

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising an effective amount of an antigen-binding protein construct (ABPC) comprising:

a first antigen-binding domain that is capable of specifically binding DLL3 or an epitope of DLL3 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 pharmaceutical composition 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 pharmaceutical composition of claim 1 or 2, wherein the ABPC further comprises a conjugated toxin, radioisotope, drug, or small molecule.

4. A pharmaceutical composition comprising an effective amount of an antigen-binding protein construct (ABPC) comprising:

a first antigen-binding domain that is capable of specifically binding DLL3 or an epitope of DLL3 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 pharmaceutical composition of claim 1 or 4, wherein the first antigen-binding domain comprises one of (a) through (g):

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

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

(b) a heavy chain variable domain of SC16.4 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of SC16.4 comprises SEQ ID NO: 119; and/or

a light chain variable domain of SC16.4 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of SC16.4 comprises SEQ ID NO: 120;

(c) a heavy chain variable domain of SC16.13 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of SC16.13 comprises SEQ ID NO: 236; and/or

a light chain variable domain of SC16.13 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of SC16.13 comprises SEQ ID NO: 237;

(d) a heavy chain variable domain of SC16.15 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of SC16.15 comprises SEQ ID NO: 335; and/or

a light chain variable domain of SC16.15 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of SC16.15 comprises SEQ ID NO: 336;

(e) a heavy chain variable domain of SC16.25 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of SC16.25 comprises SEQ ID NO: 401; and/or

a light chain variable domain of SC16.25 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of SC16.25 comprises SEQ ID NO: 402;

(f) a heavy chain variable domain of SC16.34 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of SC16.34 comprises SEQ ID NO: 470; and/or

a light chain variable domain of SC16.34 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of SC16.34 comprises SEQ ID NO: 471; and

(g) a heavy chain variable domain of SC16.67 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of SC16.67 comprises SEQ ID NO: 537; and/or

a light chain variable domain of SC16.67 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of SC16.67 comprises SEQ ID NO: 538.

6. The pharmaceutical composition of claim 1 or 4, wherein the first DLL3-binding domain comprises one of (a) through (g):

(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: 622-624, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 622-624 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 625-627, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 625-627 substituted with a histidine;

(c) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 628-630, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 628-630 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 631-633, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 631-633 substituted with a histidine;

(d) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 634-636, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 634-636 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 637-639, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 637-639 substituted with a histidine;

(e) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 640-642, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 640-642 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 643-645, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 643-645 substituted with a histidine;

(f) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 646-648, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 646-648 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 649-651, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 649-651 substituted with a histidine; and

(g) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 652-654, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 652-654 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 655-657, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 655-657 substituted with a histidine.

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

(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: 27, 29, 31, 32, 34, 35, 50, 53, 54, 55, 58, 97, 98, 101, 103, 105, and 106; 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: 25, 26, 29, 32, 33, 34, 51, 54, 89, 90, 93, 94, 95, and 96;

(b) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 119, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 119 selected from the group consisting of: 32, 50, 52, 53, 57, 58, 59, 60, 62, 64, 65, 97, 98, 99, 100, 102, 104, and 105; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 120, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 120 selected from the group consisting of: 29, 32, 34, 91, 92, 93, 94 and 96;

(c) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 236, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 236 selected from the group consisting of: 27, 29, 31, 33, 34, 35, 36, 37, 54, 55, 56, 58, 60, 98, 100, 102, 106, 108, and 110; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 237, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 237 selected from the group consisting of 25, 29, 32, 33, 49, 50, 90, 91, 93, and 95;

(d) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 335, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 335 selected from the group consisting of: 27, 32, 33, 34, 50, 98, 101, 102, 103, 104, and 105; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 336, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 336 selected from the group consisting of: 27, 29, 32, 34, 52, 53, 89, 90, 91, 92, 93, 94, and 96;

(e) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 401, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 401 selected from the group consisting of: 27, 101, 103, 104, 108, and 109; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 402, wherein

the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 402 selected from the group consisting of: 30 and 31;

(f) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 470, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 470 selected from the group consisting of 24, 27, 29, 32, 34, 35, 50, 51, 53, 54, 56, 58, 59, 60, 63, 98, 101, 103, 105, 106, and 107; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 471, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 471 selected from the group consisting of: 29, 32, 33, 34, 50, 51, 53, 55, 89, 92, 94, 96 and 97; and

(g) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 537, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 537 selected from the group consisting of: 26, 29, 31, 32, 53, 54, 57, 58, 59, 65, 67, 68, 103, 104, and 106; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 538, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 538 selected from the group consisting of: 28, 34, 53, 93, 94, and 98.

