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(71) **Demandeur/Applicant:**
MYTHIC THERAPEUTICS, INC., US

(72) **Inventeurs/Inventors:**
FISKE, BRIAN P., US;
GERA, NIMISH, US;
NICHOLS, ALEXANDER J., US

(74) **Agent:** SMART & BIGGAR LP

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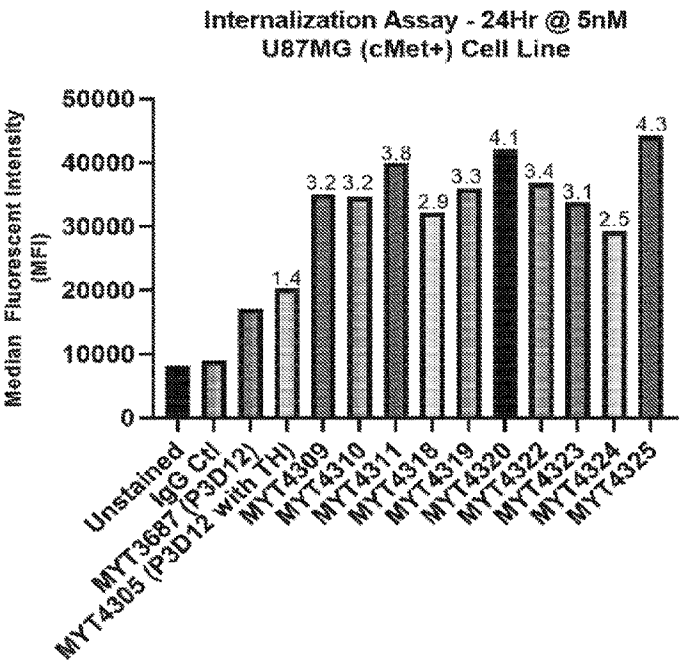



FIG. 1B

(57) **Abrégé/Abstract:**
Provided herein are antibodies and uses of the same.

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(71) Applicant: **MYTHIC THERAPEUTICS, INC.** [US/US]; 100 Beaver Street, Suite 303, Waltham, Massachusetts 02453 (US).

(72) Inventors: **FISKE, Brian P.**; 380 Prospect Street #3, Cambridge, Massachusetts 02139 (US). **GERA, Nimish**; 78 Pine Hill Circle, Waltham, Massachusetts 02451 (US). **NICHOLS, Alexander J.**; 25 Morningside Lane, Lincoln, Massachusetts 01773 (US).

(74) Agent: **REITER, Tiffany** et al.; Fish & Richardson P.C., P.O. Box 1022, Minneapolis, Minnesota 55440-1022 (US).

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(57) Abstract: Provided herein are antibodies and uses of the same.

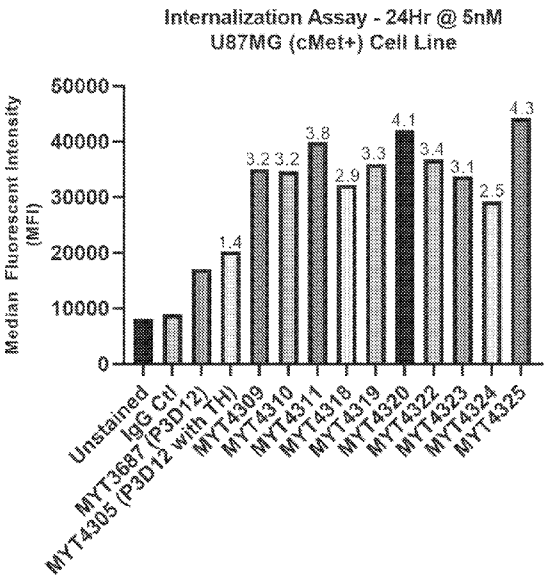



FIG. 1B

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# DEMANDE OU BREVET VOLUMINEUX

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CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 243

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# ANTI-MET ANTIBODIES AND USES THEREOF

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application Serial No. 63/145,348, filed February 3, 2021; the entire contents of which are herein incorporated by reference.

## TECHNICAL FIELD

The present disclosure relates to the field of biotechnology, and more specifically, to antigen-binding molecules, such as antibodies.

## BACKGROUND

Antibody-drug conjugates have been designed to combat a variety of diseases. One particular advantage of this approach is the ability for antibody-drug conjugates to have cytostatic or cytotoxic effects. Despite years of development, improved antibody-drug conjugates are desired.

## SUMMARY

The present invention is based on the concept that antibodies can be generated that display enhanced efficacy (e.g., one or more of an increase (e.g., a detectable increase) in toxin liberation in a target mammalian cell, an increase (e.g., a detectable increase) in target mammalian cell killing, and an increase (e.g., a detectable increase) in endolysosomal delivery).

Provided herein are antibodies that include: (a) a heavy chain variable domain and a light chain variable domain selected from the group of: (i) SEQ ID NO: 5 and SEQ ID NO: 6, respectively; (ii) SEQ ID NO: 7 and SEQ ID NO: 8, respectively; (iii) SEQ ID NO: 9 and SEQ ID NO: 10, respectively; (iv) SEQ ID NO: 11 and SEQ ID NO: 12, respectively; (v) SEQ ID NO: 13 and SEQ ID NO: 14, respectively; (vi) SEQ ID NO: 15 and SEQ ID NO: 16, respectively; (vii) SEQ ID NO: 17 and SEQ ID NO: 18, respectively; (viii) SEQ ID NO: 19 and SEQ ID NO: 20, respectively; (ix) SEQ ID NO: 21 and SEQ ID NO: 22, respectively; (x) SEQ ID NO: 23 and SEQ ID NO: 24, respectively; (xi) SEQ ID NO: 25 and SEQ ID NO: 26, respectively; (xii) SEQ ID NO: 27 and SEQ ID NO: 28, respectively; (xiii) SEQ ID NO: 29 and SEQ ID NO: 30, respectively; (xiv) SEQ ID NO: 31 and SEQ ID NO: 32, respectively; (xv) SEQ

ID NO: 33 and SEQ ID NO: 34, respectively; and (b) a heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprising one or more of the following: (i) a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; (ii) a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139, (iii) a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; (iv) an alanine to a cysteine substitution at amino acid position 1; and/or a light chain $C_L$ sequence of SEQ ID NO: 157 comprising a valine to cysteine substitution at amino acid position 98.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 35 and SEQ ID NO: 41, respectively; (ii) SEQ ID NO: 43 and SEQ ID NO: 49, respectively; (iii) SEQ ID NO: 51 and SEQ ID NO: 57, respectively; (iv) SEQ ID NO: 59 and SEQ ID NO: 65, respectively; (v) SEQ ID NO: 67 and SEQ ID NO: 73, respectively; (vi) SEQ ID NO: 75 and SEQ ID NO: 81, respectively; (vii) SEQ ID NO: 83 and SEQ ID NO: 89, respectively; (viii) SEQ ID NO: 91 and SEQ ID NO: 97, respectively; (ix) SEQ ID NO: 99 and SEQ ID NO: 105, respectively; (x) SEQ ID NO: 107 and SEQ ID NO: 113, respectively; (xi) SEQ ID NO: 115 and SEQ ID NO: 121, respectively; (xii) SEQ ID NO: 123 and SEQ ID NO: 129, respectively; (xiii) SEQ ID NO: 131 and SEQ ID NO: 137, respectively; (xiv) SEQ ID NO: 139 and SEQ ID NO: 145, respectively; or (xv) SEQ ID NO: 147 and SEQ ID NO: 153, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 36 and SEQ ID NO: 41, respectively; (ii) SEQ ID NO: 44 and SEQ

ID NO: 49, respectively; (iii) SEQ ID NO: 52 and SEQ ID NO: 57, respectively; (iv) SEQ ID NO: 60 and SEQ ID NO: 65, respectively; (v) SEQ ID NO: 68 and SEQ ID NO: 73, respectively; (vi) SEQ ID NO: 76 and SEQ ID NO: 81, respectively; (vii) SEQ ID NO: 84 and SEQ ID NO: 89, respectively; (viii) SEQ ID NO: 92 and SEQ ID NO: 97, respectively; (ix) SEQ ID NO: 100 and SEQ ID NO: 105, respectively; (x) SEQ ID NO: 108 and SEQ ID NO: 113, respectively; (xi) SEQ ID NO: 116 and SEQ ID NO: 121, respectively; (xii) SEQ ID NO: 124 and SEQ ID NO: 129, respectively; (xiii) SEQ ID NO: 132 and SEQ ID NO: 137, respectively; (xiv) SEQ ID NO: 140 and SEQ ID NO: 145, respectively; or (xv) SEQ ID NO: 148 and SEQ ID NO: 153, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 37 and SEQ ID NO: 41, respectively; (ii) SEQ ID NO: 45 and SEQ ID NO: 49, respectively; (iii) SEQ ID NO: 53 and SEQ ID NO: 57, respectively; (iv) SEQ ID NO: 61 and SEQ ID NO: 65, respectively; (v) SEQ ID NO: 69 and SEQ ID NO: 73, respectively; (vi) SEQ ID NO: 77 and SEQ ID NO: 81, respectively; (vii) SEQ ID NO: 85 and SEQ ID NO: 89, respectively; (viii) SEQ ID NO: 93 and SEQ ID NO: 97, respectively; (ix) SEQ ID NO: 101 and SEQ ID NO: 105, respectively; (x) SEQ ID NO: 109 and SEQ ID NO: 113, respectively; (xi) SEQ ID NO: 117 and SEQ ID NO: 121, respectively; (xii) SEQ ID NO: 125 and SEQ ID NO: 129, respectively; (xiii) SEQ ID NO: 133 and SEQ ID NO: 137, respectively; (xiv) SEQ ID NO: 141 and SEQ ID NO: 145, respectively; or (xv) SEQ ID NO: 149 and SEQ ID NO: 153, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine

substitution at amino acid position 98. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 35 and SEQ ID NO: 42, respectively; (ii) SEQ ID NO: 43 and SEQ ID NO: 50, respectively; (iii) SEQ ID NO: 51 and SEQ ID NO: 58, respectively; (iv) SEQ ID NO: 59 and SEQ ID NO: 66, respectively; (v) SEQ ID NO: 67 and SEQ ID NO: 74, respectively; (vi) SEQ ID NO: 75 and SEQ ID NO: 82, respectively; (vii) SEQ ID NO: 83 and SEQ ID NO: 90, respectively; (viii) SEQ ID NO: 91 and SEQ ID NO: 98, respectively; (ix) SEQ ID NO: 99 and SEQ ID NO: 106, respectively; (x) SEQ ID NO: 107 and SEQ ID NO: 114, respectively; (xi) SEQ ID NO: 115 and SEQ ID NO: 122, respectively; (xii) SEQ ID NO: 123 and SEQ ID NO: 130, respectively; (xiii) SEQ ID NO: 131 and SEQ ID NO: 138, respectively; (xiv) SEQ ID NO: 139 and SEQ ID NO: 146, respectively; or (xv) SEQ ID NO: 147 and SEQ ID NO: 154, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 36 and SEQ ID NO: 42, respectively; (ii) SEQ ID NO: 44 and SEQ ID NO: 50, respectively; (iii) SEQ ID NO: 52 and SEQ ID NO: 58, respectively; (iv) SEQ ID NO: 60 and SEQ ID NO: 66, respectively; (v) SEQ ID NO: 68 and SEQ ID NO: 74, respectively; (vi) SEQ ID NO: 76 and SEQ ID NO: 82, respectively; (vii) SEQ ID NO: 84 and SEQ ID NO: 90, respectively; (viii) SEQ ID NO: 92 and SEQ ID NO: 98, respectively; (ix) SEQ ID NO: 100 and SEQ ID NO: 106, respectively; (x) SEQ ID NO: 108 and SEQ ID NO: 114, respectively; (xi) SEQ ID NO: 116 and SEQ ID NO: 122, respectively; (xii) SEQ ID NO: 124 and SEQ ID NO: 130, respectively; (xiii) SEQ ID NO: 132 and SEQ ID NO: 138, respectively; (xiv) SEQ ID NO: 140 and SEQ ID NO: 146, respectively; or (xv) SEQ ID NO: 148 and SEQ ID NO: 154, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine

substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139; and the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 37 and SEQ ID NO: 42, respectively; (ii) SEQ ID NO: 45 and SEQ ID NO: 50, respectively; (iii) SEQ ID NO: 53 and SEQ ID NO: 58, respectively; (iv) SEQ ID NO: 61 and SEQ ID NO: 66, respectively; (v) SEQ ID NO: 69 and SEQ ID NO: 74, respectively; (vi) SEQ ID NO: 77 and SEQ ID NO: 82, respectively; (vii) SEQ ID NO: 85 and SEQ ID NO: 90, respectively; (viii) SEQ ID NO: 93 and SEQ ID NO: 98, respectively; (ix) SEQ ID NO: 101 and SEQ ID NO: 106, respectively; (x) SEQ ID NO: 109 and SEQ ID NO: 114, respectively; (xi) SEQ ID NO: 117 and SEQ ID NO: 122, respectively; (xii) SEQ ID NO: 125 and SEQ ID NO: 130, respectively; (xiii) SEQ ID NO: 133 and SEQ ID NO: 138, respectively; (xiv) SEQ ID NO: 141 and SEQ ID NO: 146, respectively; or (xv) SEQ ID NO: 149 and SEQ ID NO: 154, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: amino acid a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at positions 106 and 108; and an alanine to a cysteine substitution at amino acid position 1. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 38 and SEQ ID NO: 41, respectively; (ii) SEQ ID NO: 46 and SEQ ID NO: 49, respectively; (iii) SEQ ID NO: 54 and SEQ ID NO: 57, respectively; (iv) SEQ ID NO: 62 and SEQ ID NO: 65, respectively; (v) SEQ ID NO: 70 and SEQ ID NO: 73, respectively; (vi) SEQ ID NO: 78 and SEQ ID NO: 81, respectively; (vii) SEQ ID NO: 86 and SEQ ID NO: 89, respectively; (viii) SEQ ID NO: 94 and SEQ ID NO: 97, respectively; (ix) SEQ ID NO: 102 and SEQ ID NO: 105, respectively; (x) SEQ ID NO: 110 and SEQ ID NO: 113, respectively; (xi) SEQ ID NO: 118 and SEQ ID NO: 121, respectively; (xii) SEQ ID NO: 126 and SEQ ID NO: 129, respectively; (xiii) SEQ ID NO: 134 and SEQ ID NO: 137, respectively; (xiv) SEQ ID NO: 142 and SEQ ID NO: 145, respectively; or (xv) SEQ ID NO: 150 and SEQ ID NO: 153, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and an alanine to a cysteine substitution at amino acid position 1. In some embodiments of any of the antibodies described herein, the antibody comprises a heavy chain and a light chain sequence selected from the group of: (i) SEQ ID NO: 39 and SEQ ID NO: 41, respectively; (ii) SEQ ID NO: 47 and SEQ ID NO: 49, respectively; (iii) SEQ ID NO: 55 and SEQ ID NO: 57, respectively; (iv) SEQ ID NO: 63 and SEQ ID NO: 65, respectively; (v) SEQ ID NO: 71 and SEQ ID NO: 73, respectively; (vi) SEQ ID NO: 79 and SEQ ID NO: 81, respectively; (vii) SEQ ID NO: 87 and SEQ ID NO: 89, respectively; (viii) SEQ ID NO: 95 and SEQ ID NO: 97, respectively; (ix) SEQ ID NO: 103 and SEQ ID NO: 105, respectively; (x) SEQ ID NO: 111 and SEQ ID NO: 113, respectively; (xi) SEQ ID NO: 119 and SEQ ID NO: 121, respectively; (xii) SEQ ID NO: 127 and SEQ ID NO: 129, respectively; (xiii) SEQ ID NO: 135 and SEQ ID NO: 137, respectively; (xiv) SEQ ID NO: 143 and SEQ ID NO: 145, respectively; or (xv) SEQ ID NO: 151 and SEQ ID NO: 153, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139; and an alanine to a cysteine substitution at amino acid position 1. In some embodiments of any of the antibodies described herein, the antibody comprises a heavy chain and a light chain sequence selected from the group of: (i) SEQ ID NO: 40 and SEQ ID NO: 41, respectively; (ii) SEQ ID NO: 48 and SEQ ID NO: 49, respectively; (iii) SEQ ID NO: 56 and SEQ ID NO: 57, respectively; (iv) SEQ ID NO: 64 and SEQ ID NO: 65, respectively; (v) SEQ ID NO: 72 and SEQ ID NO: 73, respectively; (vi) SEQ ID NO: 80 and SEQ ID NO: 81, respectively; (vii) SEQ ID NO: 88 and SEQ ID NO: 89, respectively; (viii) SEQ ID NO: 96 and SEQ ID NO: 97, respectively; (ix) SEQ ID NO: 104 and SEQ ID NO: 105, respectively; (x) SEQ ID NO: 112 and SEQ ID NO: 113, respectively; (xi) SEQ ID NO: 120 and SEQ ID NO: 121, respectively; (xii) SEQ ID NO: 128 and SEQ ID NO: 129, respectively; (xiii) SEQ ID NO: 136

and SEQ ID NO: 137, respectively; (xiv) SEQ ID NO: 144 and SEQ ID NO: 145, respectively; or (xv) SEQ ID NO: 152 and SEQ ID NO: 153, respectively.

In some embodiments of any of the antibodies described herein, the antibody further comprises a cytotoxic drug conjugated to one or more of the following: (a) a heavy chain CH1-CH2-CH3 of SEQ ID NO: 155 or SEQ ID NO: 189 comprising one or more of the following: (i) the cysteine at amino acid position 103; (ii) the cysteine of a lysine to cysteine substitution at amino acid position 105; (iii) the cysteine at amino acid position 109; and (iv) the cysteine at amino acid position 112; and/or (b) the cysteine at amino acid position 107 of SEQ ID NO: 157.

In some embodiments of any of the antibodies described herein, the antibody further comprises a cytotoxic or cytostatic agent is conjugated to the cysteine at position 98 of SEQ ID NO: 157.

In some embodiments of any of the antibodies described herein, the antibody further comprises a cytotoxic or cytostatic agent is conjugated to the cysteine at position 1 of SEQ ID NO: 155 or SEQ ID NO: 189.

In some embodiments of any of the antibodies described herein, the cytotoxic or cytostatic agent is a conjugated toxin, a radioisotope, drug, or a small molecule.

In some embodiments of any of the antibodies described herein, (a) the dissociation rate of the antibody 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 antibody 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. In some embodiments of any of the antibodies described herein, a composition comprising the antibody: provides for one or more of: an increase in toxin liberation in a target mammalian cell as compared to a composition comprising the same amount of a control antibody; an increase in target mammalian cell killing as compared to a composition comprising the same amount of a control antibody; and an increase in endolysosomal delivery in the target mammalian cell as compared to a composition comprising the same amount of a control antibody.

In some embodiments of any of the antibodies described herein, a composition comprising the antibody: results in a less of a reduction in the level of MET presented on the surface of a target mammalian cell as compared to a composition comprising the same amount of a control antibody; or does not result in a detectable reduction in the level of MET presented on the surface of the target mammalian cell.

In some embodiments of any of the antibodies described herein, the antibody is degraded in a target mammalian cell following internalization of the antibody by a target mammalian cell. In some embodiments of any of the antibodies described herein, the target mammalian cell is a cancer cell. In some embodiments of any of the antibodies described herein, the antibody is cytotoxic or cytostatic to the target mammalian cell. In some embodiments of any of the antibodies described herein, the antibody has an avidity that results in increased selectivity for cancer cells over non-cancerous cells.

