of SEQ ID NOS:1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, 57, 61, 65, 69, 73, 77, 81, 85, 89, 93, 302, 314, 326, 338, 350, 362, 374, and 386; and (b) the light chain variable region comprises the amino acid sequence selected from the group consisting of SEQ ID NOS:2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, 50, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 303, 315, 327, 339, 351, 363, 375, and 387.

30. The CAR of any one of claims 1-29, wherein:

(a) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:1, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:2;

(b) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:5, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:6;

(c) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:9, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:10;

(d) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:13, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:14;

(e) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:17, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:18;

(f) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:21, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:22;

(g) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:25, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:26;

(h) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:29, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:30;

(i) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:33, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:34;

(j) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:37, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:38;

(k) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:41, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:42;

(l) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:45, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:46;

(m) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:49, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:50;

(n) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:53, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:54;

(o) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:57, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:58;

(p) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:61, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:62;

(q) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:65, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:66;

(r) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:69, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:70;

(s) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:73, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:74;

(t) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:77, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:78;

(u) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:81, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:82;

(v) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:85, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:86;

(w) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:89, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:90;

(x) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:93, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:94;

(y) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:302, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:303;

(z) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:314, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:315;

(aa) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:326, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:327;

(ab) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:338, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:339;

(ac) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:350, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:351;

(ad) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:362, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:363;

(ae) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:374, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:375; or

(af) the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:386, and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:387.

31. The CAR of claim 30, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:53; and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:54.

32. The CAR of claim 30, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:57; and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:58.

33. The CAR of claim 30, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:61; and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:62.

34. The CAR of claim 30, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:65; and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:66.

35. The CAR of claim 30, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:69; and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:70.

36. The CAR of any one of claims 1-35, wherein the extracellular antigen-binding domain further comprises a linker between the heavy chain variable region and the light chain variable region.

37. The CAR of any one of claims 1-36, wherein (a) the heavy chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 202, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 203 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 204; and (b) the light chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 205, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 206 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 207.

38. The CAR of any one of claims 1-36, wherein (a) the heavy chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 208, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 209 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 210; and (b) the light chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 211, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 212 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 213.

39. The CAR of any one of claims 1-36, wherein (a) the heavy chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 214, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 215 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 216; and (b) the light chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 217, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 218 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 219.

40. The CAR of any one of claims 1-36, wherein (a) the heavy chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 220, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 221 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 222; and (b) the light chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 223, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 224 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 225.

41. The CAR of any one of claims 1-36, wherein (a) the heavy chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 226, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 227 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 228; and (b) the light chain variable region comprises a CDR1 comprising the amino acid sequence set forth in SEQ ID NO: 229, a CDR2 comprising the amino acid sequence set forth in SEQ ID NO: 230 and a CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 231.

42. The CAR of any one of claims 1-41, wherein a signal peptide is covalently joined to the 5' terminus of the extracellular antigen-binding domain.

43. The CAR of any one of claims 1-42, wherein the GPRC5D comprises the amino acid sequence set forth in SEQ ID NO:97.

44. The CAR of claim 43, wherein the extracellular antigen-binding domain binds to one, two, three or four epitope region selected from the group consisting of an epitope region in N-terminal region comprising amino acids 1-27 of SEQ ID NO:97, an epitope region in ECL1 region comprising amino acids 85-93 of SEQ ID NO:97, an epitope region in ECL2 region comprising amino acids 145-167 of SEQ ID NO:97, and an epitope region in ECL3 region comprising amino acids 226-239 of SEQ ID NO:97.

45. The CAR of claim 44, wherein the extracellular antigen-binding domain binds to an epitope region comprising amino acids 16-23 of SEQ ID NO:97.

46. The CAR of claim 45, wherein the extracellular antigen-binding domain binds to an epitope region comprising amino acids 15-23 of SEQ ID NO:97.

47. The CAR of claim 45, wherein the extracellular antigen-binding domain binds to an epitope region comprising amino acids 16-25 of SEQ ID NO:97.