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

(a) a light chain variable domain of SEQ ID NO: 2, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 59, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 69, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, or SEQ ID NO: 118, and/or

a heavy chain variable domain of SEQ ID NO: 1, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 34, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 81, SEQ ID NO:

82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, or SEQ ID NO: 98,

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: 17, 19, 21, 22, 24-26, 29-31, 34, 43, 44, 47, 49, 51, 52, and 81-98; 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: 55, 56, 59, 62-66, 69, 72, 73, 76-79, and 99-118;

(b) a light chain variable domain of SEQ ID NO: 120, SEQ ID NO: 163, SEQ ID NO: 166, SEQ ID NO: 168, SEQ ID NO: 178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 181, SEQ ID NO: 183, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, SEQ ID NO: 233, SEQ ID NO: 234, or SEQ ID NO: 235, and/or

a heavy chain variable domain of SEQ ID NO: 119, SEQ ID NO: 127, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 143, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 153, SEQ ID NO: 155, SEQ ID NO: 156; SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 187, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 190, SEQ ID NO: 191, SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID NO: 204, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 220, SEQ ID NO: 221, or SEQ ID NO: 223,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 120 and a heavy chain variable domain of SEQ ID NO: 119; (ii) a light chain variable domain of SEQ ID NO: 120 and heavy chain variable domain that is not one of SEQ ID NOs: 127, 130, 131, 133, 134, 138-141, 143, 145, 146, 148-151, 153, 155, 156, 185-214, 216-218, 220, 221, and 223; or (iii) a heavy chain variable domain of SEQ ID NO: 119 and

a light chain variable domain that is not one of SEQ ID NOs: 163, 166, 168, 178-181, 183, and 226-235;

(c) a light chain variable domain of SEQ ID NO: 237, SEQ ID NO: 283, SEQ ID NO: 287, SEQ ID NO: 290, SEQ ID NO: 291, SEQ ID NO: 292, SEQ ID NO: 293, SEQ ID NO: 301, SEQ ID NO: 302, SEQ ID NO: 304, SEQ ID NO: 306, or SEQ ID NO: 334, and/or

a heavy chain variable domain of SEQ ID NO: 236, SEQ ID NO: 239, SEQ ID NO: 241, SEQ ID NO: 243, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248, SEQ ID NO: 249, SEQ ID NO: 250, SEQ ID NO: 252, SEQ ID NO: 253, SEQ ID NO: 254, SEQ ID NO: 256, SEQ ID NO: 258, SEQ ID NO: 266, SEQ ID NO: 268, SEQ ID NO: 270, SEQ ID NO: 274, SEQ ID NO: 276, SEQ ID NO: 278, SEQ ID NO: 308, SEQ ID NO: 309, SEQ ID NO: 310, SEQ ID NO: 311, SEQ ID NO: 312, SEQ ID NO: 313, SEQ ID NO: 314, SEQ ID NO: 315, SEQ ID NO: 316, SEQ ID NO: 317, SEQ ID NO: 318, SEQ ID NO: 319, SEQ ID NO: 320, SEQ ID NO: 321, SEQ ID NO: 322, SEQ ID NO: 323, SEQ ID NO: 324, SEQ ID NO: 325, SEQ ID NO: 326, SEQ ID NO: 327, SEQ ID NO: 328, SEQ ID NO: 330, SEQ ID NO: 331, or SEQ ID NO: 332,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 237 and a heavy chain variable domain of SEQ ID NO: 236; (ii) a light chain variable domain of SEQ ID NO: 237 and heavy chain variable domain that is not one of SEQ ID NOs: 239, 241, 243, 245-250, 252-254, 256, 258, 266, 268, 270, 274, 276, 278, 308-328, and 330-332; or (iii) a heavy chain variable domain of SEQ ID NO: 236 and a light chain variable domain that is not one of SEQ ID NOs: 283, 287, 290-293, 301, 302, 304, 306, and 334;