In some embodiments of any of the antibodies described herein, the antibody is: cross-reactive with a non-human primate MET and human MET; or cross-reactive with a non-human primate MET, a human MET, and one or both of rat MET and a mouse MET. In some embodiments of any of the antibodies described herein, the half-life of the antibody in vivo is increased as compared to the half-life of a control antibody in vivo.

Also provided herein are pharmaceutical compositions comprising an effective amount of any of the antibodies described herein. Also provided herein are kits that include at least one dose of any of the antibodies described herein or any of the pharmaceutical compositions described herein.

Also provided herein are methods of treating a cancer characterized by having a population of cancer cells that have MET or an epitope of MET presented on their surface that include administering a therapeutically effective amount of any of the antibodies described herein or any of the pharmaceutical compositions described herein to a subject identified as having a cancer characterized by having the population of cancer cells.

Also provided herein are methods of reducing the volume of a tumor in a subject, where the tumor is characterized by having a population of cancer cells that have MET or an epitope of MET presented on their surface, that include: administering a therapeutically effective amount of any of the antibodies described herein or any of the pharmaceutical compositions described herein to a subject identified as having a cancer characterized by having the population of cancer cells.

Also provided herein are methods of inducing cell death in a cancer cell in a subject, wherein the cancer cell has MET or an epitope of MET presented on its surface, that include: administering a therapeutically effective amount of any of the antibodies described herein or any

of the pharmaceutical compositions described herein to a subject identified as having a cancer characterized by having a population of the cancer cells.

Also provided herein are methods of decreasing the risk of developing a metastasis or decreasing the risk of developing an additional metastasis in a subject having a cancer, where the cancer is characterized by having a population of cancer cells that have MET or an epitope of MET presented on their surface, that include: administering a therapeutically effective amount of any of the antibodies described herein or any of the pharmaceutical compositions described herein to a subject identified as having a cancer characterized by having the population of cancer cells.

Also provided herein are antibodies that include: (a) heavy chain variable domain and a light chain variable domain selected from the group consisting of: (i) SEQ ID NO: 159 and SEQ ID NO: 160, respectively; (ii) SEQ ID NO: 161 and SEQ ID NO: 162, respectively; and (iii) SEQ ID NO: 163 and SEQ ID NO: 164; respectively; and (b) a heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprising one or more of the following substitution(s): (i) a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine amino acid at positions 106 and 108; (ii) a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139, (iii) a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; (iv) an alanine to cysteine substitution at amino acid position 1; and/or a light chain $C_L$ sequence of SEQ ID NO: 157 comprising a valine to cysteine substitution at position 98.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 165 and SEQ ID NO: 171, respectively; (ii) SEQ ID NO: 173 and SEQ ID NO: 179, respectively; or (iii) SEQ ID NO: 181 and SEQ ID NO: 187, respectively.

In some embodiments of any of the antibodies described herein, the heavy CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; a

methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 166 and SEQ ID NO: 171, respectively; (ii) SEQ ID NO: 174 and SEQ ID NO: 179, respectively; or (iii) SEQ ID NO: 182 and SEQ ID NO: 187, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139. In some embodiments of any of the antibodies described herein, the antibody comprises a heavy chain and a light chain sequence selected from the group of: (i) SEQ ID NO: 167 and SEQ ID NO: 171, respectively; (ii) SEQ ID NO: 175 and SEQ ID NO: 179, respectively; or (iii) SEQ ID NO: 183 and SEQ ID NO: 187, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and the light chain $C_L$ sequence of SEQ ID NO: 157 includes a valine to cysteine substitution at amino acid position 98. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 165 and SEQ ID NO: 172, respectively; (ii) SEQ ID NO: 173 and SEQ ID NO: 180, respectively; or (iii) SEQ ID NO: 181 and SEQ ID NO: 188, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and the light chain $C_L$ sequence of SEQ ID NO: 157 includes a valine to cysteine substitution at amino acid position 98. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 166 and SEQ ID NO: 172, respectively;

(ii) SEQ ID NO: 174 and SEQ ID NO: 180, respectively; or (iii) SEQ ID NO: 182 and SEQ ID NO: 188, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139; and the light chain $C_L$ sequence of SEQ ID NO: 157 includes a valine to cysteine substitution at amino acid position 98. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 167 and SEQ ID NO: 172, respectively; (ii) SEQ ID NO: 175 and SEQ ID NO: 180, respectively; or (iii) SEQ ID NO: 183 and SEQ ID NO: 188, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and an alanine to a cysteine substitution at amino acid position 1. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 168 and SEQ ID NO: 171, respectively; (ii) SEQ ID NO: 176 and SEQ ID NO: 179, respectively; or (iii) SEQ ID NO: 184 and SEQ ID NO: 187, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and an alanine to a cysteine substitution at amino acid position 1. In some embodiments of any of the antibodies described herein, the antibody comprises a heavy chain and a light chain sequence selected from the group of: (i) SEQ ID NO: 169 and SEQ ID NO: 171, respectively; (ii) SEQ ID NO: 177 and SEQ ID NO: 179, respectively; or (iii) SEQ ID NO: 185 and SEQ ID NO: 187, respectively.

In some embodiments of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 includes: a lysine to cysteine

substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139; and an alanine to a cysteine substitution at amino acid position 1. In some embodiments of any of the antibodies described herein, the antibody comprises heavy chain and light chain sequences selected from the group of: (i) SEQ ID NO: 170 and SEQ ID NO: 171, respectively; (ii) SEQ ID NO: 178 and SEQ ID NO: 179, respectively; or (iii) SEQ ID NO: 186 and SEQ ID NO: 187, respectively.

In some embodiments of any of the antibodies described herein, the antibody further comprises a cytotoxic drug conjugated to one or more of the following: (a) a heavy chain CH1-CH2-CH3 of SEQ ID NO: 155 or SEQ ID NO: 189 comprising one or more of the following: (i) the cysteine at amino acid position 103; (ii) the cysteine of a lysine to cysteine substitution at amino acid position 105; (iii) the cysteine at amino acid position 109; (iv) the cysteine at amino acid position 112; and/or (b) the cysteine at amino acid position 107 of SEQ ID NO: 157 .

In some embodiments of any of the antibodies described herein, the antibody further comprises a cytotoxic or cytostatic agent is conjugated to the cysteine at position 98 of SEQ ID NO: 157. In some embodiments of any of the antibodies described herein, the antibody further comprises a cytotoxic or cytostatic agent is conjugated to the cysteine at position 1 of SEQ ID NO: 155 or SEQ ID NO: 189.

In some embodiments of any of the antibodies described herein, the cytotoxic or cytostatic agent is a conjugated toxin, a radioisotope, drug, or a small molecule. In some embodiments of any of the antibodies described herein, the antibody is cytotoxic or cytostatic to a target mammalian cell. In some embodiments of any of the antibodies described herein, the antibody is degraded in the target mammalian cell following internalization of the antibody by the target mammalian cell. In some embodiments of any of the antibodies described herein, the target mammalian cell is a cancer cell. In some embodiments of any of the antibodies described herein, the antibody has an avidity that results in increased selectivity for cancer cells over non-cancerous cells.

In some embodiments of any of the antibodies described herein, the antibody is: cross-reactive with a non-human primate MET and human MET; or cross-reactive with a non-human primate MET, a human MET, and one or both of rat MET and a mouse MET.

In some embodiments of any of the antibodies described herein, the half-life of the antibody in vivo is increased as compared to the half-life of a control antibody in vivo.

In some embodiments of any of the antibodies described herein, the target mammalian cell is a cancer cell.

Also provided herein are pharmaceutical compositions comprising an effective amount of any of the antibodies described herein. Also provided herein are kits that include at least one dose of any of the antibodies described herein or any of the pharmaceutical compositions described herein.

Also provided herein are methods of treating a cancer characterized by having a population of cancer cells that have MET or an epitope of MET presented on their surface that include administering a therapeutically effective amount of any of the antibodies described herein or any of the pharmaceutical compositions described herein to a subject identified as having a cancer characterized by having the population of cancer cells.

Also provided herein are methods of reducing the volume of a tumor in a subject, where the tumor is characterized by having a population of cancer cells that have MET or an epitope of MET presented on their surface, that include: administering a therapeutically effective amount of any of the antibodies described herein or any of the pharmaceutical compositions described herein to a subject identified as having a cancer characterized by having the population of cancer cells.

Also provided herein are methods of inducing cell death in a cancer cell in a subject, wherein the cancer cell has MET or an epitope of MET presented on its surface, that include: administering a therapeutically effective amount of any of the antibodies described herein or any of the pharmaceutical compositions described herein to a subject identified as having a cancer characterized by having a population of the cancer cells.

Also provided herein are methods of decreasing the risk of developing a metastasis or decreasing the risk of developing an additional metastasis in a subject having a cancer, where the cancer is characterized by having a population of cancer cells that have MET or an epitope of MET presented on their surface, that include: administering a therapeutically effective amount of any of the antibodies described herein or any of the pharmaceutical compositions described herein to a subject identified as having a cancer characterized by having the population of cancer cells.

An "antigen-binding domain" is one or more protein domain(s) (e.g., formed from amino acids from a single polypeptide or formed from amino acids from two or more polypeptides (e.g., the same or different polypeptides) that is capable of specifically binding to one or more different antigen(s). In some examples, an antigen-binding domain can bind to an antigen or epitope with specificity and affinity similar to that of naturally-occurring antibodies. In some embodiments, the antigen-binding domain can be an antibody or a fragment thereof. In some embodiments, an antigen-binding domain can include an alternative scaffold. Non-limiting examples of antigen-binding domains are described herein. Additional examples of antigen-binding domains are known in the art. In some examples, an antigen-binding domain can bind to a single antigen.

The term "antibody" is used herein in its broadest sense and includes certain types of immunoglobulin molecules that include one or more antigen-binding domains that specifically bind to an antigen or epitope. An antibody specifically includes, e.g., intact antibodies (e.g., intact immunoglobulins, e.g., human IgG (e.g., human IgG1, human IgG2, human IgG3, human IgG4)), antibody fragments, and multi-specific antibodies. One example of an antigen-binding domain is an antigen-binding domain formed by a VH -VL dimer. Additional examples of an antibody are described herein. Additional examples of an antibody are known in the art.

The phrase "endosomal/lysosomal pathway" refers to a network of endosomes (early endosomes, multi-vesicular bodies, late endosomes, and lysosomes) in the cytoplasm of a mammalian cell, wherein molecules internalized through cell-mediated internalization processes, e.g., pinocytosis, micropinocytosis, receptor-mediated endocytosis, and/or phagocytosis, are sorted.

Once the endosomes in the endosomal/lysosomal pathway are purified or isolated, assays for a target protein (e.g., an antibody described herein) can be performed using methods known in the art (ELISA, Western blot, immunofluorescence, and immunoprecipitation followed by an assay for protein concentration), and can be used to determine the concentration or relative level of the target protein in the endosomes. Alternatively, endosomes in the endosomal/lysosomal pathway can be imaged using immunofluorescence microscopy using an detectably-labelled antibody (e.g., a fluorophore-labelled, a dye-labelled, or a GFP-labelled antibody, e.g., CellLight™ Early Endosome-GFP) that specifically binds to a characteristic protein present in the endosomes (e.g., EEA1 for early endosomes) and a fluorophore-labelled antibody that

specifically binds to the protein of interest (e.g., an antibody), and the level of the target protein in the endosomes can be determined by quantitation of the overlap in the fluorescence emissions of the two different antibodies.

The phrase "endolysosomal delivery" refers to rate of accumulation over time or the total accumulation at a specific timepoint of an antibody (e.g., any of the antibodies described herein) in the endosomal/lysosomal pathway in a mammalian cell (e.g., any of the exemplary target mammalian cells described herein).

An exemplary assay for measuring endolysosomal delivery of any of the antibodies described herein include those which involve labeling of an antibody with a fluorescent dye, followed by incubation of the labeled antibody with cells and measurement of cellular fluorescence as an indicator of endolysosomal delivery of the antibody (e.g., as described generally in Wustner, *Traffic* 7(6):699-715, 2006). Alternatively, pH-sensitive dyes which preferentially fluoresce at acidic pH but not neutral pH can be used to label any of the antibodies described herein, which can then be incubated with cells and the cellular fluorescence measured as an indicator of delivery of the antibody into acidic endolysosomal compartments.

The term "population" when used before a noun means two or more of the specific noun. For example, the phrase "a population of cancer cells" means "two or more cancer cells." Non-limiting examples of cancer cells are described herein.

The phrase "cytostatic to a cell" refers to a direct or indirect decrease in the proliferation (cell division) of the cell (e.g., a cancer cell) *in vivo* or *in vitro*. When an agent is cytostatic to a cell, the agent can, e.g., directly or indirectly result in cell cycle arrest of the cell (e.g., a cancer cell). In some examples, an agent that is cytostatic to a cell can reduce the number of cells in a population of the cells that are in S phase (as compared to the number of cells in a population of the cells that are in S phase prior to contact with the agent). In some examples, an agent that is cytostatic to a cell can reduce the percentage of the cells in S phase by at least 20%, at least 40%, at least 60%, or at least 80% (e.g., as compared to the percentage of cells in a population of the cells that are in S phase prior to contact with the agent).

The phrase "cytotoxic to a cell" refers to the inducement, directly or indirectly, in the death (e.g., necrosis or apoptosis) of the cell (e.g., a mammalian cell, e.g., a cancer cell).

"Affinity" refers to the strength of the sum total of non-covalent interactions between an antigen-binding site and its binding partner (e.g., an antigen or epitope). Unless indicated

otherwise, as used herein, "affinity" refers to intrinsic binding affinity, which reflects a 1:1 interaction between members of an antigen-binding domain and an antigen or epitope. The affinity of a molecule X for its partner Y can be represented by the dissociation equilibrium constant ($K_D$). Affinity can be measured by common methods known in the art, including those described herein. Affinity can be determined, for example, using surface plasmon resonance (SPR) technology (e.g., BIACORE®) or biolayer interferometry (e.g., FORTEBIO®). Additional methods for determining the affinity for an antigen-binding domain and its corresponding antigen or epitope are known in the art.

The term "epitope" means a portion of an antigen that is specifically bound by an antigen-binding domain through a set of physical interactions between: (i) all monomers (e.g. individual amino acid residues, sugar side chains, and post-translationally modified amino acid residues) on the portion of the antigen-binding domain that specifically binds the antigen and (ii) all monomers (e.g. individual amino acid residues, sugar side chains, post-translationally modified amino acid residues) on the portion of the antigen that is specifically bound by the antigen-binding domain. Epitopes can, e.g., consist of surface-accessible amino acid residues, sugar side chains, phosphorylated amino acid residues, methylated amino acid residues, and/or acetylated amino acid residues and may have specific three-dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that binding to the former, but not the latter, may be lost in the presence of denaturing solvents. In some embodiments, an epitope is defined by a linear amino acid sequence of at least about 3 to 6 amino acids, or about 10 to 15 amino acids. In some embodiments, an epitope refers to a portion of a full-length protein or a portion thereof that is defined by a three-dimensional structure (e.g., protein folding). In some embodiments, an epitope is defined by a discontinuous amino acid sequence that is brought together via protein folding. In some embodiments, an epitope is defined by a discontinuous amino acid sequence that is brought together by quaternary structure (e.g., a cleft formed by the interaction of two different polypeptide chains). The amino acid sequences between the residues that define the epitope may not be critical to three-dimensional structure of the epitope. A conformational epitope may be determined and screened using assays that compare binding of an antibody to a denatured version of the antigen, such that a linear epitope is generated. An epitope may include

amino acid residues that are directly involved in the binding, and other amino acid residues, which are not directly involved in the binding.

Methods for identifying an epitope to which an antigen-binding domain specifically binds are known in the art, e.g., structure-based analysis (e.g. X-ray crystallography, NMR, and/or electron microscopy) (e.g. on the antigen and/or the antigen-antigen binding domain complex) and/or mutagenesis-based analysis (e.g. alanine scanning mutagenesis, glycine scanning mutagenesis, and homology scanning mutagenesis) wherein mutants are measured in a binding assay with a binding partner, many of which are known in the art.

The term "paratope" means a portion of an antigen-binding domain that specifically binds to an antigen through a set of physical interactions between: (i) all monomers (e.g. individual amino acid residues, sugar side chains, posttranslationally modified amino acid residues) on the portion of the antigen-binding domain that specifically binds the antigen and (ii) all monomers (e.g. individual amino acid residues, sugar side chains, posttranslationally modified amino acid residues) on the portion of the antigen that is specifically bound by the antigen-binding domain. Paratopes can, e.g. consist of surface-accessible amino acid residues and may have specific three-dimensional structural characteristics, as well as specific charge characteristics. In some embodiments, a paratope refers to a portion of a full-length antigen-binding domain or a portion thereof that is defined by a three-dimensional structure (e.g., protein folding). In some embodiments, a paratope is defined by a discontinuous amino acid sequence that is brought together via protein folding. In some embodiments, an epitope is defined by a discontinuous amino acid sequence that is brought together by quaternary structure (e.g., a cleft formed by the interaction of two different polypeptide chains). The amino acid sequences between the residues that define the paratope may not be critical to three-dimensional structure of the paratope. A paratope may comprise amino acid residues that are directly involved in the binding, and other amino acid residues, which are not directly involved in the binding.

Methods for identifying a paratope to which an antigen-binding domain specifically binds are known in the art, e.g., structure-based analysis (e.g., X-ray crystallography, NMR, and/or electron microscopy) (e.g. on the antigen-binding domain, and/or the antigen binding domain-antigen complex), and/or mutagenesis-based analysis (e.g., alanine scanning mutagenesis, glycine scanning mutagenesis, and homology scanning mutagenesis) wherein mutants are measured in a binding assay with a binding partner, many of which are known in the art.

The phrase "present on the surface of a mammalian cell" means (1) an antigen that physically attached to or at least partially embedded in the plasma membrane of a mammalian cell (e.g., a transmembrane protein, a peripheral membrane protein, a lipid-anchored protein (e.g., a GPI-anchor), an N-myristolyated protein, or a S-palmitoylated protein) or (2) an antigen that is stably bound to its cognate receptor, where the cognate receptor is physically attached to the plasma membrane of a mammalian cell (e.g., a ligand bound to its cognate receptor, where the cognate receptor is physically attached to the plasma membrane). Non-limiting methods for determining the presence of antigen on the surface of a mammalian cell include fluorescence-activated cell sorting (FACS), immunohistochemistry, cell-fractionation assays and Western blotting.

The phrase "control antibody" means (i) an antibody that is capable of specifically binding to MET or an epitope of MET presented on the surface of a mammalian cell (e.g., a target mammalian cell), where one or both of the following is true: (a) the dissociation rate of the first antigen-binding domain at a pH of about 4.0 to about 6.5 (e.g., any of the subranges of this range described herein) is no more than 3-fold (e.g., no more than 2.8-fold, no more than 2.6-fold, no more than 2.5-fold, no more than 2.4-fold, no more than 2.2-fold, no more than 2.0-fold, no more than 1.8-fold, no more than 1.6-fold, no more than 1.5-fold, no more than 1.4-fold, no more than 1.2-fold, no more than 1.0-fold, no more than 0.8-fold, no more than 0.6-fold, no more than 0.5-fold, no more than 0.4-fold, no more than 0.3-fold no more than 0.2-fold, or no more than 0.1-fold) faster than the dissociation rate at a pH of about 7.0 to about 8.0 (e.g., any of the subranges of this range described herein); or (b) the dissociation constant ($K_D$) of the first antigen-binding domain at a pH of about 4.0 to about 6.5 (e.g., any of the subranges of this range described herein) is no more than 3-fold (e.g., no more than 2.8-fold, no more than 2.6-fold, no more than 2.5-fold, no more than 2.4-fold, no more than 2.2-fold, no more than 2.0-fold, no more than 1.8-fold, no more than 1.6-fold, no more than 1.5-fold, no more than 1.4-fold, no more than 1.2-fold, no more than 1.0-fold, no more than 0.8-fold, no more than 0.6-fold, no more than 0.5-fold, no more than 0.4-fold, no more than 0.3-fold no more than 0.2-fold, or no more than 0.1-fold) greater than the $K_D$ at a pH of about 7.0 to about 8.0 (e.g., any of the subranges of this range described herein); and/or (ii) Telisotuzumab; (iii) Emibetuzumab; and/or (iv) P3D12.