48. The CAR of claim 44, wherein the extracellular antigen-binding domain binds to an epitope region comprising amino acids 10-17 of SEQ ID NO:97.

49. The CAR of claim 48, wherein the extracellular antigen-binding domain binds to an epitope region comprising amino acids 5-17 of SEQ ID NO:97.

50. The CAR of claim 44, wherein the extracellular antigen-binding domain binds to an epitope region comprising amino acids 85-95 of SEQ ID NO:97.

51. The CAR of claim 44, wherein the extracellular antigen-binding domain binds to an epitope region comprising amino acids 157-164 of SEQ ID NO:97.

52. The CAR of claim 51, wherein the extracellular antigen-binding domain binds to an epitope region comprising amino acids 157-167 of SEQ ID NO:97.

53. The CAR of claim 44, wherein the extracellular antigen-binding domain binds to an epitope region comprising amino acids 230-237 of SEQ ID NO:97.

54. The CAR of claim 53, wherein the extracellular antigen-binding domain binds to an epitope region comprising amino acids 229-237 of SEQ ID NO:97.

55. The CAR of claim 53, wherein the extracellular antigen-binding domain binds to an epitope region comprising amino acids 230-243 of SEQ ID NO:97.

56. The CAR of claim 53, wherein the extracellular antigen-binding domain binds to an epitope region comprising amino acids 227-237 of SEQ ID NO:97.

57. The CAR of claim 44, wherein the extracellular antigen-binding domain binds to one, two or three epitope region selected from the group consisting of an epitope region comprising amino acids 16-25 of SEQ ID NO:97, an epitope region comprising amino acids

157-164 of SEQ ID NO:97, and an epitope region comprising amino acids 229-237 of SEQ ID NO:97.

58. The CAR of claim 57, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:57 and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:58.

59. The CAR of claim 57 or 58, wherein (a) the heavy chain variable region comprises the amino acid sequences set forth in SEQ ID NOs: 208, 209 and 210; and (b) the light chain variable region comprises the amino acid sequences set forth in SEQ ID NOs: 211, 212 and 213.

60. The CAR of claim 44, wherein the extracellular antigen-binding domain binds to one, two or three epitope region selected from the group consisting of an epitope region comprising amino acids 5-17 of SEQ ID NO:97, an epitope region comprising amino acids 85-95 of SEQ ID NO:97, and an epitope region comprising amino acids 157-164 of SEQ ID NO:97.

61. The CAR of claim 60, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:61 and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:62.

62. The CAR of claim 60 or 61, wherein (a) the heavy chain variable region comprises the amino acid sequences set forth in SEQ ID NOs: 214, 215 and 216; and (b) the light chain variable region comprises the amino acid sequences set forth in SEQ ID NOs: 217, 218 and 219.

63. The CAR of claim 44, wherein the extracellular antigen-binding domain binds to one or two epitope region selected from the group consisting of an epitope region comprising amino acids 15-23 of SEQ ID NO:97, and an epitope region comprising amino acids 230-243 of SEQ ID NO:97.

64. The CAR of claim 63, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:65 and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:66.

65. The CAR of claim 63 or 64, wherein (a) the heavy chain variable region comprises the amino acid sequences set forth in SEQ ID NOs: 220, 221 and 222; and (b) the light chain variable region comprises the amino acid sequences set forth in SEQ ID NOs: 223, 224 and 225.

66. The CAR of claim 44, wherein the extracellular antigen-binding domain binds to one, two or three epitope region selected from the group consisting of an epitope region comprising amino acids 10-17 of SEQ ID NO:97, an epitope region comprising amino acids 157-167 of SEQ ID NO:97, and an epitope region comprising amino acids 227-237 of SEQ ID NO:97.

67. The CAR of claim 66, wherein the heavy chain variable region comprises the amino acid sequence set forth in SEQ ID NO:69 and the light chain variable region comprises the amino acid sequence set forth in SEQ ID NO:70.