(d) a light chain variable domain of SEQ ID NO: 336, SEQ ID NO: 377, SEQ ID NO: 379, SEQ ID NO: 382, SEQ ID NO: 384, SEQ ID NO: 387, SEQ ID NO: 388, SEQ ID NO: 392, SEQ ID NO: 393, SEQ ID NO: 394, SEQ ID NO: 395, SEQ ID NO: 396, SEQ ID NO: 397, or SEQ ID NO: 399, and/or

a heavy chain variable domain of SEQ ID NO: 335, SEQ ID NO: 341, SEQ ID NO: 346, SEQ ID NO: 347, SEQ ID NO: 348, SEQ ID NO: 349, SEQ ID NO: 350, SEQ ID NO: 368, SEQ ID NO: 371, SEQ ID NO: 372, SEQ ID NO: 373, SEQ ID NO: 374, or SEQ ID NO: 375,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 336 and a heavy chain variable domain of SEQ ID NO: 335; (ii) a light chain variable domain of SEQ ID NO: 336 and heavy chain variable domain that is not one of

SEQ ID NOs: 341, 346-350, 368, and 371-375; or (iii) a heavy chain variable domain of SEQ ID NO: 335 and a light chain variable domain that is not one of SEQ ID NOs: 377, 379, 382, 384, 387, 388, 392-397, and 399;

(e) a light chain variable domain of SEQ ID NO: 402, SEQ ID NO: 450, or SEQ ID NO: 451, and/or

a heavy chain variable domain of SEQ ID NO: 401, SEQ ID NO: 404, SEQ ID NO: 434, SEQ ID NO: 436, SEQ ID NO: 437, SEQ ID NO: 441, or SEQ ID NO: 442,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 402 and a heavy chain variable domain of SEQ ID NO: 401; (ii) a light chain variable domain of SEQ ID NO: 402 and heavy chain variable domain that is not one of SEQ ID NOs: 404, 434, 436, 437, 441, and 442; or (iii) a heavy chain variable domain of SEQ ID NO: 401 and a light chain variable domain that is not one of SEQ ID NO: 450 or 451;

(f) a light chain variable domain of SEQ ID NO: 471, SEQ ID NO: 515, SEQ ID NO: 518, SEQ ID NO: 519, SEQ ID NO: 520, SEQ ID NO: 521, SEQ ID NO: 522, SEQ ID NO: 524, SEQ ID NO: 526, SEQ ID NO: 528, SEQ ID NO: 531, SEQ ID NO: 533, SEQ ID NO: 535, or SEQ ID NO: 536, and/or

a heavy chain variable domain of SEQ ID NO: 470, SEQ ID NO: 473, SEQ ID NO: 476, SEQ ID NO: 478, SEQ ID NO: 481, SEQ ID NO: 483, SEQ ID NO: 484, SEQ ID NO: 485, SEQ ID NO: 486, SEQ ID NO: 488, SEQ ID NO: 489, SEQ ID NO: 491, SEQ ID NO: 493, SEQ ID NO: 494, SEQ ID NO: 495, SEQ ID NO: 498, SEQ ID NO: 503, SEQ ID NO: 506, SEQ ID NO: 508, SEQ ID NO: 510, SEQ ID NO: 511, or SEQ ID NO: 512,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 471 and a heavy chain variable domain of SEQ ID NO: 470; (ii) a light chain variable domain of SEQ ID NO: 471 and heavy chain variable domain that is not one of SEQ ID NOs: 473, 476, 478, 481, 483-486, 488, 489, 491, 493-495, 498, 503, 506, 508, and 510-512; or (iii) a heavy chain variable domain of SEQ ID NO: 470 and a light chain variable domain that is not one of SEQ ID NOs: 515, 518-522, 524, 526, 528, 531, 533, 535, and 536; and