The term "extracellular space" means the liquid exterior to the plasma membrane of a mammalian cell. When a mammalian cell is *in vitro*, the extracellular space can be a liquid

culture medium. When a mammalian cell is *in vivo*, the extracellular space can be, e.g., plasma, serum, blood, interstitial fluid, or lymph.

The term "endolysosomal space" means the fluid encapsulated by the vesicles and organelles that make-up the endosomal/lysosomal pathway in a mammalian cell.

The phrase "a reduced level" or "a decreased level" can be a reduction or decrease of at least a 1% (e.g., at least 2%, at least 4%, at least 6%, at least 8%, at least 10%, at least 12%, at least 14%, at least 16%, at least 18%, at least 20%, at least 22%, at least 24%, at least 26%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%) reduction as compared to a reference level or value.

The term "cell killing potency" refers to the ability of an agent (e.g., any of the antibodies described herein) to induce, directly or indirectly, the apoptosis and/or necrosis of a mammalian cell (e.g., a cancer cell), measured as a rate over time or at a relevant timepoint. Methods for determining the cell killing potency of a cell are known in the art (e.g., trypan blue staining, microscopy, fluorescence-assisted cell sorting, and assays to detect markers of apoptosis (e.g., Annexin V)). In non-limiting examples, cell killing potency can be measured, e.g., by cell killing at a single concentration of an agent, by the IC50 of the agent (i.e. the concentration of the agent whereby half the maximal cell killing potency is achieved), or by the ratio of an agent's dissociation constant KD on mammalian cells divided by its IC50. In some non-limiting examples, the IC50s and/or the KD ratios described herein are compared to those of a control antibody (as defined herein), and, optionally, demonstrate that the antibodies described herein have a higher cell killing potency as compared to the control antibody.

The term "toxin liberation" refers to the ability of a mammalian cell (e.g., a non-cancerous mammalian cell or a cancer cell) to internalize (e.g., via pinocytosis and/or receptor-mediated endocytosis) any of the antibodies described herein (e.g., any of antibodies or control antibodies described herein) that are conjugated to a toxin, and subsequently release the toxin conjugated to the antibody, measured as a rate over time or at a specific timepoint. Toxin liberation can be assessed using a variety of different exemplary assays, e.g., ELISA, immunofluorescence, cell killing assays, cell cycle arrest assays, DNA damage assays, mass spectrometry, HPLC, and/or an isotope-labeled toxin.

The phrase "target cell" or "target mammalian cell" or "mammalian target cell" means a mammalian cell that has at least one MET present on its surface. In some examples, a mammalian target cell can be a cancer cell. In some embodiments of a target mammalian cell can have a total of about 1 to about 10,000,000, about 1 to about 9,000,000, about 1 to about 8,000,000, about 1 to about 7,000,000, about 1 to about 6,000,000, about 1 to about 5,000,000, about 1 to about 4,000,000, about 1 to about 3,000,000, about 1 to about 2,000,000, about 1 to about 1,000,000, about 1 to about 800,000, about 1 to about 600,000, about 1 to about 400,000, about 1 to about 200,000, about 1 to about 100,000, about 1 to about 80,000, about 1 to about 80,000, about 1 to about 75,000, about 1 to about 70,000, about 1 to about 65,000, about 1 to about 60,000, about 1 to about 55,000, about 1 to about 50,000, about 1 to about 45,000, about 1 to about 40,000, about 1 to about 35,000, about 1 to about 30,000, about 1 to about 25,000, about 1 to about 20,000, about 1 to about 15,000, about 1 to about 10,000, about 1 to about 7,500, about 1 to about 5,000, about 1 to about 4,000, about 1 to about 3,000, about 1 to about 2,000, about 1 to about 1,000, about 1 to about 500, about 1 to about 100, about 1 to about 50, about 1 to about 10, about 10 to about 10,000,000, about 10 to about 9,000,000, about 10 to about 8,000,000, about 10 to about 7,000,000, about 10 to about 6,000,000, about 10 to about 5,000,000, about 10 to about 4,000,000, about 10 to about 3,000,000, about 10 to about 2,000,000, about 10 to about 1,000,000, about 10 to about 800,000, about 10 to about 600,000, about 10 to about 400,000, about 10 to about 200,000, about 10 to about 100,000, about 10 to about 80,000, about 10 to about 80,000, about 10 to about 75,000, about 10 to about 70,000, about 10 to about 65,000, about 10 to about 60,000, about 10 to about 55,000, about 10 to about 50,000, about 10 to about 45,000, about 10 to about 40,000, about 10 to about 35,000, about 10 to about 30,000, about 10 to about 25,000, about 10 to about 20,000, about 10 to about 15,000, about 10 to about 10,000, about 10 to about 7,500, about 10 to about 5,000, about 10 to about 4,000, about 10 to about 3,000, about 10 to about 2,000, about 10 to about 1,000, about 10 to about 500, about 10 to about 100, about 10 to about 50, about 50 to about 10,000,000, about 50 to about 9,000,000, about 50 to about 8,000,000, about 50 to about 7,000,000, about 50 to about 6,000,000, about 50 to about 5,000,000, about 50 to about 4,000,000, about 50 to about 3,000,000, about 50 to about 2,000,000, about 50 to about 1,000,000, about 50 to about 800,000, about 50 to about 600,000, about 50 to about 400,000, about 50 to about 200,000, about 50 to about 100,000, about 50 to about 80,000, about 50 to about 80,000, about 50 to about 75,000,

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The phrase "antigen density" means the number of MET present on the surface of a target mammalian cell or the average number of MET on the surface of a population of particular type of target mammalian cells. It can be measured, e.g., using the Quantibright bead kit or radiolabel (e.g., BD Biosciences PE Phycoerythrin Fluorescence Quantitation Kit, catalog #340495).

The phrase "amino acid substituted with a histidine" means the substitution of an amino acid residue that is not histidine in a reference polypeptide sequence with a histidine. Non-limiting methods for substituting an amino acid residue in a reference polypeptide with a histidine are described herein. Additional methods for substituting an amino acid residue in a reference polypeptide with a histidine are known in the art.

The phrase "amino acid substituted with an alanine" means the substitution of an amino acid residue that is a histidine in a reference polypeptide sequence with an alanine. Non-limiting methods for substituting a histidine in a reference polypeptide with an alanine are described herein. Additional methods for substituting a histidine in a reference polypeptide with an alanine are known in the art.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

## BRIEF DESCRIPTION OF DRAWINGS

**Figures 1A-C: Internalization and endolysosomal delivery of histidine scanning and alanine scanning variants of EMIIBETUZUMAB and P3D12 in Detroit 562 cells.** MYT4826 (EMIBETUZUMAB) and MYT4325 (P3D12), heavy chain combination histidine scanning and alanine scanning variants, were assayed for internalization on Detroit 562 cells using Incucyte Human FabFluor-pH red antibody labeling reagent at the indicated timepoint and final concentration of ABPC. Fold-increases in internalization and endolysosomal delivery are indicated by the numbers above each variant. All variants include the TH and YTE substitution format.

**Figure 2: Binding of histidine scanning and alanine scanning variants of TELISOTUZUMAB to MET by biolayer interferometry.** MYT4953 heavy chain combination histidine scanning and alanine scanning variants, were captured on anti-human Fc biosensors and associated with MET at pH 7.4. Dissociation was at pH 7.4 (black trace) or pH 5.4 (grey trace). All variants include the TH and YTE substitution format.

**Figures 3A to 3C: Binding of histidine scanning and alanine scanning variants of P3D12 to MET by biolayer interferometry.** MYT4312, MYT4313, and MYT4325, heavy chain combination histidine scanning and alanine scanning variants, were captured on anti-human Fc biosensors and associated with MET at low pH or high pH, as specified in the figures. All variants include the TH and YTE substitution format.

**Figures 4A to 4D: Binding of histidine scanning and alanine scanning variants of P3D12 and Emibetuzumab to MET by biolayer interferometry.** MYT5344, MYT5351, MYT5367, and MYT4826, paired heavy and light chain histidine scanning and alanine scanning variants, combining light chain histidine and alanine scanning variants or light chain combination histidine scanning and alanine scanning variants with heavy chain histidine and alanine scanning variants or heavy chain combination histidine scanning and alanine scanning variants, were captured on anti-human Fc biosensors and associated with MET at pH 7.4. Dissociation was at pH 7.4 (black trace) or pH 5.4 (grey trace). All variants include the TH and YTE substitution format.

**Figure 5: Table of different tested antibodies with the variable heavy and variable light chain sequences listed.**

**Figure 6**: **Internalization and endolysosomal delivery of histidine scanning and alanine scanning variants of MYT variants in Detroit 562 cells**
MYT4826 , MYT4827, MYT4837, MYT4325, MYT5351, MYT4312, MYT5309, MYT4849, MYTH4888, MYT5344, MYT4313, MYT5367, MYT4942, MYT4953, and MYT4940, heavy chain combination histidine scanning and alanine scanning variants, were assayed for internalization on Detroit 562 cells using Incucyte Human FabFluor-pH red antibody labeling

reagent at the indicated timepoint and final concentration of antibody. Fold-increases in internalization and endolysosomal delivery are indicated by the numbers next to each variant. All variants include the TH and YTE substitution format.

**Figures 7A-G: Binding of histidine scanning and alanine scanning variants to MET by biolayer interferometry**

MYT4940, MYT4942, MYT4888, MYT4827, MYT4837, MYT4849, and MYT5309, paired heavy and light chain histidine scanning and alanine scanning variants, combining light chain histidine and alanine scanning variants or light chain combination histidine scanning and alanine scanning variants with heavy chain histidine and alanine scanning variants or heavy chain combination histidine scanning and alanine scanning variants, were captured on anti-human Fc biosensors and associated with MET at pH 7.4. The black trace represents pH 7.4, the red trace represents association at 7.4 and then dissociation at pH 6.4, and the orange trace represents pH 6.4 All variants include the TH and YTE substitution format.

## DETAILED DESCRIPTION

Provided herein are antibodies that are capable of specifically binding MET or an epitope of MET presented on the surface of a target mammalian cell, where: (a) the dissociation rate 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; and/or (b) the dissociation constant ($K_D$) 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. In some examples of these antibodies, the antibody is degraded in the target mammalian cell following internalization of the antibody by the target mammalian cell. Some examples of any of the antibodies described herein can further include a conjugated toxin, radioisotope, drug, or small molecule (e.g., a fluorophore or dye).

Also provided are antibodies that are capable of specifically binding MET or an epitope of MET presented on the surface of a target mammalian cell; and a conjugated toxin, radioisotope, drug, or small molecule, where: (a) the dissociation rate 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; and/or the dissociation constant ($K_D$) 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) a composition including the antibody provides for one or more (e.g., two or three) of: an increase (e.g., a detectable increase) in toxin liberation in the target

mammalian cell as compared to a composition comprising the same amount of a control antibody; an increase (e.g., a detectable increase) in target mammalian cell killing as compared to a composition comprising the same amount of a control antibody; and an increase (e.g., a detectable increase) in endolysosomal delivery in the target mammalian cell as compared to a composition comprising the same amount of a control antibody.

In some examples of any of the antibodies described herein, the antibody comprises a heavy chain variable domain and a light chain variable domain of Telisotuzumab and or more substitutions in the heavy chain CH1-CH2-CH3 domain and/or the $C_L$ domain of Telisotuzumab. In some examples of any of the antibodies described herein, the antibody includes a heavy chain variable domain and a light chain variable domain of Emibetuzumab and one or more amino acid substitutions in the heavy CH1-CH2-CH3 domain and/or the $C_L$ domain of Emibetuzumab. In some example of any of the antibodies described herein, the antibody includes a heavy chain variable domain and a light chain variable domain of P3D12 anti-cMET and one or more amino acid substitutions in the heavy CH1-CH2-CH3 domain and/or the $C_L$ domain of P3D12-cMet.

In some examples of any of the antibodies described herein, the antibody comprises (a) a heavy chain variable domain and a light chain variable domain selected from the group of: (i) SEQ ID NO: 5 and SEQ ID NO: 6, respectively; (ii) SEQ ID NO: 7 and SEQ ID NO: 8, respectively; (iii) SEQ ID NO: 9 and SEQ ID NO: 10, respectively; (iv) SEQ ID NO: 11 and SEQ ID NO: 12, respectively; (v) SEQ ID NO: 13 and SEQ ID NO: 14, respectively; (vi) SEQ ID NO: 15 and SEQ ID NO: 16, respectively; (vii) SEQ ID NO: 17 and SEQ ID NO: 18, respectively; (viii) SEQ ID NO: 19 and SEQ ID NO: 20, respectively; (ix) SEQ ID NO: 21 and SEQ ID NO: 22, respectively; (x) SEQ ID NO: 23 and SEQ ID NO: 24, respectively; (xi) SEQ ID NO: 25 and SEQ ID NO: 26, respectively; (xii) SEQ ID NO: 27 and SEQ ID NO: 28, respectively; (xiii) SEQ ID NO: 29 and SEQ ID NO: 30, respectively; (xiv) SEQ ID NO: 31 and SEQ ID NO: 32, respectively; (xv) SEQ ID NO: 33 and SEQ ID NO: 34, respectively; and (b) a heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprising one or more of the following: (i) a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; (ii) a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139, (iii) a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at

amino acid position 317; (iv) an alanine to a cysteine substitution at amino acid position 1; and/or a light chain $C_L$ sequence of SEQ ID NO: 157 comprising a valine to cysteine substitution at amino acid position 98.

In some examples of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108. In some examples of any of the antibodies described herein, the heavy chain and light chain sequences are: (i) SEQ ID NO: 35 and SEQ ID NO: 41, respectively; (ii) SEQ ID NO: 43 and SEQ ID NO: 49, respectively; (iii) SEQ ID NO: 51 and SEQ ID NO: 57, respectively (iv) SEQ ID NO: 59 and SEQ ID NO: 65, respectively; (v) SEQ ID NO: 67 and SEQ ID NO: 73, respectively; (vi) SEQ ID NO: 75 and SEQ ID NO: 81, respectively; (vii) SEQ ID NO: 83 and SEQ ID NO: 89, respectively; (viii) SEQ ID NO: 91 and SEQ ID NO: 97, respectively; (ix) SEQ ID NO: 99 and SEQ ID NO: 105, respectively; (x) SEQ ID NO: 107 and SEQ ID NO: 113, respectively; (xi) SEQ ID NO: 115 and SEQ ID NO: 121, respectively; (xii) SEQ ID NO: 123 and SEQ ID NO: 129, respectively; (xiii) SEQ ID NO: 131 and SEQ ID NO: 137, respectively; (xiv) SEQ ID NO: 139 and SEQ ID NO: 145, respectively; or (xv) SEQ ID NO: 147 and SEQ ID NO: 153, respectively.

In some examples of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317. In some examples of any of the antibodies described herein, the heavy chain and light chain sequences are: (i) SEQ ID NO: 36 and SEQ ID NO: 41, respectively; (ii) SEQ ID NO: 44 and SEQ ID NO: 49, respectively; (iii) SEQ ID NO: 52 and SEQ ID NO: 57, respectively; (iv) SEQ ID NO: 60 and SEQ ID NO: 65, respectively; (v) SEQ ID NO: 68 and SEQ ID NO: 73, respectively; (vi) SEQ ID NO: 76 and SEQ ID NO: 81, respectively; (vii) SEQ ID NO: 84 and SEQ ID NO: 89, respectively; (viii) SEQ ID NO: 92 and SEQ ID NO: 97, respectively; (ix) SEQ ID NO: 100 and SEQ ID NO: 105, respectively; (x) SEQ ID NO: 108 and SEQ ID NO: 113, respectively; (xi) SEQ ID NO: 116 and SEQ ID NO: 121, respectively; (xii) SEQ ID NO: 124 and SEQ ID NO: 129, respectively; (xiii) SEQ ID NO: 132

and SEQ ID NO: 137, respectively; (xiv) SEQ ID NO: 140 and SEQ ID NO: 145, respectively; or (xv) SEQ ID NO: 148 and SEQ ID NO: 153, respectively.

In some examples of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139. In some examples of any of the antibodies described herein, the heavy chain and a light chain sequences are: (i) SEQ ID NO: 37 and SEQ ID NO: 41, respectively; (ii) SEQ ID NO: 45 and SEQ ID NO: 49, respectively; (iii) SEQ ID NO: 53 and SEQ ID NO: 57, respectively (iv) SEQ ID NO: 61 and SEQ ID NO: 65, respectively; (v) SEQ ID NO: 69 and SEQ ID NO: 73, respectively; (vi) SEQ ID NO: 77 and SEQ ID NO: 81, respectively; (vii) SEQ ID NO: 85 and SEQ ID NO: 89, respectively; (viii) SEQ ID NO: 93 and SEQ ID NO: 97, respectively; (ix) SEQ ID NO: 101 and SEQ ID NO: 105, respectively; (x) SEQ ID NO: 109 and SEQ ID NO: 113, respectively; (xi) SEQ ID NO: 117 and SEQ ID NO: 121, respectively; (xii) SEQ ID NO: 125 and SEQ ID NO: 129, respectively; (xiii) SEQ ID NO: 133 and SEQ ID NO: 137, respectively; (xiv) SEQ ID NO: 141 and SEQ ID NO: 145, respectively; or (xv). SEQ ID NO: 149 and SEQ ID NO: 153, respectively.

In some examples of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98. In some examples of any of the antibodies described herein, heavy chain and light chain sequences are: (i) SEQ ID NO: 35 and SEQ ID NO: 42, respectively; (ii) SEQ ID NO: 43 and SEQ ID NO: 50, respectively; (iii) SEQ ID NO: 51 and SEQ ID NO: 58, respectively (iv) SEQ ID NO: 59 and SEQ ID NO: 66, respectively; (v) SEQ ID NO: 67 and SEQ ID NO: 74, respectively; (vi) SEQ ID NO: 75 and SEQ ID NO: 82, respectively; (vii) SEQ ID NO: 83 and SEQ ID NO: 90, respectively; (viii) SEQ ID NO: 91 and SEQ ID NO: 98, respectively; (ix) SEQ ID NO: 99 and SEQ ID NO: 106, respectively; (x) SEQ ID NO: 107 and SEQ ID NO: 114, respectively; (xi) SEQ ID NO: 115 and SEQ ID NO: 122, respectively; (xii) SEQ ID NO: 123 and SEQ ID NO: 130, respectively; (xiii) SEQ ID NO: 131

and SEQ ID NO: 138, respectively; (xiv) SEQ ID NO: 139 and SEQ ID NO: 146, respectively; or (xv) SEQ ID NO: 147 and SEQ ID NO: 154, respectively.

