

**WHAT IS CLAIMED IS:**

1. An antigen-binding protein construct (ABPC) comprising:  
a first antigen-binding domain that is capable of specifically binding LRRC15 or an epitope of LRRC15 presented on the surface of a target mammalian cell,  
wherein:
  - (a) the dissociation rate of the first antigen-binding domain at a pH of about 4.0 to about 6.5 is faster than the dissociation rate at a pH of about 7.0 to about 8.0; or
  - (b) the dissociation constant ( $K_D$ ) of the first antigen-binding domain at a pH of about 4.0 to about 6.5 is greater than the  $K_D$  at a pH of about 7.0 to about 8.0.
2. The ABPC of claim 1, wherein the ABPC is degraded in the target mammalian cell following internalization of the ABPC by the target mammalian cell.
3. The ABPC of claim 1 or 2, wherein the ABPC further comprises a conjugated toxin, radioisotope, drug, or small molecule.
4. An antigen-binding protein construct (ABPC) comprising:  
a first antigen-binding domain that is capable of specifically binding LRRC15 or an epitope of LRRC15 presented on the surface of a target mammalian cell; and  
a conjugated toxin, radioisotope, drug, or small molecule,  
wherein:
  - (a) the dissociation rate of the first antigen-binding domain at a pH of about 4.0 to about 6.5 is faster than the dissociation rate at a pH of about 7.0 to about 8.0; or  
the dissociation constant ( $K_D$ ) of the first antigen-binding domain at a pH of about 4.0 to about 6.5 is greater than the  $K_D$  at a pH of about 7.0 to about 8.0; and
  - (b) the composition provides for one or more of:
    - an increase in toxin liberation in the target mammalian cell as compared to a composition comprising the same amount of a control ABPC;
    - an increase in target mammalian cell killing as compared to a composition comprising the same amount of a control ABPC; and

an increase in endolysosomal delivery in the target mammalian cell as compared to a composition comprising the same amount of a control ABPC.

5. The ABPC of claim 1 or 4, wherein the first antigen-binding domain comprises one of (a) through (d):

(a) a heavy chain variable domain of samrotamab with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of samrotamab comprises SEQ ID NO: 1; and/or

a light chain variable domain of samrotamab with one or more amino acids substituted with a histidine, wherein the light chain variable domain of samrotamab comprises SEQ ID NO: 2;

(b) a heavy chain variable domain of hu139.10 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of hu139.10 comprises SEQ ID NO: 84; and/or

a light chain variable domain of hu139.10 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of hu139.10 comprises SEQ ID NO: 85;

(c) a heavy chain variable domain of huAD208.4.1 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of huAD208.4.1 comprises SEQ ID NO: 178; and/or

a light chain variable domain of huAD208.4.1 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of huAD208.4.1 comprises SEQ ID NO: 179; and

(d) a heavy chain variable domain of huAD208.12.1 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of huAD208.12.1 comprises SEQ ID NO: 272; and/or

a light chain variable domain of huAD208.12.1 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of huAD208.12.1 comprises SEQ ID NO: 273.

6. The ABPC of claim 1 or 4, wherein the first LRRC15-binding domain comprises one of (a) through (d):

(a) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 3-5, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 3-5 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 6-8, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 6-8 substituted with a histidine;

(b) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 86-88, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 86-88 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 89-91, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 89-91 substituted with a histidine;

(c) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 180-182, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 180-182 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 183-185, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 183-185 substituted with a histidine; and

(d) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 274-276, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 274-276 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 277-279, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 277-279 substituted with a histidine.

7. The ABPC of any one of claims 1 and 4-6, wherein the first antigen-binding domain comprises one of (a) through (d):

(a) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 1, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 1 selected from the group consisting of: 33, 34, 50, 52, 57, 59, 100, 102, 103, 107, 108, and 109; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 2, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 2 selected from the group consisting of: 32, 34, 50, 51, 89, 90, 92, 93, 94, and 96;

(b) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 84, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 84 selected from the group consisting of: 27, 29, 32, 50, 54, 58, 99, 100, 102, 104, and 105; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 85, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 85 selected from the group consisting of: 29, 31, 32, 34, 36, 37, 38, 40, 56, 60, 61, 95, 96, 97, and 100;

(c) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 178, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 178 selected from the group consisting of: 33, 52, 56, 57, or 106; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 179, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 179 selected from the group consisting of 25, 26, 28, 29, 31, 36, 37, 57, 59, 94, 95, 96, and 100; and

(d) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 272, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 272 selected from the group consisting of: 24, 27, 29, 62, 63, 98, and 108; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 273, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 273 selected from the group consisting of 27, 28, 29, 31, 32, 89, 92, and 93.

8. The ABPC of claim 1 or 4, wherein the first antigen-binding domain comprises one of (a) through (d):

(a) a light chain variable domain of SEQ ID NO: 2, SEQ ID NO: 61, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, or SEQ ID NO: 78 and/or

a heavy chain variable domain of SEQ ID NO: 1, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 23, SEQ ID NO: 25, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 43, SEQ ID NO:

45, SEQ ID NO: 46, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, or SEQ ID NO: 83,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 2 and a heavy chain variable domain of SEQ ID NO: 1; (ii) a light chain variable domain of SEQ ID NO: 2 and heavy chain variable domain that is not one of SEQ ID NOs: 20, 21, 23, 25, 30, 32, 43, 45, 46, 50-52, or 80-83; or (iii) a heavy chain variable domain of SEQ ID NO: 1 and a light chain variable domain that is not one of SEQ ID NOs: 61, 63-65, 71, 72, 74-76, or 78;