(g) a light chain variable domain of SEQ ID NO: 538, SEQ ID NO: 581, SEQ ID NO: 587, SEQ ID NO: 591, SEQ ID NO: 599, SEQ ID NO: 600, or SEQ ID NO: 604, and/or

a heavy chain variable domain of of SEQ ID NO: 537, SEQ ID NO: 539, SEQ ID NO: 542, SEQ ID NO: 544, SEQ ID NO: 545, SEQ ID NO: 552, SEQ ID NO: 553, SEQ ID NO: 556,

SEQ ID NO: 557, SEQ ID NO: 558, SEQ ID NO: 564, SEQ ID NO: 566, SEQ ID NO: 567, SEQ ID NO: 572, SEQ ID NO: 573, or SEQ ID NO: 575,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 538 and a heavy chain variable domain of SEQ ID NO: 537; (ii) a light chain variable domain of SEQ ID NO: 538 and heavy chain variable domain that is not one of SEQ ID NOs: 539, 542, 544, 545, 552, 553, 556-558, 564, 566, 567, 572, 573, and 575; or (iii) a heavy chain variable domain of SEQ ID NO: 537 and a light chain variable domain that is not one of SEQ ID NOs: 581, 587, 591, 599, 600, and 604.

9. The pharmaceutical composition of any one of claims 1-8, wherein the composition provides for:

an increase in toxin liberation in the target mammalian cell as compared to a composition comprising the same amount of a control ABPC; and/or

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

10. The pharmaceutical composition of any one of claims 1-9, wherein the composition provides for an increase in endolysosomal delivery in the target mammalian cell as compared to a composition comprising the same amount of a control ABPC.

11. The pharmaceutical composition of any one of claims 1-10, wherein the composition: results in a less of a reduction in the level of DLL3 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 DLL3 presented on the surface of the target mammalian cell.

12. The pharmaceutical composition of any one of claims 1-11, wherein the target mammalian cell is a cancer cell.

13. The pharmaceutical composition of any one of claims 1-12, wherein the ABPC is cytotoxic or cytostatic to the target mammalian cell.

14. The pharmaceutical composition of any one of claims 1-13, wherein the ABPC is:
cross-reactive with a non-human primate DLL3 and human DLL3; or
cross-reactive with a non-human primate DLL3, a human DLL3, and one or both of rat DLL3 and a mouse DLL3.

15. The pharmaceutical composition of any one of claims 1-14, wherein the ABPC comprises a single polypeptide.

16. The pharmaceutical composition of claim 15, wherein the antigen-binding domain is selected from the group consisting of: a VH domain, a VHH domain, a VNAR domain, and a scFv.

17. The pharmaceutical composition of any one of claims 1-14, wherein the ABPC comprises two or more polypeptides.

18. The pharmaceutical composition of claim 17, wherein the ABPC is an antibody.

19. The pharmaceutical composition of any of claims 1-18, wherein the half-life of the ABPC *in vivo* is decreased as compared to the half-life of a control ABPC *in vivo*.

20. The pharmaceutical composition of any one of claims 1-19, wherein the ABPC further comprises a second antigen-binding domain.

21. An antigen-binding protein construct (ABPC) comprising:
a first antigen-binding domain that is capable of specifically binding DLL3 or an epitope of DLL3 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.

22. The ABPC of claim 21, wherein the ABPC is degraded in the target mammalian cell following internalization of the ABPC by the target mammalian cell.

23. The ABPC of claim 21 or 22, wherein the ABPC further comprises a conjugated toxin, radioisotope, drug, or small molecule.

24. An antigen-binding protein construct (ABPC) comprising:
a first antigen-binding domain that is capable of specifically binding DLL3 or an epitope of DLL3 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.