In some examples of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98. In some examples of any of the antibodies described herein, the heavy chain and light chain sequences are: (i) SEQ ID NO: 36 and SEQ ID NO: 42, respectively;(ii) SEQ ID NO: 44 and SEQ ID NO: 50, respectively; (iii) SEQ ID NO: 52 and SEQ ID NO: 58, respectively; (iv) SEQ ID NO: 60 and SEQ ID NO: 66, respectively; (v) SEQ ID NO: 68 and SEQ ID NO: 74, respectively; (vi) SEQ ID NO: 76 and SEQ ID NO: 82, respectively; (vii) SEQ ID NO: 84 and SEQ ID NO: 90, respectively; (viii) SEQ ID NO: 92 and SEQ ID NO: 98, respectively; (ix) SEQ ID NO: 100 and SEQ ID NO: 106, respectively; (x) SEQ ID NO: 108 and SEQ ID NO: 114, respectively; (xi) SEQ ID NO: 116 and SEQ ID NO: 122, respectively; (xii) SEQ ID NO: 124 and SEQ ID NO: 130, respectively; (xiii) SEQ ID NO: 132 and SEQ ID NO: 138, respectively; (xiv) SEQ ID NO: 140 and SEQ ID NO: 146, respectively; or (xv) SEQ ID NO: 148 and SEQ ID NO: 154, respectively.

In some examples of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139; and the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98. In some examples of any of the antibodies described herein, the heavy chain and light chain sequences are: (i) SEQ ID NO: 37 and SEQ ID NO: 42, respectively; (ii) SEQ ID NO: 45 and SEQ ID NO: 50, respectively; (iii) SEQ ID NO: 53 and SEQ ID NO: 58, respectively; (iv) SEQ ID NO: 61 and SEQ ID NO: 66, respectively; (v) SEQ ID NO: 69 and SEQ ID NO: 74, respectively; (vi) SEQ ID NO: 77 and SEQ ID NO: 82, respectively; (vii) SEQ ID NO: 85 and SEQ ID NO: 90, respectively; (viii) SEQ ID NO: 93 and SEQ ID NO: 98, respectively; (ix) SEQ ID NO: 101 and SEQ ID NO: 106, respectively; (x) SEQ

ID NO: 109 and SEQ ID NO: 114, respectively; (xi) SEQ ID NO: 117 and SEQ ID NO: 122, respectively; (xii) SEQ ID NO: 125 and SEQ ID NO: 130, respectively; (xiii) SEQ ID NO: 133 and SEQ ID NO: 138, respectively; (xiv) SEQ ID NO: 141 and SEQ ID NO: 146, respectively; or (xv) SEQ ID NO: 149 and SEQ ID NO: 154, respectively.

In some examples of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and an alanine to a cysteine substitution at amino acid position 1. In some examples of any of the antibodies described herein, heavy chain and light chain sequences are: (i) SEQ ID NO: 38 and SEQ ID NO: 41, respectively; (ii) SEQ ID NO: 46 and SEQ ID NO: 49, respectively; (iii) SEQ ID NO: 54 and SEQ ID NO: 57, respectively; (iv) SEQ ID NO: 62 and SEQ ID NO: 65, respectively; (v) SEQ ID NO: 70 and SEQ ID NO: 73, respectively; (vi) SEQ ID NO: 78 and SEQ ID NO: 81, respectively; (vii) SEQ ID NO: 86 and SEQ ID NO: 89, respectively; (viii) SEQ ID NO: 94 and SEQ ID NO: 97, respectively; (ix) SEQ ID NO: 102 and SEQ ID NO: 105, respectively; (x) SEQ ID NO: 110 and SEQ ID NO: 113, respectively; (xi) SEQ ID NO: 118 and SEQ ID NO: 121, respectively; (xii) SEQ ID NO: 126 and SEQ ID NO: 129, respectively; (xiii) SEQ ID NO: 134 and SEQ ID NO: 137, respectively; (xiv) SEQ ID NO: 142 and SEQ ID NO: 145, respectively; or (xv) SEQ ID NO: 150 and SEQ ID NO: 153, respectively.

In some examples of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and an alanine to a cysteine substitution at amino acid position 1. In some examples of any of the antibodies described herein, heavy chain and light chain sequences are: (i) SEQ ID NO: 39 and SEQ ID NO: 41, respectively; (ii) SEQ ID NO: 47 and SEQ ID NO: 49, respectively; (iii) SEQ ID NO: 55 and SEQ ID NO: 57, respectively; (iv) SEQ ID NO: 63 and SEQ ID NO: 65, respectively; (v) SEQ ID NO: 71 and SEQ ID NO: 73, respectively; (vi) SEQ ID NO: 79 and SEQ ID NO: 81, respectively; (vii) SEQ ID NO: 87 and SEQ ID NO: 89, respectively; (viii) SEQ ID NO: 95 and SEQ ID NO: 97, respectively; (ix) SEQ ID NO: 103 and SEQ ID NO: 105, respectively; (x) SEQ ID NO: 111 and

SEQ ID NO: 113, respectively; (xi) SEQ ID NO: 119 and SEQ ID NO: 121, respectively; (xii) SEQ ID NO: 127 and SEQ ID NO: 129, respectively; (xiii) SEQ ID NO: 135 and SEQ ID NO: 137, respectively; (xiv) SEQ ID NO: 143 and SEQ ID NO: 145, respectively; or (xv) SEQ ID NO: 151 and SEQ ID NO: 153, respectively.

In some examples of any of any of the antibodies described herein, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139; and an alanine to a cysteine substitution at amino acid position 1. In some examples of any of the antibodies described herein, the heavy chain and a light chain sequences are: (i) SEQ ID NO: 40 and SEQ ID NO: 41, respectively; (ii) SEQ ID NO: 48 and SEQ ID NO: 49, respectively; (iii) SEQ ID NO: 56 and SEQ ID NO: 57, respectively; (iv) SEQ ID NO: 64 and SEQ ID NO: 65, respectively; (v) SEQ ID NO: 72 and SEQ ID NO: 73, respectively; (vi) SEQ ID NO: 80 and SEQ ID NO: 81, respectively; (vii) SEQ ID NO: 88 and SEQ ID NO: 89, respectively; (viii) SEQ ID NO: 96 and SEQ ID NO: 97, respectively; (ix) SEQ ID NO: 104 and SEQ ID NO: 105, respectively; (x) SEQ ID NO: 112 and SEQ ID NO: 113, respectively; (xi) SEQ ID NO: 120 and SEQ ID NO: 121, respectively; (xii) SEQ ID NO: 128 and SEQ ID NO: 129, respectively; (xiii) SEQ ID NO: 136 and SEQ ID NO: 137, respectively; (xiv) SEQ ID NO: 144 and SEQ ID NO: 145, respectively; or (xv) SEQ ID NO: 152 and SEQ ID NO: 153, respectively.

In some embodiments, (a) the dissociation rate of the antibody at a pH of about 4.0 to about 6.5 is not 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 antibody 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.

In such examples, the antibody comprises (a) heavy chain variable domain and a light chain variable domain selected from the group consisting of: (i) SEQ ID NO: 159 and SEQ ID NO: 160, respectively; (ii) SEQ ID NO: 161 and SEQ ID NO: 162, respectively; (iii) SEQ ID NO: 163 and SEQ ID NO: 164; respectively; (b) a heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprising one or more of the following substitution(s): (i) a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine amino acid

at positions 106 and 108; (ii) a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139, (iii) a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and (iv) an alanine to cysteine substitution at amino acid position 1; and/or a light chain $C_L$ sequence of SEQ ID NO: 157 comprising a valine to cysteine substitution at position 98.

In such examples, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108 of SEQ ID NO: 155 or SEQ ID NO: 189. In some examples, the heavy chain and light chain sequences are: (i) SEQ ID NO: 165 and SEQ ID NO: 171, respectively; (ii) SEQ ID NO: 173 and SEQ ID NO: 179, respectively; or (iii) SEQ ID NO: 181 and SEQ ID NO: 187, respectively.

In some examples, the heavy CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317. In some examples, the heavy chain and light chain sequences are: (i) SEQ ID NO: 166 and SEQ ID NO: 171, respectively; (ii) SEQ ID NO: 174 and SEQ ID NO: 179, respectively; or (iii) SEQ ID NO: 182 and SEQ ID NO: 187, respectively.

In some examples, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98. In some examples, heavy chain and light chain sequences are: (i) SEQ ID NO: 165 and SEQ ID NO: 172, respectively; (ii) SEQ ID NO: 173 and SEQ ID NO: 180, respectively; or (iii) SEQ ID NO: 181 and SEQ ID NO: 188, respectively.

In some examples, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at

amino acid position 98. In some examples, heavy chain and light chain sequences are: (i) SEQ ID NO: 166 and SEQ ID NO: 172, respectively; (ii) SEQ ID NO: 174 and SEQ ID NO: 180, respectively; or (iii) SEQ ID NO: 182 and SEQ ID NO: 188, respectively.

In some examples, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139; and the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98. In some examples, the heavy chain and light chain sequences are: (i) SEQ ID NO: 167 and SEQ ID NO: 172, respectively; (ii) SEQ ID NO: 175 and SEQ ID NO: 180, respectively; or (iii) SEQ ID NO: 183 and SEQ ID NO: 188, respectively.

In such examples, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and an alanine to a cysteine substitution at amino acid position 1. In such examples, the heavy chain and light chain sequences are: (i) SEQ ID NO: 168 and SEQ ID NO: 171, respectively; (ii) SEQ ID NO: 176 and SEQ ID NO: 179, respectively; or (iii) SEQ ID NO: 184 and SEQ ID NO: 187, respectively.

In some examples, heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and an alanine to a cysteine substitution at amino acid position 1. In some examples, the heavy chain and light chain sequences are: (i) SEQ ID NO: 169 and SEQ ID NO: 171, respectively; (ii) SEQ ID NO: 177 and SEQ ID NO: 179, respectively; or (iii) SEQ ID NO: 185 and SEQ ID NO: 187, respectively.

In some examples, the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises: a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139; and an alanine to a cysteine

substitution at amino acid position 1. In some examples, the heavy chain and light chain sequences are: (i) SEQ ID NO: 170 and SEQ ID NO: 171, respectively; (ii) SEQ ID NO: 178 and SEQ ID NO: 179, respectively; or (iii) SEQ ID NO: 186 and SEQ ID NO: 187, respectively.

Also provided herein are pharmaceutical compositions including any of the antibodies described herein. Also provided herein are methods of treating a subject in need thereof that include administering a therapeutically effective amount of any of the antibodies described herein to the subject.

In some examples of any of the antibodies described herein, a composition including the antibody (e.g., any of the antibodies described herein) can provide for an increase (e.g., a detectable increase) (e.g., at least a 1% increase, at least a 2% increase, at least a 5% increase, at least a 10% increase, at least a 15% increase, at least a 20% increase, at least a 25% increase, at least a 30% increase, at least a 35% increase, at least a 40% increase, at least a 45% increase, at least a 50% increase, at least a 55% increase, at least a 60% increase, at least a 65% increase, at least a 70% increase, at least a 75% increase, at least a 80% increase, at least a 85% increase, at least a 90% increase, at least a 95% increase, at least a 100% increase, at least a 120% increase, at least a 140% increase, at least a 160% increase, at least a 180% increase, at least a 200% increase, at least a 250% increase, at least a 300% increase, at least a 350% increase, at least a 400% increase, at least a 450% increase, at least a 500% increase, at least a 1,000% increase, at least a 2,000% increase, at least a 3,000% increase, at least a 4,000% increase, at least a 5,000% increase, at least a 6,000% increase, at least a 7,000% increase, at least a 8,000% increase, at a least a 9,000% increase, or at least a 10,000% increase, or about a 1% increase to about 10,000% increase, about a 1% increase to about a 9,000% increase, about a 1% increase to about a 8,000% increase, about a 1% increase to about a 7,000% increase, about a 1% increase to about a 6,000% increase, about a 1% increase to about a 5,000% increase, about a 1% increase to about a 4,000% increase, about a 1% increase to about a 3,000% increase, about a 1% increase to about a 2,000% increase, about a 1% increase to about a 1,000% increase, about a 1% increase to about a 500% increase, about a 1% increase to about a 450% increase, about a 1% increase to about a 400% increase, about a 1% increase to about a 350% increase, about a 1% increase to about a 300% increase, about a 1% increase to about a 250% increase, about a 1% increase to about a 200% increase, about a 1% increase to about a 180% increase, about a 1% increase to about a 160% increase, about a 1% increase to about a 140% increase, about a 1% increase to about a

120% increase, about a 1% increase to about a 100% increase, about a 1% increase to about a 95% increase, about a 1% increase to about a 90% increase, about a 1% increase to about a 85% increase, about a 1% increase to about a 80% increase, about a 1% increase to about a 75% increase, about a 1% increase to about a 70% increase, about a 1% increase to about a 65% increase, about a 1% increase to about a 60% increase, about a 1% increase to about a 55% increase, about a 1% increase to about a 50% increase, about a 1% increase to about a 45% increase, about a 1% increase to about a 40% increase, about a 1% increase to about a 35% increase, about a 1% increase to about a 25% increase, about a 1% increase to about a 20% increase, about a 1% increase to about a 15% increase, about a 1% increase to about a 10% increase, about a 1% increase to about a 5% increase, about a 2% increase to about 10,000% increase, about a 2% increase to about a 9,000% increase, about a 2% increase to about a 8,000% increase, about a 2% increase to about a 7,000% increase, about a 2% increase to about a 6,000% increase, about a 2% increase to about a 5,000% increase, about a 2% increase to about a 4,000% increase, about a 2% increase to about a 3,000% increase, about a 2% increase to about a 2,000% increase, about a 2% increase to about a 1,000% increase, about a 2% increase to about a 500% increase, about a 2% increase to about a 450% increase, about a 2% increase to about a 400% increase, about a 2% increase to about a 350% increase, about a 2% increase to about a 300% increase, about a 2% increase to about a 250% increase, about a 2% increase to about a 200% increase, about a 2% increase to about a 180% increase, about a 2% increase to about a 160% increase, about a 2% increase to about a 140% increase, about a 2% increase to about a 120% increase, about a 2% increase to about a 100% increase, about a 2% increase to about a 95% increase, about a 2% increase to about a 90% increase, about a 2% increase to about a 85% increase, about a 2% increase to about a 80% increase, about a 2% increase to about a 75% increase, about a 2% increase to about a 70% increase, about a 2% increase to about a 65% increase, about a 2% increase to about a 60% increase, about a 2% increase to about a 55% increase, about a 2% increase to about a 50% increase, about a 2% increase to about a 45% increase, about a 2% increase to about a 40% increase, about a 2% increase to about a 35% increase, about a 2% increase to about a 25% increase, about a 2% increase to about a 20% increase, about a 2% increase to about a 15% increase, about a 2% increase to about a 10% increase, about a 2% increase to about a 5% increase, about a 5% increase to about 10,000% increase, about a 5% increase to about a 9,000% increase, about a 5% increase to about a 8,000%

increase, about a 5% increase to about a 7,000% increase, about a 5% increase to about a 6,000% increase, about a 5% increase to about a 5,000% increase, about a 5% increase to about a 4,000% increase, about a 5% increase to about a 3,000% increase, about a 5% increase to about a 2,000% increase, about a 5% increase to about a 1,000% increase, about a 5% increase to about a 500% increase, about a 5% increase to about a 450% increase, about a 5% increase to about a 400% increase, about a 5% increase to about a 350% increase, about a 5% increase to about a 300% increase, about a 5% increase to about a 250% increase, about a 5% increase to about a 200% increase, about a 5% increase to about a 180% increase, about a 5% increase to about a 160% increase, about a 5% increase to about a 140% increase, about a 5% increase to about a 120% increase, about a 5% increase to about a 100% increase, about a 5% increase to about a 95% increase, about a 5% increase to about a 90% increase, about a 5% increase to about a 85% increase, about a 5% increase to about a 80% increase, about a 5% increase to about a 75% increase, about a 5% increase to about a 70% increase, about a 5% increase to about a 65% increase, about a 5% increase to about a 60% increase, about a 5% increase to about a 55% increase, about a 5% increase to about a 50% increase, about a 5% increase to about a 45% increase, about a 5% increase to about a 40% increase, about a 5% increase to about a 35% increase, about a 5% increase to about a 25% increase, about a 5% increase to about a 20% increase, about a 5% increase to about a 15% increase, about a 5% increase to about a 10% increase, about a 10% increase to about 10,000% increase, about a 10% increase to about a 9,000% increase, about a 10% increase to about a 8,000% increase, about a 10% increase to about a 7,000% increase, about a 10% increase to about a 6,000% increase, about a 10% increase to about a 5,000% increase, about a 10% increase to about a 4,000% increase, about a 10% increase to about a 3,000% increase, about a 10% increase to about a 2,000% increase, about a 10% increase to about a 1,000% increase, about a 10% increase to about a 500% increase, about a 10% increase to about a 450% increase, about a 10% increase to about a 400% increase, about a 10% increase to about a 350% increase, about a 10% increase to about a 300% increase, about a 10% increase to about a 250% increase, about a 10% increase to about a 200% increase, about a 10% increase to about a 180% increase, about a 10% increase to about a 160% increase, about a 10% increase to about a 140% increase, about a 10% increase to about a 120% increase, about a 10% increase to about a 100% increase, about a 10% increase to about a 95% increase, about a 10% increase to about a 90% increase, about a 10% increase to about a 85% increase, about a

10% increase to about a 80% increase, about a 10% increase to about a 75% increase, about a 10% increase to about a 70% increase, about a 10% increase to about a 65% increase, about a 10% increase to about a 60% increase, about a 10% increase to about a 55% increase, about a 10% increase to about a 50% increase, about a 10% increase to about a 45% increase, about a 10% increase to about a 40% increase, about a 10% increase to about a 35% increase, about a 10% increase to about a 30% increase, about a 10% increase to about a 25% increase, about a 10% increase to about a 20% increase, about a 10% increase to about a 15% increase, about a 15% increase to about 10,000% increase, about a 15% increase to about a 9,000% increase, about a 15% increase to about a 8,000% increase, about a 15% increase to about a 7,000% increase, about a 15% increase to about a 6,000% increase, about a 15% increase to about a 5,000% increase, about a 15% increase to about a 4,000% increase, about a 15% increase to about a 3,000% increase, about a 15% increase to about a 2,000% increase, about a 15% increase to about a 1,000% increase, about a 15% increase to about a 500% increase, about a 15% increase to about a 450% increase, about a 15% increase to about a 400% increase, about a 15% increase to about a 350% increase, about a 15% increase to about a 300% increase, about a 15% increase to about a 250% increase, about a 15% increase to about a 200% increase, about a 15% increase to about a 180% increase, about a 15% increase to about a 160% increase, about a 15% increase to about a 140% increase, about a 15% increase to about a 120% increase, about a 15% increase to about a 100% increase, about a 15% increase to about a 95% increase, about a 15% increase to about a 90% increase, about a 15% increase to about a 85% increase, about a 15% increase to about a 80% increase, about a 15% increase to about a 75% increase, about a 15% increase to about a 70% increase, about a 15% increase to about a 65% increase, about a 15% increase to about a 60% increase, about a 15% increase to about a 55% increase, about a 15% increase to about a 50% increase, about a 15% increase to about a 45% increase, about a 15% increase to about a 40% increase, about a 15% increase to about a 35% increase, about a 15% increase to about a 30% increase, about a 15% increase to about a 25% increase, about a 15% increase to about a 20% increase, about a 20% increase to about 10,000% increase, about a 20% increase to about a 9,000% increase, about a 20% increase to about a 8,000% increase, about a 20% increase to about a 7,000% increase, about a 20% increase to about a 6,000% increase, about a 20% increase to about a 5,000% increase, about a 20% increase to about a 4,000% increase, about a 20% increase to about a 3,000% increase, about a 20% increase to

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In some examples of any of the antibodies described herein, a composition including the antibody (e.g., any of the antibodies described herein) can provide for an increase (e.g., a detectable increase) (e.g., at least a 0.1-fold increase, at least a 0.2-fold increase, at least a 0.3-fold increase, at least a 0.4-fold increase, at least a 0.5-fold increase, at least a 0.6-fold increase, at least a 0.7-fold increase, at least a 0.8-fold increase, at least a 0.9-fold increase, at least a 1.0-fold increase, at least a 1.2-fold increase, at least a 1.4-fold increase, at least a 1.5-fold increase, at least a 1.6-fold increase, at least a 1.8-fold increase, at least a 2.0-fold increase, at least a 2.2-

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40-fold increase to about a 100-fold increase, about 40-fold increase to about a 90-fold increase, about 40-fold increase to about a 80-fold increase, about a 40-fold increase to about a 70-fold increase, about a 40-fold increase to about a 60-fold increase, about a 40-fold increase to about a 50-fold increase, about a 50-fold increase to about a 100-fold increase, about 50-fold increase to about a 90-fold increase, about 50-fold increase to about a 80-fold increase, about a 50-fold increase to about a 70-fold increase, about a 50-fold increase to about a 60-fold increase, about a 60-fold increase to about a 100-fold increase, about 60-fold increase to about a 90-fold increase, about 60-fold increase to about a 80-fold increase, about a 60-fold increase to about a 70-fold increase, about a 70-fold increase to about a 100-fold increase, about 70-fold increase to about a 90-fold increase, about 70-fold increase to about a 80-fold increase, about a 80-fold increase to about a 100-fold increase, about 80-fold increase to about a 90-fold increase, or about a 90-fold increase to about a 100-fold increase) in toxin liberation in the target mammalian cell (e.g., any of the target mammalian cells described herein) as compared to a composition including the same amount of a control antibody (e.g., any of the exemplary control antibodies described herein).