(b) a light chain variable domain of SEQ ID NO: 84, SEQ ID NO: 137, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 142, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 161, SEQ ID NO: 169, SEQ ID NO: 170, SEQ ID NO: 171, SEQ ID NO: 172, SEQ ID NO: 173, SEQ ID NO: 174, SEQ ID NO: 175, SEQ ID NO: 176, or SEQ ID NO: 177, and/or

a heavy chain variable domain of SEQ ID NO: 85, SEQ ID NO: 93, SEQ ID NO: 95, SEQ ID NO: 98, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 106, SEQ ID NO: 110, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 126, SEQ ID NO: 127, or SEQ ID NO: 166,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 85 and a heavy chain variable domain of SEQ ID NO: 84; (ii) a light chain variable domain of SEQ ID NO: 85 and heavy chain variable domain that is not one of SEQ ID NOs: 93, 95, 98, 101, 102, 106, 110, 120-122, 124, 126, 127, or 166; or (iii) a heavy chain variable domain of SEQ ID NO: 84 and a light chain variable domain that is not one of SEQ ID NOs: 137, 139, 140, 142, 144-146, 148, 149, 153, 154, 156-158, 161, or 169-177;

(c) a light chain variable domain of SEQ ID NO: 179, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 232, SEQ ID NO: 233, SEQ ID NO: 235, SEQ ID NO: 240, SEQ ID NO: 241, SEQ ID NO: 246, SEQ ID NO: 248, SEQ ID NO: 251, SEQ ID NO: 252, SEQ ID NO: 253, SEQ ID NO: 257, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 268, SEQ ID NO: 269, SEQ ID NO: 270, or SEQ ID NO: 271, and/or

a heavy chain variable domain of SEQ ID NO: 178, SEQ ID NO: 196, SEQ ID NO: 201, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 225, SEQ ID NO: 258, SEQ ID NO: 259, SEQ ID NO: 260, or SEQ ID NO: 261,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 179 and a heavy chain variable domain of SEQ ID NO: 178; (ii) a light chain variable domain of SEQ ID NO: 179 and heavy chain variable domain that is not one of SEQ ID NOs: 196, 201, 205, 206, 225, or 258-261; or (iii) a heavy chain variable domain of SEQ ID NO: 178 and a light chain variable domain that is not one of SEQ ID NOs: 229, 230, 232, 233, 235, 240, 241, 246, 248, 251-253, 257, 263, 264, or 268-271; and

(d) a light chain variable domain of SEQ ID NO: 273, SEQ ID NO: 327, SEQ ID NO: 328, SEQ ID NO: 329, SEQ ID NO: 331, SEQ ID NO: 332, SEQ ID NO: 342, SEQ ID NO: 345, or SEQ ID NO: 346 and/or

a heavy chain variable domain of SEQ ID NO: 272, SEQ ID NO: 281, SEQ ID NO: 284, SEQ ID NO: 286, SEQ ID NO: 305, SEQ ID NO: 306, SEQ ID NO: 311, or SEQ ID NO: 321,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 273 and a heavy chain variable domain of SEQ ID NO: 272; (ii) a light chain variable domain of SEQ ID NO: 273 and heavy chain variable domain that is not one of SEQ ID NOs: 281, 284, 286, 305, 306, 311, or 321; or (iii) a heavy chain variable domain of SEQ ID NO: 272 and a light chain variable domain that is not one of SEQ ID NOs: 327-329, 331, 332, 342, 345, or 346.

9. The ABPC of any one of claims 1-8, wherein a composition comprising the ABPC: results in a less of a reduction in the level of LRRC15 presented on the surface of the target mammalian cell as compared to a composition comprising the same amount of a control ABPC; or does not result in a detectable reduction in the level of LRRC15 presented on the surface of the target mammalian cell;

the ABPC is cytotoxic or cytostatic to the target mammalian cell; and/or

the half-life of the ABPC in vivo is decreased as compared to the half-life of a control ABPC in vivo.

10. The ABPC of any one of claims 1-9, wherein:

the target mammalian cell is a cancer cell; and/or  
the ABPC is cytotoxic or cytostatic to the target mammalian cell.

11. The ABPC of any one of claims 1-10, wherein the ABPC comprises a single polypeptide, optionally, wherein the antigen-binding domain is selected from the group consisting of: a VH domain, a VHH domain, a VNAR domain, and a scFv.

12. The ABPC of any one of claims 1-10, wherein the ABPC comprises two or more polypeptides, optionally, wherein the ABPC is an antibody.

13. The ABPC of any of claims 1-12, wherein the half-life of the ABPC *in vivo* is decreased as compared to the half-life of a control ABPC *in vivo*.

14. The ABPC of any one of claims 1-13, wherein the ABPC further comprises a second antigen-binding domain.

15. A pharmaceutical composition comprising an effective amount of an antigen-binding domain construct (ABPC) of any one of claims 1-14.

16. A kit comprising at least one dose of the pharmaceutical composition of claim 15 or the ABPC of any one of claims 1-14.

17. The ABPC of any one of claims 1-14 for use in a method of treating a cancer characterized by having a population of cancer cells that have LRRC15 or an epitope of LRRC15 presented on their surface.

18. The ABPC of any one of claims 1-14 for use in a method of reducing the volume of a tumor in a subject, wherein the tumor is characterized by having a population of cancer cells that have LRRC15 or an epitope of LRRC15 presented on their surface.

19. The ABPC of any one of claims 1-14 for use in a method of inducing cell death in a cancer cell in a subject, wherein the cancer cell has LRRC15 or an epitope of LRRC15 presented on its surface.

20. The ABPC of any one of claims 1-14 for use in a method of decreasing the risk of developing a metastasis or decreasing the risk of developing an additional metastasis in a subject having a cancer, wherein the cancer is characterized by having a population of cancer cells that have LRRC15 or an epitope of LRRC15 presented on their surface.