25. The ABPC of claim 21 or 24, wherein the first antigen-binding domain comprises one of (a) through (g):

(a) a heavy chain variable domain of rovalpituzumab with one or more amino acids

substituted with a histidine, wherein the heavy chain variable domain of rovalpituzumab comprises SEQ ID NO: 1; and/or

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

(b) a heavy chain variable domain of SC16.4 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of SC16.4 comprises SEQ ID NO: 119; and/or

a light chain variable domain of SC16.4 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of SC16.4 comprises SEQ ID NO: 120;

(c) a heavy chain variable domain of SC16.13 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of SC16.13 comprises SEQ ID NO: 236; and/or

a light chain variable domain of SC16.13 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of SC16.13 comprises SEQ ID NO: 237;

(d) a heavy chain variable domain of SC16.15 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of SC16.15 comprises SEQ ID NO: 335; and/or

a light chain variable domain of SC16.15 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of SC16.15 comprises SEQ ID NO: 336;

(e) a heavy chain variable domain of SC16.25 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of SC16.25 comprises SEQ ID NO: 401; and/or

a light chain variable domain of SC16.25 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of SC16.25 comprises SEQ ID NO: 402;

(f) a heavy chain variable domain of SC16.34 with one or more amino acids substituted with a histidine, wherein the heavy chain variable domain of SC16.34 comprises SEQ ID NO: 470; and/or

a light chain variable domain of SC16.34 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of SC16.34 comprises SEQ ID NO: 471; and

(g) a heavy chain variable domain of SC16.67 with one or more amino acids substituted

with a histidine, wherein the heavy chain variable domain of SC16.67 comprises SEQ ID NO: 537; and/or

a light chain variable domain of SC16.67 with one or more amino acids substituted with a histidine, wherein the light chain variable domain of SC16.67 comprises SEQ ID NO: 538.

26. The ABPC of claim 21 or 24, wherein the first DLL3-binding domain comprises one of (a) through (g):

(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: 622-624, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 622-624 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 625-627, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 625-627 substituted with a histidine;

(c) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 628-630, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 628-630 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 631-633, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 631-633 substituted with a histidine;

(d) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 634-636, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 634-636 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 637-639, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 637-639 substituted with a histidine;

(e) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 640-642, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 640-642 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 643-645, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 643-645 substituted with a histidine;

(f) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 646-648, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 646-648 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 649-651, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 649-651 substituted with a histidine; and

(g) a heavy chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 652-654, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 652-654 substituted with a histidine; and/or

a light chain variable domain comprising a CDR1, a CDR2, and a CDR3 of SEQ ID NOs: 655-657, respectively, with collectively a total of one or more amino acid positions in SEQ ID NOs: 655-657 substituted with a histidine.

27. The ABPC of any one of claims 21 and 24-26, wherein the first antigen-binding domain comprises one of (a) through (g):

(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: 27, 29, 31, 32, 34, 35, 50, 53, 54, 55, 58, 97, 98, 101, 103, 105, and 106; 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: 25, 26, 29, 32, 33, 34, 51, 54, 89, 90, 93, 94, 95, and 96;

(b) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 119, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID

NO: 119 selected from the group consisting of: 32, 50, 52, 53, 57, 58, 59, 60, 62, 64, 65, 97, 98, 99, 100, 102, 104, and 105; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 120, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 120 selected from the group consisting of: 29, 32, 34, 91, 92, 93, 94 and 96;

(c) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 236, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 236 selected from the group consisting of: 27, 29, 31, 33, 34, 35, 36, 37, 54, 55, 56, 58, 60, 98, 100, 102, 106, 108, and 110; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 237, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 237 selected from the group consisting of: 25, 29, 32, 33, 49, 50, 90, 91, 93, and 95;

(d) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 335, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 335 selected from the group consisting of 27, 32, 33, 34, 50, 98, 101, 102, 103, 104, and 105; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 336, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 336 selected from the group consisting of: 27, 29, 32, 34, 52, 53, 89, 90, 91, 92, 93, 94, and 96;

(e) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 401, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 401 selected from the group consisting of: 27, 101, 103, 104, 108, and 109; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 402, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 402 selected from the group consisting of: 30 and 31;

(f) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 470, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 470 selected from the group consisting of 24, 27, 29, 32, 34, 35, 50, 51, 53, 54, 56, 58, 59, 60, 63, 98, 101, 103, 105, 106, and 107; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 471, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 471 selected from the group consisting of: 29, 32, 33, 34, 50, 51, 53, 55, 89, 92, 94, 96 and 97; and

(g) a heavy chain variable domain that is at least 90% identical to SEQ ID NO: 537, wherein the heavy chain variable domain includes a histidine at one or more positions in SEQ ID NO: 537 selected from the group consisting of 26, 29, 31, 32, 53, 54, 57, 58, 59, 65, 67, 68, 103, 104, and 106; and/or

a light chain variable domain that is at least 90% identical to SEQ ID NO: 538, wherein the light chain variable domain includes a histidine at one or more positions in SEQ ID NO: 538 selected from the group consisting of: 28, 34, 53, 93, 94, and 98.