In some examples of any of the antibodies described herein, a composition including the antibody (e.g., any of the antibodies described herein) can provide for an increase (e.g., a detectable increase) (e.g., at least a 1% increase, at least a 2% increase, at least a 5% increase, at least a 10% increase, at least a 15% increase, at least a 20% increase, at least a 25% increase, at least a 30% increase, at least a 35% increase, at least a 40% increase, at least a 45% increase, at least a 50% increase, at least a 55% increase, at least a 60% increase, at least a 65% increase, at least a 70% increase, at least a 75% increase, at least a 80% increase, at least a 85% increase, at least a 90% increase, at least a 95% increase, at least a 100% increase, at least a 120% increase, at least a 140% increase, at least a 160% increase, at least a 180% increase, at least a 200% increase, at least a 250% increase, at least a 300% increase, at least a 350% increase, at least a 400% increase, at least a 450% increase, at least a 500% increase, at least a 1,000% increase, at least a 2,000% increase, at least a 3,000% increase, at least a 4,000% increase, at least a 5,000% increase, at least a 6,000% increase, at least a 7,000% increase, at least a 8,000% increase, at a least a 9,000% increase, or at least a 10,000% increase, or about a 1% increase to about a 10,000% increase (e.g., or any of the subranges of this range described herein)) in target mammalian cell killing (e.g., any of the exemplary target mammalian cells described herein) as

compared to a composition including the same amount of a control antibody (e.g., any of the exemplary control antibodies described herein).

In some examples of any of the antibodies described herein, a composition including the antibody (e.g., any of the antibodies described herein) can provide for an increase (e.g., a detectable increase) (e.g., at least a 0.1-fold increase, at least a 0.2-fold increase, at least a 0.3-fold increase, at least a 0.4-fold increase, at least a 0.5-fold increase, at least a 0.6-fold increase, at least a 0.7-fold increase, at least a 0.8-fold increase, at least a 0.9-fold increase, at least a 1.0-fold increase, at least a 1.2-fold increase, at least a 1.4-fold increase, at least a 1.5-fold increase, at least a 1.6-fold increase, at least a 1.8-fold increase, at least a 2.0-fold increase, at least a 2.2-fold increase, at least a 2.4-fold increase, at least a 2.5-fold increase, at least a 2.6-fold increase, at least a 2.8-fold increase, at least a 3.0-fold increase, at least a 3.5-fold increase, at least a 4.0-fold increase, at least a 4.5-fold increase, at least a 5.0-fold increase, at least a 5.5-fold increase, at least a 6.0-fold increase, at least a 6.5-fold increase, at least a 7.0-fold increase, at least a 7.5-fold increase, at least a 8.0-fold increase, at least a 8.5-fold increase, at least a 9.0-fold increase, at least a 9.5-fold increase, at least a 10-fold increase, at least a 15-fold increase, at least a 20-fold increase, at least a 25-fold increase, at least a 30-fold increase, at least a 35-fold increase, at least a 40-fold increase, at least a 40-fold increase, at least a 45-fold increase, at least a 50-fold increase, at least a 55-fold increase, at least a 60-fold increase, at least a 65-fold increase, at least a 70-fold increase, at least a 80-fold increase, at least a 85-fold increase, at least a 90-fold increase, at least a 95-fold increase, or at least a 100-fold increase, or about a 0.1-fold increase to about a 100-fold increase (or any of the subranges of this range described herein)) in target mammalian cell killing (e.g., any of the exemplary target mammalian cells described herein) as compared to a composition including the same amount of a control antibody (e.g., any of the exemplary control antibodies described herein).

In some examples of any of the antibodies described herein, a composition including any of the antibodies described herein (e.g., upon contacting target mammalian cells presenting MET on their surface) results in decreased (e.g., at least a 1% decrease, at least a 5% decrease, at least a 10% decrease, at least a 15% decrease, at least a 20% decrease, at least a 25% decrease, at least a 30% decrease, at least a 35% decrease, at least a 40% decrease, at least a 45% decrease, at least a 50% decrease, at least a 55% decrease, at least a 60% decrease, at least a 65% decrease, at least a 70% decrease, at least a 75% decrease, at least a 80% decrease, at least a 85% decrease, at least

a 90% decrease, at least a 95% decrease, or at least a 99% decrease, about a 1% decrease to about a 99% decrease, or any of the subranges of this range described herein) $IC_{50}$ (for target mammalian cell killing) as compared to the $IC_{50}$ for a composition including the same amount of a control antibody (e.g., any of the control antibodies described herein) (e.g., upon contacting the same target mammalian cells).

In some examples of any of the antibodies described herein, a composition including any of the antibodies described herein (e.g., upon contacting target mammalian cells presenting MET on their surface) can provide for an increase (e.g., at least a 0.1-fold increase, at least a 0.2-fold increase, at least a 0.4-fold increase, at least a 0.6-fold increase, at least a 0.8-fold increase, at least a 1-fold increase, at least a 2-fold increase, at least a 5-fold increase, at least a 10-fold increase, at least a 15-fold increase, at least a 20-fold increase, at least a 25-fold increase, at least a 30-fold increase, at least a 35-fold increase, at least a 40-fold increase, at least a 45-fold increase, at least a 50-fold increase, at least a 55-fold increase, at least a 60-fold increase, at least a 65-fold increase, at least a 70-fold increase, at least a 75-fold increase, at least a 80-fold increase, at least a 85-fold increase, at least a 90-fold increase, at least a 95-fold increase, or at least a 100-fold increase, or about a 0.1-fold increase to about 500-fold increase (or any of the subranges of this range described herein) in the ratio of $K_D$ on target mammalian cells presenting MET on their surface at a neutral pH (a pH of about 7.0 to about 8.0) to $IC_{50}$ at the neutral pH on the same target cells, e.g., as compared to a control antibody (e.g., any of the exemplary control antibodies described herein).

In some examples of any of the antibodies described herein, a composition including the antibody (e.g., any of the antibodies described herein) can provide for an increase (e.g., a detectable increase) (e.g., at least a 1% increase, at least a 2% increase, at least a 5% increase, at least a 10% increase, at least a 15% increase, at least a 20% increase, at least a 25% increase, at least a 30% increase, at least a 35% increase, at least a 40% increase, at least a 45% increase, at least a 50% increase, at least a 55% increase, at least a 60% increase, at least a 65% increase, at least a 70% increase, at least a 75% increase, at least a 80% increase, at least a 85% increase, at least a 90% increase, at least a 95% increase, at least a 100% increase, at least a 120% increase, at least a 140% increase, at least a 160% increase, at least a 180% increase, at least a 200% increase, at least a 250% increase, at least a 300% increase, at least a 350% increase, at least a 400% increase, at least a 450% increase, at least a 500% increase, at least a 1,000% increase, at

least a 2,000% increase, at least a 3,000% increase, at least a 4,000% increase, at least a 5,000% increase, at least a 6,000% increase, at least a 7,000% increase, at least a 8,000% increase, at least a 9,000% increase, or at least a 10,000% increase, or about a 1% increase to about a 10,000% increase (e.g., or any of the subranges of this range described herein)) in endolysosomal delivery in the target mammalian cell (e.g., any of the exemplary target mammalian cells described herein) as compared to a composition including the same amount of a control antibody (e.g., any of the exemplary control antibodies described herein).

In some examples of any of the antibodies described herein, a composition including the antibody (e.g., any of the antibodies described herein) can provide for an increase (e.g., a detectable increase) (e.g., at least a 0.1-fold increase, at least a 0.2-fold increase, at least a 0.3-fold increase, at least a 0.4-fold increase, at least a 0.5-fold increase, at least a 0.6-fold increase, at least a 0.7-fold increase, at least a 0.8-fold increase, at least a 0.9-fold increase, at least a 1.0-fold increase, at least a 1.2-fold increase, at least a 1.4-fold increase, at least a 1.5-fold increase, at least a 1.6-fold increase, at least a 1.8-fold increase, at least a 2.0-fold increase, at least a 2.2-fold increase, at least a 2.4-fold increase, at least a 2.5-fold increase, at least a 2.6-fold increase, at least a 2.8-fold increase, at least a 3.0-fold increase, at least a 3.5-fold increase, at least a 4.0-fold increase, at least a 4.5-fold increase, at least a 5.0-fold increase, at least a 5.5-fold increase, at least a 6.0-fold increase, at least a 6.5-fold increase, at least a 7.0-fold increase, at least a 7.5-fold increase, at least a 8.0-fold increase, at least a 8.5-fold increase, at least a 9.0-fold increase, at least a 9.5-fold increase, at least a 10-fold increase, at least a 15-fold increase, at least a 20-fold increase, at least a 25-fold increase, at least a 30-fold increase, at least a 35-fold increase, at least a 40-fold increase, at least a 45-fold increase, at least a 50-fold increase, at least a 55-fold increase, at least a 60-fold increase, at least a 65-fold increase, at least a 70-fold increase, at least a 75-fold increase, at least a 80-fold increase, at least a 85-fold increase, at least a 90-fold increase, at least a 95-fold increase, or at least a 100-fold increase, or about a 0.1-fold increase to about a 100-fold increase (or any of the subranges of this range described herein)) in endolysosomal delivery in the target mammalian cell (e.g., any of the exemplary target mammalian cells described herein) as compared to a composition including the same amount of a control antibody (e.g., any of the exemplary control antibodies described herein).

In examples of any of the antibodies described herein, the target mammalian cell does not express an FcRn receptor, or expresses a lower (e.g., a detectably lower) level (e.g., at least a 1%

decreased, at least a 2% decreased, at least a 5% decreased, at least a 10% decrease, at least a 15% decreased, at least a 20% decreased, at least a 25% decreased, at least a 30% decreased, at least a 35% decreased, at least a 40% decreased, at least a 45% decreased, at least a 50% decreased, at least a 55% decreased, at least a 60% decreased, at least a 65% decreased, at least a 70% decreased, at least a 75% decreased, at least a 80% decreased, at least a 85% decreased, at least a 90% decreased, at least a 95% decreased, or at least a 99% decreased level) of FcRn receptor as compared to a FcRn expressing control cell (e.g., HUVEC – ThermoFisher #C0035C). In some examples of any of the antibodies described herein, the target mammalian cell is a cancer cell. In some examples of any of the antibodies described herein, the antibody is cytotoxic or cytostatic to the target mammalian cell.

In some examples of any of the antibodies described herein, a composition including any of the antibodies described herein (e.g., upon administration to a subject) results in less (e.g., a 1% decrease to about a 99% decrease, or any of the subranges of this range described herein) of a reduction in the level of MET presented on the surface of the target cell as compared to a composition including the same amount of a control antibody (e.g., any of the control antibodies described herein). In some examples of any of the antibodies described herein, the composition does not result in a detectable reduction in the level of the MET presented on the surface of the target mammalian cell.

In some examples of any of the antibodies described herein, the antibody is cross-reactive with a non-human primate MET and a human MET. In some examples of any of the antibodies described herein, the antibody is cross-reactive with a non-human primate MET, a human MET, and one or both of rat MET and a mouse MET. In some examples of any of the antibodies described herein, the antibody is cross-reactive with a non-human primate MET, a human MET, a rat MET, and a mouse MET. In some examples of any of the antibodies described herein, the antibody is cross-reactive with mouse MET and rat MET. In some examples of any of the antibodies described herein, the antigen-binding domain binds to an epitope of MET that is present on the surface of cells from an Old World Monkey.

Some examples of any of the antibodies described herein can further include a second antigen-binding domain (e.g., any of the exemplary antigen-binding domains described herein). Non-limiting aspects of these methods are described below, and can be used in any combination without limitation. Additional aspects of these methods are known in the art.

**MET or Epitope of MET**

MET Proto-Oncogene, Receptor Tyrosine Kinase (MET) is a tumor antigen that is known in the art, and is the target of therapeutic antibodies in oncology (Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000). The sequence of the mature Human MET can be found in SEQ ID NO: 1. The sequence of the cDNA encoding the mature Human MET can be found in SEQ ID NO: 2. The sequence of the extracellular domain of MET can be found in SEQ ID NO: 3. The sequence of the cDNA encoding the extracellular domain of MET can be found in SEQ ID NO: 4.

***Exemplary Properties of Antibodies***

In some embodiments of any of the antibodies described herein, the dissociation rate at a pH of about 4.0 to about 6.5 (e.g., about 4.0 to about 6.4, about 4.0 to about 6.3, about 4.0 to about 6.2, about 4.0 to about 6.1, about 4.0 to about 6.0, about 4.0 to about 5.9, about 4.0 to about 5.8, about 4.0 to about 5.7, about 4.0 to about 5.6, about 4.0 to about 5.5, about 4.0 to about 5.4, about 4.0 to about 5.3, about 4.0 to about 5.2, about 4.0 to about 5.1, about 4.0 to about 5.0, about 4.0 to about 4.9, about 4.0 to about 4.8, about 4.0 to about 4.7, about 4.0 to about 4.6, about 4.0 to about 4.5, about 4.0 to about 4.4, about 4.0 to about 4.3, about 4.0 to about 4.2, about 4.0 to about 4.1, about 4.1 to about 6.5, about 4.1 to about 6.4, about 4.1 to about 6.3, about 4.1 to about 6.2, about 4.1 to about 6.1, about 4.1 to about 6.0, about 4.1 to about 5.9, about 4.1 to about 5.8, about 4.1 to about 5.7, about 4.1 to about 5.6, about 4.1 to about 5.5, about 4.1 to about 5.4, about 4.1 to about 5.3, about 4.1 to about 5.2, about 4.1 to about 5.1, about 4.1 to about 5.0, about 4.1 to about 4.9, about 4.1 to about 4.8, about 4.1 to about 4.7, about 4.1 to about 4.6, about 4.1 to about 4.5, about 4.1 to about 4.4, about 4.1 to about 4.3, about 4.1 to about 4.2, about 4.2 to about 6.5, about 4.2 to about 6.4, about 4.2 to about 6.3, about 4.2 to about 6.2, about 4.2 to about 6.1, about 4.2 to about 6.0, about 4.2 to about 5.9, about 4.2 to about 5.8, about 4.2 to about 5.7, about 4.2 to about 5.6, about 4.2 to about 5.5, about 4.2 to about 5.4, about 4.2 to about 5.3, about 4.2 to about 5.2, about 4.2 to about 5.1, about 4.2 to about 5.0, about 4.2 to about 4.9, about 4.2 to about 4.8, about 4.2 to about 4.7, about 4.2 to about 4.6, about 4.2 to about 4.5, about 4.2 to about 4.4, about 4.2 to about 4.3, about 4.3 to about 6.5, about 4.3 to about 6.4, about 4.3 to about 6.3, about 4.3 to

about 6.2, about 4.3 to about 6.1, about 4.3 to about 6.0, about 4.3 to about 5.9, about 4.3 to about 5.8, about 4.3 to about 5.7, about 4.3 to about 5.6, about 4.3 to about 5.5, about 4.3 to about 5.4, about 4.3 to about 5.3, about 4.3 to about 5.2, about 4.3 to about 5.1, about 4.3 to about 5.0, about 4.3 to about 4.9, about 4.3 to about 4.8, about 4.3 to about 4.7, about 4.3 to about 4.6, about 4.3 to about 4.5, about 4.3 to about 4.4, about 4.4 to about 6.5, about 4.4 to about 6.4, about 4.4 to about 6.3, about 4.4 to about 6.2, about 4.4 to about 6.1, about 4.4 to about 6.0, about 4.4 to about 5.9, about 4.4 to about 5.8, about 4.4 to about 5.7, about 4.4 to about 5.6, about 4.4 to about 5.5, about 4.4 to about 5.4, about 4.4 to about 5.3, about 4.4 to about 5.2, about 4.4 to about 5.1, about 4.4 to about 5.0, about 4.4 to about 4.9, about 4.4 to about 4.8, about 4.4 to about 4.7, about 4.4 to about 4.6, about 4.4 to about 4.5, about 4.5 to about 6.5, about 4.5 to about 6.4, about 4.5 to about 6.3, about 4.5 to about 6.2, about 4.5 to about 6.1, about 4.5 to about 6.0, about 4.5 to about 5.9, about 4.5 to about 5.8, about 4.5 to about 5.7, about 4.5 to about 5.6, about 4.5 to about 5.5, about 4.5 to about 5.4, about 4.5 to about 5.3, about 4.5 to about 5.2, about 4.5 to about 5.1, about 4.5 to about 5.0, about 4.5 to about 4.9, about 4.5 to about 4.8, about 4.5 to about 4.7, about 4.5 to about 4.6, about 4.6 to about 6.5, about 4.6 to about 6.4, about 4.6 to about 6.3, about 4.6 to about 6.2, about 4.6 to about 6.1, about 4.6 to about 6.0, about 4.6 to about 5.9, about 4.6 to about 5.8, about 4.6 to about 5.7, about 4.6 to about 5.6, about 4.6 to about 5.5, about 4.6 to about 5.4, about 4.6 to about 5.3, about 4.6 to about 5.2, about 4.6 to about 5.1, about 4.6 to about 5.0, about 4.6 to about 4.9, about 4.6 to about 4.8, about 4.6 to about 4.7, about 4.7 to about 6.5, about 4.7 to about 6.4, about 4.7 to about 6.3, about 4.7 to about 6.2, about 4.7 to about 6.1, about 4.7 to about 6.0, about 4.7 to about 5.9, about 4.7 to about 5.8, about 4.7 to about 5.7, about 4.7 to about 5.6, about 4.7 to about 5.5, about 4.7 to about 5.4, about 4.7 to about 5.3, about 4.7 to about 5.2, about 4.7 to about 5.1, about 4.7 to about 5.0, about 4.7 to about 4.9, about 4.7 to about 4.8, about 4.8 to about 6.5, about 4.8 to about 6.4, about 4.8 to about 6.3, about 4.8 to about 6.2, about 4.8 to about 6.1, about 4.8 to about 6.0, about 4.8 to about 5.9, about 4.8 to about 5.8, about 4.8 to about 5.7, about 4.8 to about 5.6, about 4.8 to about 5.5, about 4.8 to about 5.4, about 4.8 to about 5.3, about 4.8 to about 5.2, about 4.8 to about 5.1, about 4.8 to about 5.0, about 4.8 to about 4.9, about 4.9 to about 6.5, about 4.9 to about 6.4, about 4.9 to about 6.3, about 4.9 to about 6.2, about 4.9 to about 6.1, about 4.9 to about 6.0, about 4.9 to about 5.9, about 4.9 to about 5.8, about 4.9 to about 5.7, about 4.9 to about 5.6, about 4.9 to