68. The CAR of claim 66 or 67, wherein (a) the heavy chain variable region comprises the amino acid sequences set forth in SEQ ID NOs: 226, 227 and 228; and (b) the light chain variable region comprises the amino acid sequences set forth in SEQ ID NOs: 229, 230 and 231.

69. The CAR of any one of claims 1-68, wherein the transmembrane domain comprises a CD8 polypeptide, a CD28 polypeptide, a CD3ζ polypeptide, a CD4 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a CTLA-4 polypeptide, a PD-1 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, a BTLA polypeptide, or a combination thereof.

70. The CAR of claim 69, wherein the transmembrane domain comprises a CD8 polypeptide.

71. The CAR of claim 69, wherein the transmembrane domain comprises a CD28 polypeptide.

72. The CAR of any one of claims 1-71, wherein the intracellular domain comprises a CD3ζ polypeptide.

73. The CAR of any one of claims 1-72, wherein the intracellular domain further comprises at least one signaling region.

74. The CAR of claim 73, wherein the at least one signaling region comprises a CD28 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a DAP-10 polypeptide, a PD-1 polypeptide, a CTLA-4 polypeptide, a LAG-3 polypeptide, a 2B4 polypeptide, a BTLA polypeptide, or a combination thereof.

75. The CAR of claim 73 or 74, wherein the at least one signaling region is a co-stimulatory signaling region.

76. The CAR of claim 75, wherein the at least one co-stimulatory signaling region comprises a CD28 polypeptide, a 4-1BB polypeptide, an OX40 polypeptide, an ICOS polypeptide, a DAP-10 polypeptide, or a combination thereof.

77. The CAR of claim 76, wherein the at least one co-stimulatory signaling region comprises a CD28 polypeptide.

78. The CAR of claim 76, wherein the at least one co-stimulatory signaling region comprises a 4-1BB polypeptide.

79. The CAR of any one of claims 73-77, wherein the transmembrane domain comprises a CD28 polypeptide, and the intracellular domain comprises a CD3ζ polypeptide and at least one signaling region that comprises a CD28 polypeptide.

80. The CAR of any one of claims 73-76 and 78, wherein the transmembrane domain comprises a CD8 polypeptide, and the intracellular domain comprises a CD3ζ polypeptide and at least one signaling region that comprises a 4-1BB polypeptide.

81. The CAR of any one of claims 73-76 and 78, wherein the transmembrane domain comprises a CD28 polypeptide, and the intracellular domain comprises a CD3ζ polypeptide and at least one signaling region that comprises a 4-1BB polypeptide.

82. The CAR of any one of claims 1-81, wherein the CAR is recombinantly expressed.

83. The CAR of any one of claims 1-82, wherein the CAR is expressed from a vector.

84. The CAR of claim 83, wherein the vector is a γ-retroviral rector.

85. The CAR of claim 83, wherein the vector is a lentiviral vector.

86. An immunoresponsive cell comprising the CAR of any one of claims 1-85.

87. The immunoresponsive cell of claim 86, wherein the immunoresponsive cell is transduced with the CAR.

88. The immunoresponsive cell of claim 86 or 87, wherein the CAR is constitutively expressed on the surface of the immunoresponsive cell.

89. The immunoresponsive cell of any one of claims 86-88, wherein the immunoresponsive cell is further transduced with at least one co-stimulatory ligand such that the immunoresponsive cell expresses the at least one co-stimulatory ligand.

90. The immunoresponsive cell of claim 89, wherein the at least one co-stimulatory ligand is selected from the group consisting of 4-1BBL, CD80, CD86, CD70, OX40L, CD48, TNFRSF14, and combinations thereof.

91. The immunoresponsive cell of any one of claims 86-90, wherein the immunoresponsive cell is further transduced with at least one cytokine such that the immunoresponsive cell secretes the at least one cytokine.

92. The immunoresponsive cell of claim 91,wherein the at least one cytokine is selected from the group consisting of IL-2, IL-3, IL-6, IL-7, IL-11, IL-12, IL-15, IL-17, IL-21, and combinations thereof.