28. The ABPC of claim 21 or 24, wherein the first antigen-binding domain comprises one of (a) through (g):

(a) a light chain variable domain of SEQ ID NO: 2, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 59, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 69, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, or SEQ ID NO: 118, and/or

a heavy chain variable domain of SEQ ID NO: 1, SEQ ID NO: 17, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 34, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 47, SEQ ID NO: 49, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, or SEQ ID NO: 98,

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: 17, 19, 21, 22, 24-26, 29-31, 34, 43, 44, 47, 49, 51, 52, and 81-98; 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: 55, 56, 59, 62-66, 69, 72, 73, 76-79, and 99-118;

(b) a light chain variable domain of SEQ ID NO: 120, SEQ ID NO: 163, SEQ ID NO: 166, SEQ ID NO: 168, SEQ ID NO: 178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 181, SEQ ID NO: 183, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229, SEQ ID NO: 230, SEQ ID NO: 231, SEQ ID NO: 232, SEQ ID NO: 233, SEQ ID NO: 234, or SEQ ID NO: 235, and/or

a heavy chain variable domain of SEQ ID NO: 119, SEQ ID NO: 127, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 143, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 153, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 187, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 190, SEQ ID NO: 191, SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID NO: 204, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 220, SEQ ID NO: 221, or SEQ ID NO: 223,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 120 and a heavy chain variable domain of SEQ ID NO: 119; (ii) a light chain variable domain of SEQ ID NO: 120 and heavy chain variable domain that is not one of SEQ ID NOs: 127, 130, 131, 133, 134, 138-141, 143, 145, 146, 148-151, 153, 155, 156, 185-214, 216-218, 220, 221, and 223; or (iii) a heavy chain variable domain of SEQ ID NO: 119 and a light chain variable domain that is not one of SEQ ID NOs: 163, 166, 168, 178-181, 183, and 226-235;

(c) a light chain variable domain of SEQ ID NO: 237, SEQ ID NO: 283, SEQ ID NO: 287, SEQ ID NO: 290, SEQ ID NO: 291, SEQ ID NO: 292, SEQ ID NO: 293, SEQ ID NO: 301, SEQ ID NO: 302, SEQ ID NO: 304, SEQ ID NO: 306, or SEQ ID NO: 334; and/or

a heavy chain variable domain of SEQ ID NO: 236, SEQ ID NO: 239, SEQ ID NO: 241, SEQ ID NO: 243, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248, SEQ ID NO: 249, SEQ ID NO: 250, SEQ ID NO: 252, SEQ ID NO: 253, SEQ ID NO: 254, SEQ ID NO: 256, SEQ ID NO: 258, SEQ ID NO: 266, SEQ ID NO: 268, SEQ ID NO: 270, SEQ ID NO: 274, SEQ ID NO: 276, SEQ ID NO: 278, SEQ ID NO: 308, SEQ ID NO: 309, SEQ ID NO: 310, SEQ ID NO: 311, SEQ ID NO: 312, SEQ ID NO: 313, SEQ ID NO: 314, SEQ ID NO: 315, SEQ ID NO: 316, SEQ ID NO: 317, SEQ ID NO: 318, SEQ ID NO: 319, SEQ ID NO: 320, SEQ ID NO: 321, SEQ ID NO: 322, SEQ ID NO: 323, SEQ ID NO: 324, SEQ ID NO: 325, SEQ ID NO: 326, SEQ ID NO: 327, SEQ ID NO: 328, SEQ ID NO: 330, SEQ ID NO: 331, or SEQ ID NO: 332,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 237 and a heavy chain variable domain of SEQ ID NO: 236; (ii) a light chain variable domain of SEQ ID NO: 237 and heavy chain variable domain that is not one of SEQ ID NOs: 239, 241, 243, 245-250, 252-254, 256, 258, 266, 268, 270, 274, 276, 278, 308-328, and 330-332; or (iii) a heavy chain variable domain of SEQ ID NO: 236 and a light chain variable domain that is not one of SEQ ID NOs: 283, 287, 290-293, 301, 302, 304, 306, and 334;