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about 6.4, or about 6.4 to about 6.5) is faster (e.g., (e.g., at least 5% faster, at least 10% faster, at least 15% faster, at least 20%, at least 25% faster, at least 30% faster, at least 35% faster, at least 40% faster, at least 45% faster, at least 50% faster, at least 55% faster, at least 60% faster, at least 65% faster, at least 70% faster, at least 75% faster, at least 80% faster, at least 85% faster, at least 90% faster, at least 95% faster, at least 100% faster, at least 120% faster, at least 140% faster, at least 160% faster, at least 180% faster, at least 200% faster, at least 220% faster at least 240% faster at least 260% faster at least 280% faster at least 300% faster at least 320% faster at least 340% faster at least 360% faster at least 380% faster at least 400% faster at least 420% faster at least 440% faster at least 460% faster at least 480% faster, at least 500% faster, at least 1,000% faster, at least 2,000% faster, at least 3,000% faster, at least 4,000% faster, at least 5,000%, at least 6,000% faster, at least 7,000% faster, at least 8,000% faster, at least 9,000% faster, or at least 10,000% faster, or about 5% faster to about 10,000% faster, about 5% faster to about 9,000% faster, about 5% faster to about 8,000% faster, about 5% faster to about 7,000% faster, about 5% faster to about 6,000% faster, about 5% faster to about 5,000% faster, about 5% faster to about 4,000% faster, about 5% faster to about 3,000% faster, about 5% faster to about 2,000% faster, about 5% faster to about 1,000% faster, about 5% faster to about 500% faster, about 5% faster to about 480% faster, about 5% faster to about 460% faster, about 5% faster to about 440% faster, about 5% faster to about 420% faster, about 5% faster to about 400% faster, about 5% faster to about 380% faster, about 5% faster to about 360% faster, about 5% faster to about 340% faster, about 5% faster to about 320% faster, about 5% faster to about 300% faster, about 5% faster to about 280% faster, about 5% faster to about 260% faster, about 5% faster to about 240% faster, about 5% faster to about 220% faster, about 5% faster to about 200% faster, about 5% faster to about 180% faster, about 5% faster to about 160% faster, about 5% faster to about 140% faster, about 5% faster to about 120% faster, about 5% faster to about 100% faster, about 5% faster to about 95% faster, about 5% faster to about 90% faster, about 5% faster to about 85% faster, about 5% faster to about 80% faster, about 5% faster to about 75% faster, about 5% faster to about 70% faster, about 5% faster to about 65% faster, about 5% faster to about 60% faster, about 5% faster to about 55% faster, about 5% faster to about 50% faster, about 5% faster to about 45% faster, about 5% faster to about 40% faster, about 5% faster to about 35% faster, about 5% faster to about 30% faster, about 5% faster to about 25% faster, about 5% faster to about 20% faster, about 5% faster to about 15% faster, about 5% faster to

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In some embodiments of any of the antibodies described herein, the dissociation constant ($K_D$) at a pH of about 4.0 to about 6.5 (e.g., any of the subranges of this range described herein) is greater (e.g., detectably greater) (e.g., at least 5% greater, at least 10% greater, at least 15% greater, at least 20% greater, at least 25% greater, at least 30% greater, at least 35% greater, at least 40% greater, at least 45% greater, at least 50% greater, at least 55% greater, at least 60% greater, at least 65% greater, at least 70% greater, at least 80% greater, at least 85% greater, at least 90% greater, at least 95% greater, at least 100% greater, at least 120% greater, at least 140% greater, at least 160% greater, at least 180% greater, at least 200% greater, at least 220% greater, at least 240% greater, at least 260% greater, at least 280% greater, at least 300% greater,

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greater, about 4,000% greater to about 7,000% greater, about 4,000% greater to about 6,000% greater, about 4,000% greater to about 5,000% greater, about 5,000% greater to about 10,000% greater, about 5,000% greater to about 9,000% greater, about 5,000% greater to about 8,000% greater, about 5,000% greater to about 7,000% greater, about 5,000% greater to about 6,000% greater, about 6,000% greater to about 10,000% greater, about 6,000% greater to about 9,000% greater, about 6,000% greater to about 8,000% greater, about 6,000% greater to about 7,000% greater, about 7,000% greater to about 10,000% greater, about 7,000% greater to about 9,000% greater, about 7,000% greater to about 8,000% greater, about 8,000% greater to about 10,000% greater, about 8,000% greater to about 9,000% greater, or about 9,000% greater to about 10,000% greater) than the $K_D$ at a pH of about 7.0 to about 8.0 (e.g., any of the subranges of this range described herein).

In some embodiments of any of the antibodies described herein, the dissociation rate at a pH of about 4.0 to about 6.5 (e.g., any of the subranges of this range described herein) is faster (e.g., at least 0.2-fold faster, at least 0.3-fold, at least 0.4-fold, at least 0.5-fold, at least 0.6-fold, at least 0.7-fold, at least 0.8-fold, at least 0.9-fold, at least 1.0-fold, at least 1.5-fold, at least 2.0-fold, at least 2.5-fold, at least 3.0 fold, at least 3.5-fold, at least 4.0-fold, at least 4.5-fold, at least 5.0-fold, at least 5.5-fold, at least 6.0-fold, at least 6.5-fold, at least 7.0-fold, at least 7.5-fold, at least 8.0-fold, at least 8.5-fold, at least 9.0-fold, at least 9.5-fold, at least 10.0-fold, at least 10.5-fold, at least 11.0-fold, at least 11.5-fold, at least 12.0-fold, at least 12.5-fold, at least 13.0-fold, at least 13.5-fold, at least 14.0-fold, at least 14.5-fold, at least 15.0-fold, at least 15.5-fold, at least 16.0-fold, at least 16.5-fold, at least 17.0-fold, at least 17.5-fold, at least 18.0-fold, at least 18.5-fold, at least 19.0-fold, at least 19.5-fold, at least 20-fold, at least 25-fold, at least 30-fold, at least 35-fold, at least 40-fold, at least 45-fold, at least 50-fold, at least 55-fold, at least 60-fold, at least 65-fold, at least 70-fold, at least 75-fold, at least 80-fold, at least 85-fold, at least 90-fold, at least 95-fold, or at least 100-fold faster or about 0.2-fold to about 100-fold faster, about 0.2-fold to about 90-fold faster, about 0.2-fold to about 80-fold faster, about 0.2-fold to about 70-fold faster, about 0.2-fold to about 60-fold faster, about 0.2-fold to about 50-fold faster, about 0.2-fold to about 40-fold faster, about 0.2-fold to about 30-fold faster, about 0.2-fold to about 20-fold faster, about 0.2-fold to about 15-fold faster, about 0.2-fold to about 10-fold faster, about 0.2-fold to about 5-fold, about 0.2-fold to about 2-fold faster, about 0.2-fold to about 1-fold faster, about 0.2-fold to about 0.5-fold faster, about 0.5-fold to about 100-fold faster, about 0.5-fold to

about 90-fold faster, about 0.5-fold to about 80-fold faster, about 0.5-fold to about 70-fold faster, about 0.5-fold to about 60-fold faster, about 0.5-fold to about 50-fold faster, about 0.5-fold to about 40-fold faster, about 0.5-fold to about 30-fold faster, about 0.5-fold to about 20-fold faster, about 0.5-fold to about 15-fold faster, about 0.5-fold to about 10-fold faster, about 0.5-fold to about 5-fold, about 0.5-fold to about 2-fold faster, about 0.5-fold to about 1-fold faster, about 1-fold to about 100-fold faster, about 1-fold to about 90-fold faster, about 1-fold to about 80-fold faster, about 1-fold to about 70-fold faster, about 1-fold to about 60-fold faster, about 1-fold to about 50-fold faster, about 1-fold to about 40-fold faster, about 1-fold to about 30-fold faster, about 1-fold to about 20-fold faster, about 1-fold to about 15-fold faster, about 1-fold to about 10-fold faster, about 1-fold to about 5-fold, about 1-fold to about 2-fold faster, about 2-fold to about 100-fold faster, about 2-fold to about 90-fold faster, about 2-fold to about 80-fold faster, about 2-fold to about 70-fold faster, about 2-fold to about 60-fold faster, about 2-fold to about 50-fold faster, about 2-fold to about 40-fold faster, about 2-fold to about 30-fold faster, about 2-fold to about 20-fold faster, about 2-fold to about 15-fold faster, about 2-fold to about 10-fold faster, about 2-fold to about 5-fold, about 5-fold to about 100-fold faster, about 5-fold to about 90-fold faster, about 5-fold to about 80-fold faster, about 5-fold to about 70-fold faster, about 5-fold to about 60-fold faster, about 5-fold to about 50-fold faster, about 5-fold to about 40-fold faster, about 5-fold to about 30-fold faster, about 5-fold to about 20-fold faster, about 5-fold to about 15-fold faster, about 5-fold to about 10-fold faster, about 10-fold to about 100-fold faster, about 10-fold to about 90-fold faster, about 10-fold to about 80-fold faster, about 10-fold to about 70-fold faster, about 10-fold to about 60-fold faster, about 10-fold to about 50-fold faster, about 10-fold to about 40-fold faster, about 10-fold to about 30-fold faster, about 10-fold to about 20-fold faster, about 10-fold to about 15-fold faster, about 15-fold to about 100-fold faster, about 15-fold to about 90-fold faster, about 15-fold to about 80-fold faster, about 15-fold to about 70-fold faster, about 15-fold to about 60-fold faster, about 15-fold to about 50-fold faster, about 15-fold to about 40-fold faster, about 15-fold to about 30-fold faster, about 15-fold to about 20-fold faster, about 20-fold to about 100-fold faster, about 20-fold to about 90-fold faster, about 20-fold to about 80-fold faster, about 20-fold to about 70-fold faster, about 20-fold to about 60-fold faster, about 20-fold to about 50-fold faster, about 20-fold to about 40-fold faster, about 20-fold to about 30-fold faster, about 30-fold to about 100-fold faster, about 30-fold to about 90-fold faster, about 30-fold to about 80-fold faster, about 30-fold to about 70-fold faster,

about 30-fold to about 60-fold faster, about 30-fold to about 50-fold faster, about 30-fold to about 40-fold faster, about 40-fold to about 100-fold faster, about 40-fold to about 90-fold faster, about 40-fold to about 80-fold faster, about 40-fold to about 70-fold faster, about 40-fold to about 60-fold faster, about 40-fold to about 50-fold faster, about 50-fold to about 100-fold faster, about 50-fold to about 90-fold faster, about 50-fold to about 80-fold faster, about 50-fold to about 70-fold faster, about 50-fold to about 60-fold faster, about 60-fold to about 100-fold faster, about 60-fold to about 90-fold faster, about 60-fold to about 80-fold faster, about 60-fold to about 70-fold faster, about 70-fold to about 100-fold faster, about 70-fold to about 90-fold faster, about 70-fold to about 80-fold faster, about 80-fold to about 100-fold faster, about 80-fold to about 90-fold faster, or about 90-fold to about 100-fold faster) than the dissociation rate at a pH of about 7.0 to about 8.0 (e.g., or any of the subranges of this range described herein).

In some embodiments of any of the antibodies described herein, the dissociation constant ($K_D$) at a pH of about 4.0 to about 6.5 (e.g., any of the subranges of this range described herein) is greater (e.g., detectably greater) (e.g., at least 0.2-fold greater, at least 0.3-fold, at least 0.4-fold, at least 0.5-fold, at least 0.6-fold, at least 0.7-fold, at least 0.8-fold, at least 0.9-fold, at least 1.0-fold, at least 1.5-fold, at least 2.0-fold, at least 2.5-fold, at least 3.0 fold, at least 3.5-fold, at least 4.0-fold, at least 4.5-fold, at least 5.0-fold, at least 5.5-fold, at least 6.0-fold, at least 6.5-fold, at least 7.0-fold, at least 7.5-fold, at least 8.0-fold, at least 8.5-fold, at least 9.0-fold, at least 9.5-fold, at least 10.0-fold, at least 10.5-fold, at least 11.0-fold, at least 11.5-fold, at least 12.0-fold, at least 12.5-fold, at least 13.0-fold, at least 13.5-fold, at least 14.0-fold, at least 14.5-fold, at least 15.0-fold, at least 15.5-fold, at least 16.0-fold, at least 16.5-fold, at least 17.0-fold, at least 17.5-fold, at least 18.0-fold, at least 18.5-fold, at least 19.0-fold, at least 19.5-fold, at least 20-fold greater, at least 25-fold greater, at least 30-fold greater, at least 35-fold greater, at least 40-fold greater, at least 45-fold greater, at least 50-fold greater, at least 55-fold greater, at least 60-fold greater, at least 65-fold greater, at least 70-fold greater, at least 75-fold greater, at least 80-fold greater, at least 85-fold greater, at least 90-fold greater, at least 95-fold greater, or at least 100-fold greater, or about 0.2-fold to about 100-fold greater, about 0.2-fold to about 90-fold greater, about 0.2-fold to about 80-fold greater, about 0.2-fold to about 70-fold greater, about 0.2-fold to about 60-fold greater, about 0.2-fold to about 50-fold greater, about 0.2-fold to about 40-fold greater, about 0.2-fold to about 30-fold greater, about 0.2-fold to about 25-fold greater, about 0.2-fold to about 20-fold greater, about 0.2-fold to about 15-fold greater, about 0.2-fold to

about 10-fold greater, about 0.2-fold to about 8-fold greater, about 0.2-fold to about 5-fold greater, about 0.2-fold to about 2-fold greater, about 0.2-fold to about 1-fold greater, about 0.2-fold to about 0.5-fold greater, about 0.5-fold to about 100-fold greater, about 0.5-fold to about 90-fold greater, about 0.5-fold to about 80-fold greater, about 0.5-fold to about 70-fold greater, about 0.5-fold to about 60-fold greater, about 0.5-fold to about 50-fold greater, about 0.5-fold to about 40-fold greater, about 0.5-fold to about 30-fold greater, about 0.5-fold to about 25-fold greater, about 0.5-fold to about 20-fold greater, about 0.5-fold to about 15-fold greater, about 0.5-fold to about 10-fold greater, about 0.5-fold to about 8-fold greater, about 0.5-fold to about 5-fold greater, about 0.5-fold to about 2-fold greater, about 0.5-fold to about 1-fold greater, about 1-fold to about 100-fold greater, about 1-fold to about 90-fold greater, about 1-fold to about 80-fold greater, about 1-fold to about 70-fold greater, about 1-fold to about 60-fold greater, about 1-fold to about 50-fold greater, about 1-fold to about 40-fold greater, about 1-fold to about 30-fold greater, about 1-fold to about 25-fold greater, about 1-fold to about 20-fold greater, about 1-fold to about 15-fold greater, about 1-fold to about 10-fold greater, about 1-fold to about 8-fold greater, about 1-fold to about 5-fold greater, about 1-fold to about 2-fold greater, about 2-fold to about 100-fold greater, about 2-fold to about 90-fold greater, about 2-fold to about 80-fold greater, about 2-fold to about 70-fold greater, about 2-fold to about 60-fold greater, about 2-fold to about 50-fold greater, about 2-fold to about 40-fold greater, about 2-fold to about 30-fold greater, about 2-fold to about 25-fold greater, about 2-fold to about 20-fold greater, about 2-fold to about 15-fold greater, about 2-fold to about 10-fold greater, about 2-fold to about 8-fold greater, about 2-fold to about 5-fold greater, about 5-fold to about 100-fold greater, about 5-fold to about 90-fold greater, about 5-fold to about 80-fold greater, about 5-fold to about 70-fold greater, about 5-fold to about 60-fold greater, about 5-fold to about 50-fold greater, about 5-fold to about 40-fold greater, about 5-fold to about 30-fold greater, about 5-fold to about 25-fold greater, about 5-fold to about 20-fold greater, about 5-fold to about 15-fold greater, about 5-fold to about 10-fold greater, about 5-fold to about 8-fold greater, about 8-fold to about 100-fold greater, about 8-fold to about 90-fold greater, about 8-fold to about 80-fold greater, about 8-fold to about 70-fold greater, about 8-fold to about 60-fold greater, about 8-fold to about 50-fold greater, about 8-fold to about 40-fold greater, about 8-fold to about 30-fold greater, about 8-fold to about 25-fold greater, about 8-fold to about 20-fold greater, about 8-fold to about 15-fold greater, about 8-fold to about 10-fold greater, about 10-fold to about 100-fold greater, about 10-

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In some embodiments of any of the antibodies described herein, the $K_D$ at a pH of about 7.0 to about 8.0 (e.g., any of the subranges of this range described herein) is between about 1 pM to about 5 μM (e.g., about 1 pM to about 2 μM, about 1 pM to about 1 μM, about 1 pM to about

500 nM, about 1 pM to about 250 nM, about 1 pM to about 240 nM, about 1 pM to about 230 nM, about 1 pM to about 220 nM, about 1 pM to about 210 nM, about 1 pM to about 200 nM, about 1 pM to about 190 nM, about 1 pM to about 180 nM, about 1 pM to about 170 nM, about 1 pM to about 160 nM, about 1 pM to about 150 nM, about 1 pM to about 140 nM, about 1 pM to about 130 nM, about 1 pM to about 120 nM, about 1 pM to about 110 nM, about 1 pM to about 100 nM, about 1 pM to about 95 nM, about 1 pM to about 90 nM, about 1 pM to about 85 nM, about 1 pM to about 80 nM, about 1 pM to about 75 nM, about 1 pM to about 70 nM, about 1 pM to about 65 nM, about 1 pM to about 60 nM, about 1 pM to about 55 nM, about 1 pM to about 50 nM, about 1 pM to about 45 nM, about 1 pM to about 40 nM, about 1 pM to about 35 nM, about 1 pM to about 30 nM, about 1 pM to about 25 nM, about 1 pM to about 20 nM, about 1 pM to about 15 nM, about 1 pM to about 10 nM, about 1 pM to about 5 nM, about 1 pM to about 2 nM, about 1 pM to about 1 nM, about 1 pM to about 950 pM, about 1 pM to about 900 pM, about 1 pM to about 850 pM, about 1 pM to about 800 pM, about 1 pM to about 750 pM, about 1 pM to about 700 pM, about 1 pM to about 650 pM, about 1 pM to about 600 pM, about 1 pM to about 550 pM, about 1 pM to about 500 pM, about 1 pM to about 450 pM, about 1 pM to about 400 pM, about 1 pM to about 350 pM, about 1 pM to about 300 pM, about 1 pM to about 250 pM, about 1 pM to about 200 pM, about 1 pM to about 150 pM, about 1 pM to about 100 pM, about 1 pM to about 90 pM, about 1 pM to about 80 pM, about 1 pM to about 70 pM, about 1 pM to about 60 pM, about 1 pM to about 50 pM, about 1 pM to about 40 pM, about 1 pM to about 30 pM, about 1 pM to about 20 pM, about 1 pM to about 10 pM, about 1 pM to about 5 pM, about 1 pM to about 4 pM, about 1 pM to about 3 pM, about 1 pM to about 2 pM, about 2 pM to about 5 μM, about 2 pM to about 2 μM, about 2 pM to about 1 μM, about 2 pM to about 500 nM, about 2 pM to about 250 nM, about 2 pM to about 240 nM, about 2 pM to about 230 nM, about 2 pM to about 220 nM, about 2 pM to about 210 nM, about 2 pM to about 200 nM, about 2 pM to about 190 nM, about 2 pM to about 180 nM, about 2 pM to about 170 nM, about 2 pM to about 160 nM, about 2 pM to about 150 nM, about 2 pM to about 140 nM, about 2 pM to about 130 nM, about 2 pM to about 120 nM, about 2 pM to about 110 nM, about 2 pM to about 100 nM, about 2 pM to about 95 nM, about 2 pM to about 90 nM, about 2 pM to about 85 nM, about 2 pM to about 80 nM, about 2 pM to about 75 nM, about 2 pM to about 70 nM, about 2 pM to about 65 nM, about 2 pM to about 60 nM, about 2 pM to about 55 nM, about 2 pM to about 50 nM, about 2 pM to about 45 nM, about 2 pM to about 40 nM, about 2 pM to about 35

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about 500 nM to about 2 μM, about 500 nM to about 1 μM, about 1 μM to about 5 μM, about 1 μM to about 2 μM, or about 2 μM to about 5 μM).