93. The immunoresponsive cell of any one of claims 86-92, wherein the immunoresponsive cell is selected from the group consisting of a T cell, a Natural Killer (NK) cell, a cytotoxic T lymphocyte (CTL), a regulatory T cell, a human embryonic stem cell, a lymphoid progenitor cell, a T cell-precursor cell, and a pluripotent stem cell from which lymphoid cells may be differentiated.

94. The immunoresponsive cell of claim 93, wherein the immunoresponsive cell is a T cell.

95. A nucleic acid molecule encoding the chimeric antigen receptor (CAR) of any one of claims 1-85.

96. The nucleic acid molecule of claim 95, comprising the nucleotide sequence set forth in SEQ ID NO:397.

97. The nucleic acid molecule of claim 95, comprising the nucleotide sequence set forth in SEQ ID NO:398.

98. The nucleic acid molecule of claim 95, comprising the nucleotide sequence set forth in SEQ ID NO:399.

99. The nucleic acid molecule of claim 95, comprising the nucleotide sequence set forth in SEQ ID NO:400.

100. The nucleic acid molecule of claim 95, comprising the nucleotide sequence set forth in SEQ ID NO:401.

101. The nucleic acid molecule of claim 95, comprising the nucleotide sequence set forth in SEQ ID NO:402.

102. The nucleic acid molecule of claim 95, comprising the nucleotide sequence set forth in SEQ ID NO:403.

103. The nucleic acid molecule of claim 95,comprising the nucleotide sequence set forth in SEQ ID NO:406.

104. The nucleic acid molecule of claim 95, comprising the nucleotide sequence set forth in SEQ ID NO:407.

105. The nucleic acid molecule of claim 95, comprising the nucleotide sequence set forth in SEQ ID NO:408.

106. A vector comprising the nucleic acid molecule of any one of claims 95-105.

107. The vector of claim 106, wherein the vector is a γ-retroviral vector.

108. The vector of claim 106, wherein the vector is a lentiviral vector.

109. A host cell expressing the nucleic acid molecule of any one of claims 95-105.

110. The host cell of claim 109,wherein the host cell is a T cell.

111. Use of an effective amount of the immunoresponsive cell of any one of claims 86-94 in the manufacture of a medicament for reducing tumor burden in a subject with multiple myeloma.

112. The use of claim 111, wherein the immunoresponsive cell reduces the number of tumor cells.

113. The use of claim 111, wherein the immunoresponsive cell reduces tumor size.

114. The use of claim 111, wherein the immunoresponsive cell eradicates the tumor in the subject.

115. The use of any one of claims 111-114, wherein the subject is a human.

116. The use of any one of claims 111-115, wherein the immunoresponsive cell is a T cell.

117. Use of an effective amount of the immunoresponsive cell of any one of claims 86-94 in the manufacture of a medicament for increasing or lengthening survival of a subject having multiple myeloma.

118. The use of claim 117, wherein the immunoresponsive cell reduces or eradicates tumor burden in the subject.

119. A method for producing an immunoresponsive cell that binds to a G-protein coupled receptor family C group 5 member D (GPRC5D), comprising introducing into the immunoresponsive cell a nucleic acid molecule of any one of claims 95-105.

120. A pharmaceutical composition comprising an effective amount of the immunoresponsive cell of any one of claims 86-94 and a pharmaceutically acceptable excipient.

121. The pharmaceutical composition of claim 120, wherein the pharmaceutical composition is for treating a neoplasia.

122. The pharmaceutical composition of claim 121, wherein the neoplasia is multiple myeloma or Waldenstrom's Macroglobulinemia.

123. The pharmaceutical composition of claim 122, wherein the neoplasia is multiple myeloma.

124. A kit for treating a neoplasia, comprising the immunoresponsive cell of any one of claims 86-94.

125. The kit of claim 124, wherein the kit further comprises written instructions for using the immunoresponsive cell for treating a subject having a neoplasia.

126. The kit of claim 124 or 125, wherein the neoplasia is multiple myeloma or Waldenstrom's Macroglobulinemia.

127. The kit of claim 126, wherein the neoplasia is multiple myeloma.