(d) a light chain variable domain of SEQ ID NO: 336, SEQ ID NO: 377, SEQ ID NO: 379, SEQ ID NO: 382, SEQ ID NO: 384, SEQ ID NO: 387, SEQ ID NO: 388, SEQ ID NO: 392, SEQ ID NO: 393, SEQ ID NO: 394, SEQ ID NO: 395, SEQ ID NO: 396, SEQ ID NO: 397, or SEQ ID NO: 399, and/or

a heavy chain variable domain of SEQ ID NO: 335, SEQ ID NO: 341, SEQ ID NO: 346, SEQ ID NO: 347, SEQ ID NO: 348, SEQ ID NO: 349, SEQ ID NO: 350, SEQ ID NO: 368, SEQ ID NO: 371, SEQ ID NO: 372, SEQ ID NO: 373, SEQ ID NO: 374, or SEQ ID NO: 375,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 336 and a heavy chain variable domain of SEQ ID NO: 335; (ii) a light chain variable domain of SEQ ID NO: 336 and heavy chain variable domain that is not one of SEQ ID NOs: 341, 346-350, 368, and 371-375; or (iii) a heavy chain variable domain of SEQ ID NO: 335 and a light chain variable domain that is not one of SEQ ID NOs: 377, 379, 382, 384, 387, 388, 392-397, and 399;

(e) a light chain variable domain of SEQ ID NO: 402, SEQ ID NO: 450, or SEQ ID NO: 451; and/or

a heavy chain variable domain of SEQ ID NO: 401, SEQ ID NO: 404, SEQ ID NO: 434, SEQ ID NO: 436, SEQ ID NO: 437, SEQ ID NO: 441, or SEQ ID NO: 442,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 402 and a heavy chain variable domain of SEQ ID NO: 401; (ii) a light chain variable domain of SEQ ID NO: 402 and heavy chain variable domain that is not one of SEQ ID NOs: 404, 434, 436, 437, 441, and 442; or (iii) a heavy chain variable domain of SEQ ID NO: 401 and a light chain variable domain that is not one of SEQ ID NO: 450 or 451;

(f) a light chain variable domain of SEQ ID NO: 471, SEQ ID NO: 515, SEQ ID NO: 518, SEQ ID NO: 519, SEQ ID NO: 520, SEQ ID NO: 521, SEQ ID NO: 522, SEQ ID NO: 524, SEQ ID NO: 526, SEQ ID NO: 528, SEQ ID NO: 531, SEQ ID NO: 533, SEQ ID NO: 535, or SEQ ID NO: 536, and/or

a heavy chain variable domain of SEQ ID NO: 470, SEQ ID NO: 473, SEQ ID NO: 476, SEQ ID NO: 478, SEQ ID NO: 481, SEQ ID NO: 483, SEQ ID NO: 484, SEQ ID NO: 485, SEQ ID NO: 486, SEQ ID NO: 488, SEQ ID NO: 489, SEQ ID NO: 491, SEQ ID NO: 493, SEQ ID NO: 494, SEQ ID NO: 495, SEQ ID NO: 498, SEQ ID NO: 503, SEQ ID NO: 506, SEQ ID NO: 508, SEQ ID NO: 510, SEQ ID NO: 511, or SEQ ID NO: 512,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 471 and a heavy chain variable domain of SEQ ID NO: 470; (ii) a light chain variable domain of SEQ ID NO: 471 and heavy chain variable domain that is not one of SEQ ID NOs: 473, 476, 478, 481, 483-486, 488, 489, 491, 493-495, 498, 503, 506, 508, and 510-512; or (iii) a heavy chain variable domain of SEQ ID NO: 470 and a light chain variable domain that is not one of SEQ ID NOs: 515, 518-522, 524, 526, 528, 531, 533, 535, and 536; and