In some embodiments of any of the antibodies described herein, the $K_D$ at a pH of about 4.0 to about 6.5 (e.g., any of the subranges of this range described herein) can be greater than 1 nM (e.g., between about 1 nM to about 1 mM, about 1 nM to about 900 μM, about 1 nM to about 800 μM, about 1 nM to about 700 μM, about 1 nM to about 600 μM, about 1 nM to about 500 μM, about 1 nM to about 400 μM, about 1 nM to about 300 μM, about 1 nM to about 200 μM, about 1 nM to about 100 μM, about 1 nM to about 90 μM, about 1 nM to about 80 μM, about 1 nM to about 70 μM, about 1 nM to about 60 μM, about 1 nM to about 50 μM, about 1 nM to about 40 μM, about 1 nM to about 30 μM, about 1 nM to about 20 μM, about 1 nM to about 10 μM, about 1 nM to about 5 μM, about 1 nM to about 4 μM, about 1 nM to about 2 μM, about 1 nM to about 1 μM, about 1 nM to about 900 nM, about 1 nM to about 800 nM, about 1 nM to about 700 nM, about 1 nM to about 600 nM, about 1 nM to about 500 nM, about 1 nM to about 400 nM, about 1 nM to about 300 nM, about 1 nM to about 200 nM, about 1 nM to about 100 nM, about 1 nM to about 90 nM, about 1 nM to about 80 nM, about 1 nM to about 70 nM, about 1 nM to about 60 nM, about 1 nM to about 50 nM, about 1 nM to about 40 nM, about 1 nM to about 30 nM, about 2 nM to about 1 mM, about 2 nM to about 900 μM, about 2 nM to about 800 μM, about 2 nM to about 700 μM, about 2 nM to about 600 μM, about 2 nM to about 500 μM, about 2 nM to about 400 μM, about 2 nM to about 300 μM, about 2 nM to about 200 μM, about 2 nM to about 100 μM, about 2 nM to about 90 μM, about 2 nM to about 80 μM, about 2 nM to about 70 μM, about 2 nM to about 60 μM, about 2 nM to about 50 μM, about 2 nM to about 40 μM, about 2 nM to about 30 μM, about 2 nM to about 20 μM, about 2 nM to about 10 μM, about 2 nM to about 5 μM, about 2 nM to about 4 μM, about 2 nM to about 2 μM, about 2 nM to about 1 μM, about 2 nM to about 900 nM, about 2 nM to about 800 nM, about 2 nM to about 700 nM, about 2 nM to about 600 nM, about 2 nM to about 500 nM, about 2 nM to about 400 nM, about 2 nM to about 300 nM, about 2 nM to about 200 nM, about 2 nM to about 100 nM, about 2 nM to about 90 nM, about 2 nM to about 80 nM, about 2 nM to about 70 nM, about 2 nM to about 60 nM, about 2 nM to about 50 nM, about 2 nM to about 40 nM, about 2 nM to about 30 nM, about 5 nM to about 1 mM, about 5 nM to about 900 μM, about 5 nM to about 800 μM, about 5 nM to about 700 μM, about 5 nM to about 600 μM, about 5 nM to about 500 μM, about 5 nM to about 400 μM, about 5 nM to about 300 μM, about 5 nM to about 200

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A variety of different methods known in the art can be used to determine the $K_D$ values of any of the antibodies described herein (e.g., an electrophoretic mobility shift assay, a filter binding assay, surface plasmon resonance, a biomolecular binding kinetics assay, in vitro binding assay on antigen-expressing cells, etc.).

In some embodiments, the half-life of any of the antibodies described herein, the half-life of the antibody in vivo is increased (e.g., a detectable increase) relatively to a control antibody (e.g., the same antibody but not including the amino acid substitutions or insertions in the CH1-CH2-CH3 of the heavy chain or any the amino acid substitutions in the $C_L$ domain). In some embodiments, one or more amino acid substitutions can increase the half-life of any of the antibodies described herein. Non-limiting examples of amino acid substitutions that can increase the half-life of the antibody in vivo include a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317 of SEQ ID NO: 155 or SEQ ID NO: 189 and/or a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid

substitution at amino acid position 139 of SEQ ID NO: 155 or SEQ ID NO: 189. In some embodiments, the half-life of the antibody in vivo is increased (e.g., a detectable increase) (e.g., at least a 1% decrease, at least a 5% decrease, at least a 10% decrease, at least a 15% decrease, at least a 20% decrease, at least a 25% decrease, at least a 30% decrease, at least a 35% decrease, at least a 40% decrease, at least a 45% decrease, at least a 50% decrease, at least a 55% decrease, at least a 60% decrease, at least a 65% decrease, at least a 70% decrease, at least a 75% decrease, at least a 80% decrease, at least a 85% decrease, at least a 90% decrease, at least a 95% decrease, or at least a 99% decrease, or about a 1% decrease to about a 99% decrease, about a 1% decrease to about a 95% decrease, about a 1% decrease to about a 90% decrease, about a 1% decrease to about a 85% decrease, about a 1% decrease to about a 80% decrease, about a 1% decrease to about a 75% decrease, about a 1% decrease to about a 70% decrease, about a 1% decrease to about a 65% decrease, about a 1% decrease to about a 60% decrease, about a 1% decrease to about a 55% decrease, about a 1% decrease to about a 50% decrease, about a 1% decrease to about a 45% decrease, about a 1% decrease to about a 40% decrease, about a 1% decrease to about a 35% decrease, about a 1% decrease to about a 30% decrease, about a 1% decrease to about a 25% decrease, about a 1% decrease to about a 20% decrease, about a 1% decrease to about a 15% decrease, about a 1% decrease to about a 10% decrease, about a 1% decrease to about a 5% decrease, about a 5% decrease to about a 99% decrease, about a 5% decrease to about a 95% decrease, about a 5% decrease to about a 90% decrease, about a 5% decrease to about a 85% decrease, about a 5% decrease to about a 80% decrease, about a 5% decrease to about a 75% decrease, about a 5% decrease to about a 70% decrease, about a 5% decrease to about a 65% decrease, about a 5% decrease to about a 60% decrease, about a 5% decrease to about a 55% decrease, about a 5% decrease to about a 50% decrease, about a 5% decrease to about a 45% decrease, about a 5% decrease to about a 40% decrease, about a 5% decrease to about a 35% decrease, about a 5% decrease to about a 30% decrease, about a 5% decrease to about a 25% decrease, about a 5% decrease to about a 20% decrease, about a 5% decrease to about a 15% decrease, about a 5% decrease to about a 10% decrease, about a 10% decrease to about a 99% decrease, about a 10% decrease to about a 95% decrease, about a 10% decrease to about a 90% decrease, about a 10% decrease to about a 85% decrease, about a 10% decrease to about a 80% decrease, about a 10% decrease to about a 75% decrease, about a 10% decrease to about a 70% decrease, about a 10% decrease to about a 65% decrease, about a 10% decrease to

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In some examples of any of the antibodies described herein, the half-life of the antibody *in vivo* is decreased (e.g., a detectable decrease) (e.g., at least a 1% decrease, at least a 5% decrease, at least a 10% decrease, at least a 15% decrease, at least a 20% decrease, at least a 25% decrease, at least a 30% decrease, at least a 35% decrease, at least a 40% decrease, at least a 45% decrease, at least a 50% decrease, at least a 55% decrease, at least a 60% decrease, at least a 65% decrease, at least a 70% decrease, at least a 75% decrease, at least a 80% decrease, at least a 85% decrease, at least a 90% decrease, at least a 95% decrease, or at least a 99% decrease, or about a 1% decrease to about a 99% decrease, about a 1% decrease to about a 95% decrease, about a 1% decrease to about a 90% decrease, about a 1% decrease to about a 85% decrease, about a 1%

decrease to about a 80% decrease, about a 1% decrease to about a 75% decrease, about a 1% decrease to about a 70% decrease, about a 1% decrease to about a 65% decrease, about a 1% decrease to about a 60% decrease, about a 1% decrease to about a 55% decrease, about a 1% decrease to about a 50% decrease, about a 1% decrease to about a 45% decrease, about a 1% decrease to about a 40% decrease, about a 1% decrease to about a 35% decrease, about a 1% decrease to about a 30% decrease, about a 1% decrease to about a 25% decrease, about a 1% decrease to about a 20% decrease, about a 1% decrease to about a 15% decrease, about a 1% decrease to about a 10% decrease, about a 1% decrease to about a 5% decrease, about a 5% decrease to about a 99% decrease, about a 5% decrease to about a 95% decrease, about a 5% decrease to about a 90% decrease, about a 5% decrease to about a 85% decrease, about a 5% decrease to about a 80% decrease, about a 5% decrease to about a 75% decrease, about a 5% decrease to about a 70% decrease, about a 5% decrease to about a 65% decrease, about a 5% decrease to about a 60% decrease, about a 5% decrease to about a 55% decrease, about a 5% decrease to about a 50% decrease, about a 5% decrease to about a 45% decrease, about a 5% decrease to about a 40% decrease, about a 5% decrease to about a 35% decrease, about a 5% decrease to about a 30% decrease, about a 5% decrease to about a 25% decrease, about a 5% decrease to about a 20% decrease, about a 5% decrease to about a 15% decrease, about a 5% decrease to about a 10% decrease, about a 10% decrease to about a 99% decrease, about a 10% decrease to about a 95% decrease, about a 10% decrease to about a 90% decrease, about a 10% decrease to about a 85% decrease, about a 10% decrease to about a 80% decrease, about a 10% decrease to about a 75% decrease, about a 10% decrease to about a 70% decrease, about a 10% decrease to about a 65% decrease, about a 10% decrease to about a 60% decrease, about a 10% decrease to about a 55% decrease, about a 10% decrease to about a 50% decrease, about a 10% decrease to about a 45% decrease, about a 10% decrease to about a 40% decrease, about a 10% decrease to about a 35% decrease, about a 10% decrease to about a 30% decrease, about a 10% decrease to about a 25% decrease, about a 10% decrease to about a 20% decrease, about a 10% decrease to about a 15% decrease, about a 15% decrease to about a 99% decrease, about a 15% decrease to about a 95% decrease, about a 15% decrease to about a 90% decrease, about a 15% decrease to about a 85% decrease, about a 15% decrease to about a 80% decrease, about a 15% decrease to about a 75% decrease, about a 15% decrease to about a 70% decrease, about a 15% decrease to about a 65% decrease, about a 15% decrease to about a 60% decrease, about a 15%

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**Conjugation**

In some embodiments, the antibodies provided herein can be conjugated to a drug (e.g., a chemotherapeutic drug, a small molecule), a toxin, or a radioisotope. Non-limiting examples of drugs, toxins, and radioisotopes (e.g., known to be useful for the treatment of cancer) are known in the art.

In some embodiments, at least one polypeptide of any of the antibodies described herein is conjugated to the toxin, the radioisotope, or the drug via a cleavable linker. In some embodiments, the cleavable linker includes a protease cleavage site. In some embodiments, the cleavable linker is cleaved on the antibody once it is transported to the lysosome or late endosome by the target mammalian cell. In some embodiments, cleavage of the linker functionally activates the drug or toxin.

In some embodiments, at least one polypeptide of any of the antibodies described herein is conjugated to the toxin, the radioisotope, or the drug via a non-cleavable linker. In some embodiments, the conjugated toxin, radioisotope, or drug is released during lysosomal and/or late endosomal degradation of the antibody.

Non-limiting examples of cleavable linkers include: hydrazone linkers, peptide linkers, disulfide linkers, and thioether linkers. See, e.g., Carter et al., *Cancer J.* 14(3):154-169, 2008;

Sanderson et al., *Clin. Cancer Res.* 11(2 Pt1):843-852, 2005; Chari et al., *Acc. Chem. Res.* 41(1):98-107, 2008; Oflazoglu et al., *Clin. Cancer Res.* 14(19): 6171-6180, 2008; and Lu et al., *Int. J. Mol. Sci.* 17(4): 561, 2016.

Non-limiting examples of non-cleavable linkers include: maleimide alkane-linkers and meleimide cyclohexane linker (MMC) (see, e.g., those described in McCombs et al., *AAPS J.* 17(2):339-351, 2015).

In some embodiments, any of the antibodies described herein is cytotoxic or cytostatic to the target mammalian cell.

In some embodiments, the antibodies provided herein can comprise one or more amino acid substitutions to provide a conjugation site (e.g., conjugated to a drug, a toxin, a radioisotope). In some embodiments, the antibodies provided herein can have one conjugation site. In some embodiments, the antibodies described herein can have two conjugation sites. In some embodiments, the antibodies provided herein can have three or more conjugation sites. A non-limiting example of an amino acid substitution to produce a conjugation site (e.g., "a triple hinge" conjugation site) is described in U.S. Patent Application No. 2017/0348429, which is incorporated herein by reference in its entirety. For example, a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108 of SEQ ID NO: 155 or SEQ ID NO: 189 can provide a "triple hinge" conjugation site in any of the antibodies described herein. In some embodiments, an alanine to a cysteine substitution at amino acid position 1 of SEQ ID NO: 155 or SEQ ID NO: 189 can provide a conjugation site for any of the antibodies described herein. In some embodiments, a valine to cysteine substitution at amino acid position 98 of SEQ ID NO: 157 can provide a conjugation site for any of the antibodies described herein.

Naturally-occurring cysteine amino acids can also provide a conjugation (e.g., conjugated to a drug, a toxin, a radioisotope.). In some embodiments, the antibodies provided herein can have a drug, a toxin, or a radioisotope conjugated at one or more (e.g., one, two, three, or four) naturally-occurring conjugation sites. In some embodiments, the cysteine at amino acid position 103 of SEQ ID NO: 155 or 189 is a naturally occurring conjugation site. In some embodiments, the cysteine at amino acid position 109 of SEQ ID NO: 155 or 189 is a naturally occurring conjugation site. In some embodiments, the cysteine at amino acid position 112 of SEQ ID NO:

155 or SEQ 189 is a naturally-occurring conjugation site. In some embodiments, the cysteine at amino acid position 107 of SEQ ID NO: 157 is a naturally-occurring conjugation site.

In some embodiments, the antibodies provided herein can have a drug, a toxin, or a radioisotope conjugated at one or more (e.g., two, three, or four) naturally occurring conjugation sites, e.g., the cysteine at amino acid position 103, the cysteine at cysteine at amino acid position 109, and/or the cysteine at amino acid position 112 of SEQ ID NO: 155 or SEQ 189, and/or the cysteine at amino acid position 107 of SEQ ID NO: 157. In some embodiments, the antibodies provided herein can have a drug, a toxin, or a radioisotope conjugated at one or more (e.g., two, three, or four) naturally occurring conjugation sites and one or more (e.g., two, or three) engineered conjugation sites (e.g., engineered by amino acid substitutions, deletions, additions, etc.).

Conjugation through engineered cysteines is achieved by methods known in the art. Briefly, engineered cysteine-containing antibody is prepared for conjugation by treatment with a reducing agent, for example, tris (2-carboxyethyl) phosphine (TCEP), Dithiothreitol (DTT), or 2-Mercaptoethanol (BME). In the reduction reaction the reducing reagent with disulfide bonds in the antibody, breaking interchain disulfides and removing disulfide caps from the engineered cysteines. An optional reoxidation step, achieved by exposure of the solution to air, or an oxidizing agent such as dehydroascorbic acid, allows reformation of the interchain disulfide bonds, leaving the engineered cysteines with a thiolate reactive group. Conjugation with a maleimide functionality on the linker-payload, maleimide-vc-MMAE, is achieved by reaction with the payload in buffered solution, containing cosolvent such as ethanol, dimethylacetamide (DMA), or dimethyl sulfoxide (DMSO). The crude conjugated antibody solution is purified by size exclusion chromatography, or selective filtration methods, such as tangential flow filtration. In this step, residual unreacted payload, reducing agent and oxidizing agents are removed from the reaction mixture, and the conjugated ADC product may be transferred into a desirable formulation buffer.

Conjugation through hinge cysteines is achieved by similar methods, using antibodies with, or without, additional engineered cysteine conjugation sites. Briefly, the antibody is prepared for conjugation by treatment with a reducing agent, for example, tris (2-carboxyethyl) phosphine (TCEP) or Dithiothreitol (DTT). The reducing strength and concentration of the reducing agent are selected such that some or all of the interchain disulfide bonds are reduced

leaving free cysteines for conjugation. The solution may be directly conjugated in the presence of excess reducing agent. Conjugation with a maleimide functionality on the linker-payload, maleimide-vc-MMAE, is achieved by reaction with the payload in buffered solution, containing cosolvent such as ethanol, dimethylacetamide (DMA), or dimethyl sulfoxide (DMSO). Unreacted linker-payload may be rendered non-reactive by addition of a sacrificial thiolate molecule such as acetyl-cysteine. The crude conjugated antibody solution may be further purified by methods known in the art, including hydrophobic interaction chromatography, ion-exchange chromatography, or mixed-mode chromatography such as ceramic hydroxyapatite chromatography. Isolation of chromatography fractions allows selection of the desired antibody to payload ratio and removal of unreacted antibody, protein aggregates and fragments, and payload-related reaction side products. The purified antibody drug conjugate may be further purified and by size exclusion chromatography, or selective filtration methods, such as tangential flow filtration. In this step the conjugated ADC product may also be transferred into a desirable formulation buffer.