(g) a light chain variable domain of SEQ ID NO: 538, SEQ ID NO: 581, SEQ ID NO: 587, SEQ ID NO: 591, SEQ ID NO: 599, SEQ ID NO: 600, or SEQ ID NO: 604, and/or

a heavy chain variable domain of of SEQ ID NO: 537, SEQ ID NO: 539, SEQ ID NO: 542, SEQ ID NO: 544, SEQ ID NO: 545, SEQ ID NO: 552, SEQ ID NO: 553, SEQ ID NO: 556, SEQ ID NO: 557, SEQ ID NO: 558, SEQ ID NO: 564, SEQ ID NO: 566, SEQ ID NO: 567, SEQ ID NO: 572, SEQ ID NO: 573, or SEQ ID NO: 575,

wherein the first antigen-binding domain does not comprise (i) a light chain variable domain of SEQ ID NO: 538 and a heavy chain variable domain of SEQ ID NO: 537; (ii) a light chain variable domain of SEQ ID NO: 538 and heavy chain variable domain that is not one of

SEQ ID NOs: 539, 542, 544, 545, 552, 553, 556-558, 564, 566, 567, 572, 573, and 575; or (iii) a heavy chain variable domain of SEQ ID NO: 537 and a light chain variable domain that is not one of SEQ ID NOs: 581, 587, 591, 599, 600, and 604.

29. The ABPC of any one of claims 21-28, wherein a composition comprising the ABPC provides for:

an increase in toxin liberation in the target mammalian cell as compared to a composition comprising the same amount of a control ABPC; and/or

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

30. The ABPC of any one of claims 21-29, wherein a composition comprising the ABPC provides for an increase in endolysosomal delivery in the target mammalian cell as compared to a composition comprising the same amount of a control ABPC.

31. The ABPC of any one of claims 21-30, wherein a composition comprising the ABPC: results in a less of a reduction in the level of DLL3 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 DLL3 presented on the surface of the target mammalian cell.

32. The ABPC of any one of claims 21-31, wherein the target mammalian cell is a cancer cell.

33. The ABPC of any one of claims 21-32, wherein the ABPC is cytotoxic or cytostatic to the target mammalian cell.

34. The ABPC of any one of claims 21-33, wherein the ABPC is: cross-reactive with a non-human primate DLL3 and human DLL3; or

cross-reactive with a non-human primate DLL3, a human DLL3, and one or both of rat DLL3 and a mouse DLL3.

35. The ABPC of any one of claims 21-34, wherein the ABPC comprises a single polypeptide.

36. The ABPC of claim 35, wherein the antigen-binding domain is selected from the group consisting of: a VH domain, a VHH domain, a VNAR domain, and a scFv.

37. The ABPC of any one of claims 21-34, wherein the ABPC comprises two or more polypeptides.

38. The ABPC of claim 37, wherein the ABPC is an antibody.

39. The ABPC of any of claims 21-38, wherein the half-life of the ABPC *in vivo* is decreased as compared to the half-life of a control ABPC *in vivo*.

40. The ABPC of any one of claims 21-39, wherein the ABPC further comprises a second antigen-binding domain.

41. A kit comprising at least one dose of the pharmaceutical composition of any one of claims 1-20 or the ABPC of any one of claims 21-40.

42. Use of a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-20 or the ABPC of any one of claims 21-40 in the manufacture of a medicament for treating a cancer characterized by having a population of cancer cells that have DLL3 or an epitope of DLL3 presented on their surface.

43. Use of a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-20 or the ABPC of any one of claims 21-40 in the manufacture of a medicament for reducing the volume of a tumor in a subject, wherein the tumor is characterized by having a population of cancer cells that have DLL3 or an epitope of DLL3 presented on their surface.

44. Use of a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-20 or the ABPC of any one of claims 21-40 in the manufacture of a medicament for inducing cell death in a cancer cell in a subject, wherein the cancer cell has DLL3 or an epitope of DLL3 presented on its surface.

45. Use of a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-20 or the ABPC of any one of claims 21-40 in the manufacture of a medicament for 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 DLL3 or an epitope of DLL3 presented on their surface.