In some examples, an antibody conjugate can be made comprising an antibody linked to monomethyl auristatin E (MMAE) via a valine-citrulline (vc) linker (hereafter, MET-IgG-DC). Conjugation of the antigen-binding protein construct with vcMMAE begins with a partial reduction of the MET-IgG followed by reaction with maleimidocaproyl-Val-Cit-PABC-MMAE (vcMMAE). The MET-IgG (10 mg/mL) is partially reduced by addition of TCEP (molar equivalents of TCEP:mAb is 2:1) followed by incubation at 4° C overnight. The reduction reaction is then warmed to 25° C. To conjugate all of the thiols, vcMMAE is added to a final vcMMAE:reduced Cys molar ratio of 1:10. The conjugation reaction is carried out in the presence of 10% v/v of Dimethylacetamide (DMA) and allowed to proceed at 25° C for 60 minutes.

In some examples, an antibody conjugate (ADC) is made comprising the MET-binding IgG (hereafter, MET-IgG) described herein linked to monomethyl auristatin E (MMAE) via a valine-citrulline (vc) linker (hereafter, MET-IgG-DC). Conjugation of the antigen-binding protein construct with vcMMAE begins with a partial reduction of the MET-IgG followed by reaction with maleimidocaproyl-Val-Cit-PABC-MMAE (vcMMAE). The MET-IgG (10 mg/mL) is reduced by addition of DTT (molar equivalents of DTT:mAb is 100:1) followed by incubation at 25° C overnight. The reduced MET-IgG (10 mg/mL) is then re-oxidized by

exposure to DHAA (molar equivalents of DHAA:mAb is 10:1) followed by incubation at 25° C for 2 hours. To conjugate all of the thiols, vcMMAE is added to a final vcMMAE:mAb molar ratio of 4:1. The conjugation reaction is carried out in the presence of 10% v/v of DMA and allowed to proceed at 25° C for 3 hours.

**Expression of an Antibody in a Cell**

Also provided herein are methods of generating a recombinant cell that expresses an antibody (e.g., any of the antibodies described herein) that include: introducing into a cell a nucleic acid encoding the antibody to produce a recombinant cell; and culturing the recombinant cell under conditions sufficient for the expression of the antibody. In some embodiments, the introducing step includes introducing into a cell an expression vector including a nucleic acid encoding the antibody to produce a recombinant cell.

Any of the antibodies described herein can be produced by any cell, e.g., a eukaryotic cell or a prokaryotic cell. As used herein, the term "eukaryotic cell" refers to a cell having a distinct, membrane-bound nucleus. Such cells may include, for example, mammalian (e.g., rodent, non-human primate, or human), insect, fungal, or plant cells. In some embodiments, the eukaryotic cell is a yeast cell, such as *Saccharomyces cerevisiae*. In some embodiments, the eukaryotic cell is a higher eukaryote, such as mammalian, avian, plant, or insect cells. As used herein, the term "prokaryotic cell" refers to a cell that does not have a distinct, membrane-bound nucleus. In some embodiments, the prokaryotic cell is a bacterial cell.

Methods of culturing cells are well known in the art. Cells can be maintained *in vitro* under conditions that favor proliferation, differentiation, and growth. Briefly, cells can be cultured by contacting a cell (e.g., any cell) with a cell culture medium that includes the necessary growth factors and supplements to support cell viability and growth.

Methods of introducing nucleic acids and expression vectors into a cell (e.g., a eukaryotic cell) are known in the art. Non-limiting examples of methods that can be used to introduce a nucleic acid into a cell include lipofection, transfection, electroporation, microinjection, calcium phosphate transfection, dendrimer-based transfection, cationic polymer transfection, cell squeezing, sonoporation, optical transfection, impalection, hydrodynamic delivery, magnetofection, viral transduction (e.g., adenoviral and lentiviral transduction), and nanoparticle transfection.

Provided herein are methods that further include isolation of the antibodies from a cell (e.g., a eukaryotic cell) using techniques well-known in the art (e.g., ammonium sulfate precipitation, polyethylene glycol precipitation, ion-exchange chromatography (anion or cation), chromatography based on hydrophobic interaction, metal-affinity chromatography, ligand-affinity chromatography, and size exclusion chromatography).

**Methods of Treatment**

Provided herein are methods of treating a cancer characterized by having a population of cancer cells that have MET or an epitope of MET presented on their surface, that include: administering a therapeutically effective amount of any of the pharmaceutical compositions described herein or any of the antibodies described herein to a subject identified as having a cancer characterized by having the population of cancer cells.

Also provided herein are methods of reducing the volume of a tumor in a subject, wherein the tumor is characterized by having a population of cancer cells that have MET or an epitope of MET presented on their surface, that include: administering a therapeutically effective amount of any of the pharmaceutical compositions described herein or any of the antibodies described herein to a subject identified as having a cancer characterized by having the population of cancer cells. In some embodiments of any of the methods described herein, the volume of at least one (e.g., 1, 2, 3, 4, or 5) tumor (e.g., solid tumor) or tumor location (e.g., a site of metastasis) is reduced (e.g., a detectable reduction) by at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 8%, at least 10%, at least 12%, at least 14%, at least 16%, at least 18%, at least 20%, at least 22%, at least 24%, at least 26%, at least 28%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99%) reduced as compared to the size of the at least one tumor (e.g., solid tumor) before administration of the antibody .

Also provided herein are methods of inducing cell death in a cancer cell in a subject, wherein the cancer cell has MET or an epitope of MET presented on its surface, that include: administering a therapeutically effective amount of any of the pharmaceutical compositions of described herein or any of the antibodies described herein to a subject identified as having a cancer characterized as having the population of cancer cells. In some embodiments, the cell

death that is induced is necrosis. In some embodiments, the cell death that is induced is apoptosis.

In some embodiments of any of the methods described herein, the cancer is a primary tumor.

In some embodiments of any of the methods described herein, the cancer is a metastasis.

In some embodiments of any of the methods described herein, the cancer is a non-T-cell-infiltrating tumor. In some embodiments of any of the methods described herein, the cancer is a T-cell-infiltrating tumor.

Provided herein are methods 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 MET or an epitope of MET presented on their surface, that include: administering a therapeutically effective amount of any of the pharmaceutical compositions of described herein or any of the antibodies described herein to a subject identified as having a cancer characterized as having the population of cancer cells. In some embodiments, the risk of developing a metastasis or the risk of developing an additional metastasis is decreased (e.g., a detectable decrease) by at least 1%, by at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 8%, at least 10%, at least 12%, at least 14%, at least 16%, at least 18%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% in the subject as compared to the risk of a subject having a similar cancer, but administered no treatment or a treatment that does not include the administration of any of the antibodies described herein.

In some embodiments of any of the methods described herein, the cancer is a non-T-cell-infiltrating tumor. In some embodiments of any of the methods described herein, the cancer is a T-cell-infiltrating tumor. In some embodiments of any of the methods described herein, the cellular compartment is part of the endosomal/lysosomal pathway. In some embodiments of any of the methods described herein, the cellular compartment is an endosome.

The term "subject" refers to any mammal. In some embodiments, the subject or "subject suitable for treatment" may be a canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), ovine, bovine, porcine, caprine, primate, e.g., a simian (e.g., a monkey (e.g., marmoset, baboon), or an ape (e.g., a gorilla, chimpanzee, orangutan, or gibbon) or a human; or rodent (e.g., a mouse,

a guinea pig, a hamster, or a rat). In some embodiments, the subject or "subject suitable for treatment" may be a non-human mammal, especially mammals that are conventionally used as models for demonstrating therapeutic efficacy in humans (e.g., murine, lapine, porcine, canine or primate animals) may be employed.

As used herein, treating includes reducing the number, frequency, or severity of one or more (e.g., two, three, four, or five) signs or symptoms of a cancer in a patient having a cancer (e.g., any of the cancers described herein). For example, treatment can reducing cancer progression, reduce the severity of a cancer, or reduce the risk of re-occurrence of a cancer in a subject having the cancer.

Provided herein are methods of inhibiting the growth of a solid tumor in a subject (e.g., any of the subjects described herein) that include administering to the subject a therapeutically effective amount of any of the antibodies described herein or any of the pharmaceutical compositions described herein (e.g., as compared to the growth of the solid tumor in the subject prior to treatment or the growth of a similar solid tumor in a different subject receiving a different treatment or receiving no treatment).

In some embodiments of any of the methods described herein, the growth of a solid tumor is primary growth of a solid tumor. In some embodiments of any of the methods described herein, the growth of a solid tumor is recurrent growth of a solid tumor. In some embodiments of any of the methods described herein, the growth of a solid tumor is metastatic growth of a solid tumor. In some embodiments, treatment results in about a 1% decrease to about 99% decrease (or any of the subranges of this range described herein) in the growth of a solid tumor in the subject (e.g., as compared to the growth of the solid tumor in the subject prior to treatment or the growth of a similar solid tumor in a different subject receiving a different treatment or receiving no treatment). The growth of a solid tumor in a subject can be assessed by a variety of different imaging methods, e.g., positron emission tomograph, X-ray computed tomography, computed axial tomography, and magnetic resonance imaging.

Also provided herein are methods of decreasing the risk of developing a metastasis or developing an additional metastasis over a period of time in a subject identified as having a cancer (e.g., any of the exemplary cancers described herein) that include administering to the subject a therapeutically effective amount of any of the proteins described herein or any of the pharmaceutical compositions described herein (e.g., as compared to a subject having a similar

cancer and receiving a different treatment or receiving no treatment). In some embodiments of any of the methods described herein, the metastasis or additional metastasis is one or more to a bone, lymph nodes, brain, lung, liver, skin, chest wall including bone, cartilage and soft tissue, abdominal cavity, contralateral breast, soft tissue, muscle, bone marrow, ovaries, adrenal glands, and pancreas.

In some embodiments of any of the methods described herein, the period of time is about 1 month to about 3 years (e.g., about 1 month to about 2.5 years, about 1 month to about 2 years, about 2 months to about 1.5 years, about 1 month to about 1 year, about 1 month to about 10 months, about 1 month to about 8 months, about 1 month to about 6 months, about 1 month to about 5 months, about 1 month to about 4 months, about 1 month to about 3 months, about 1 month to about 2 months, about 2 months to about 3 years, about 2 months to about 2.5 years, about 2 months to about 2 years, about 2 months to about 1.5 years, about 2 months to about 1 year, about 2 months to about 10 months, about 2 months to about 8 months, about 2 months to about 6 months, about 2 months to about 5 months, about 2 months to about 4 months, about 2 months to about 3 months, about 3 months to about 3 years, about 3 months to about 2.5 years, about 3 months to about 2 years, about 3 months to about 1.5 years, about 3 months to about 1 year, about 3 months to about 10 months, about 3 months to about 8 months, about 3 months to about 6 months, about 3 months to about 5 months, about 3 months to about 4 months, about 4 months to about 3 years, about 4 months to about 2.5 years, about 4 months to about 2 years, about 4 months to about 1.5 years, about 4 months to about 1 year, about 4 months to about 10 months, about 4 months to about 8 months, about 4 months to about 6 months, about 4 months to about 5 months, about 5 months to about 3 years, about 5 months to about 2.5 years, about 5 months to about 2 years, about 5 months to about 1.5 years, about 5 months to about 1 year, about 5 months to about 10 months, about 5 months to about 8 months, about 5 months to about 6 months, about 6 months to about 3 years, about 6 months to about 2.5 years, about 6 months to about 2 years, about 6 months to about 1.5 years, about 6 months to about 1 year, about 6 months to about 10 months, about 6 months to about 8 months, about 8 months to about 3 years, about 8 months to about 2.5 years, about 8 months to about 2 years, about 8 months to about 1.5 years, about 8 months to about 1 year, about 8 months to about 10 months, about 10 months to about 3 years, about 10 months to about 2.5 years, about 10 months to about 2 years, about 10 months to about 1.5 years, about 10 months to about 1 year, about 1 year to about 3 years, about 1 year to

about 2.5 years, about 1 year to about 2 years, about 1 year to about 1.5 years, about 1.5 years to about 3 years, about 1.5 years to about 2.5 years, about 1.5 years to about 2 years, about 2 years to about 3 years, about 2 years to about 2.5 years, or about 2.5 years to about 3 years).

In some embodiments, the risk of developing a metastasis or developing an additional metastasis over a period of time in a subject identified as having a cancer is decreased by about 1% to about 99% (e.g., or any of the subranges of this range described herein), e.g., as compared to the risk in a subject having a similar cancer receiving a different treatment or receiving no treatment.

Non-limiting examples of cancer include: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), adrenocortical carcinoma, anal cancer, appendix cancer, astrocytoma, basal cell carcinoma, brain tumor, bile duct cancer, bladder cancer, bone cancer, breast cancer, bronchial tumor, Burkitt Lymphoma, carcinoma of unknown primary origin, cardiac tumor, cervical cancer, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative neoplasm, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, ductal carcinoma, embryonal tumor, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, fibrous histiocytoma, Ewing sarcoma, eye cancer, germ cell tumor, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, gestational trophoblastic disease, glioma, head and neck cancer, hairy cell leukemia, hepatocellular cancer, histiocytosis, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumor, Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ, lung cancer, lymphoma, macroglobulinemia, malignant fibrous histiocytoma, melanoma, Merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer with occult primary, midline tract carcinoma involving NUT gene, mouth cancer, multiple endocrine neoplasia syndrome, multiple myeloma, mycosis fungoides, myelodysplastic syndrome, myelodysplastic/myeloproliferative neoplasm, nasal cavity and para-nasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytomas, pituitary tumor, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell cancer, renal pelvis and ureter cancer,

retinoblastoma, rhabdoid tumor, salivary gland cancer, Sezary syndrome, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, spinal cord tumor, stomach cancer, T-cell lymphoma, teratoid tumor, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, vaginal cancer, vulvar cancer, and Wilms' tumor. Additional examples of cancer are known in the art.

In some embodiments, the patient is further administered one or more additional therapeutic agents (e.g., one or more of a chemotherapeutic agent, a recombinant cytokine or interleukin protein, a kinase inhibitor, and a checkpoint inhibitor). In some embodiments, the one or more additional therapeutic agents is administered to the patient at approximately the same time as any of the antibodies described herein are administered to the patient. In some embodiments, the one or more additional therapeutic agents are administered to the patient after the administration of any of the antibodies described herein to the patient. In some embodiments, the one or more additional therapeutic agents are administered to the patient before the administration of any of the antibodies described herein to the patient.

In some embodiments of any of the methods described herein, the cancer is a solid cancer (e.g., breast cancer, prostate cancer, or non-small cell lung cancer).

**Avidity**

Antibodies and antigens binding fragment thereof are multivalent, and thus comprise more than one binding site. Generally, the measure of total binding strength of an antibody at its binding site is termed avidity. Generally, the terms "fold avidity" and "selectivity" can refer to the fold-difference between the affinity of an antibody and the avidity of an antibody, for example as seen when measuring the total binding strength of an antibody on a cell line with high target expression (avidity; e.g. a cancer cell, e.g. Detroit-562 cells) as compared to the total binding strength of an antibody on a cell line with low target expression (affinity, e.g. a non-cancer cell, e.g. HUVEC cells). Generally, avidity is determined by four factors: the binding affinity (e.g., the strength of the binding at an individual binding site); valency (e.g., the total number of binding sites); structural arrangement (e.g., the structure of the antigen and antibody); and antigen density (e.g., the number of antigens per cell).

Provided herein are methods of decreasing the risk of developing a metastasis or decreasing the risk of developing an additional metastasis in a subject having a cancer, where the

cancer is characterized by having a population of cancer cells that have MET or an epitope of MET presented on their surface the method comprising, administering a therapeutically effective amount of any of the antibodies described herein or any of the pharmaceutical compositions described herein to a subject identified as having a cancer characterized by having the population of cancer cells. In some embodiments, the antibodies described herein can have at least new at least 5%, at least 10%, at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 100%, at least 105%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 155%, at least 160%, at least 165%, at least 170%, at least 175%, at least 180%, at least 185%, at least 190%, at least 195%, or at least 200% at least 205%, at least 210%, at least 215%, at least 220%, at least 225%, at least 230%, at least 235%, at least 240%, at least 245%, at least 250%, at least 255%, at least 260%, at least 265%, at least 270%, at least 275%, at least 280%, at least 285%, at least 290%, at least 295%, at least 300%, at least 305%, at least 310%, at least 315%, at least 320%, at least 325%, at least 330%, at least 335%, at least 340%, at least 345%, at least 350%, at least 355%, at least 360%, at least 365%, at least 370%, at least 375%, at least 380%, at least 385%, at least 390%, at least 395%, or at least 400%, increase in selectivity for a cancer cell as compared to a non-cancer cell.

**Compositions**

Also provided herein are compositions (e.g., pharmaceutical compositions) that include at least one of any of the antibodies described herein. In some embodiments, the compositions (e.g., pharmaceutical compositions) can be disposed in a sterile vial or a pre-loaded syringe.

In some embodiments, the compositions (e.g., pharmaceutical compositions) are formulated for different routes of administration (e.g., intravenous, subcutaneous, intramuscular, or intratumoral). In some embodiments, the compositions (e.g., pharmaceutical compositions) can include a pharmaceutically acceptable carrier (e.g., phosphate buffered saline). Single or multiple administrations of any of the pharmaceutical compositions described herein can be given to a subject depending on, for example: the dosage and frequency as required and tolerated by the patient. A dosage of the pharmaceutical composition should provide a sufficient quantity of the antibody to effectively treat or ameliorate conditions, diseases, or symptoms.

Also provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein) that include administering a therapeutically effective amount of at least one of any of the compositions or pharmaceutical compositions provided herein.

**Kits**

Also provided herein are kits that include any of the antibodies described herein, any of the compositions described herein, or any of the pharmaceutical compositions described herein. In some embodiments, the kits can include instructions for performing any of the methods described herein. In some embodiments, the kits can include at least one dose of any of the compositions (e.g., pharmaceutical compositions) described herein. In some embodiments, the kits can provide a syringe for administering any of the pharmaceutical compositions described herein.

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

## EXAMPLES

**Example 1. Generation of MET binders and engineering of pH binding dependence**

pH-engineered antibodies specific for MET are generated using two methods. In the first approach, published monoclonal antibodies against MET are used as a starting template for introduction of additional mutations that allow engineering of pH-dependent binding to MET and i) enhanced endolysosomal accumulation of a conjugated toxin, as well as ii) enhanced MET recycling to the cell surface. The second approach involves discovery of de novo antibodies specific for MET via antibody display methods from naive libraries or libraries with defined CDR compositions and screening under conditions designed for selection of pH-engineered antibodies specific for MET. In either case, histidine residues play an important role in engineering pH-dependent binding proteins.

Histidine residues are at least partially protonated at a pH below 6.5 owing to its pKa of 6.0. Therefore, if a histidine side chain in an antigen-binding domain participates in an electrostatic binding interaction with its antigen it will start to turn positively charged at a pH at or below 6.5. This could either weaken or enhance the binding affinity of the interaction at a pH

below 6.5, based on the corresponding charge of and interactions with the antigen epitope. Thus, systematic introduction of histidines into antibody complementarity determining regions (CDRs) in an antibody or other binder library (e.g., an scFv library) can be used to identify substitutions that will affect an antigen-binding domain's interaction with an antigen at lower pH values. The first approach therefore involves histidine-scanning of variable region sequences of published monoclonal antibodies to identify pH-dependent variants.

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding [Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000]. Briefly, for a subset of the antibody sequences, CDRs in each chain are identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest (DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To engineer pH-dependent sequence variants, individual amino acid residues within the heavy chain and/or light chain CDRs are systematically substituted with a histidine, one at a time. In cases where the starting CDR residue is a histidine, it is mutated to an alanine. Antibody variants with only one histidine or alanine mutation in a heavy/light chain CDR are generated by co-transfection of Expi293 cells with a) one heavy chain or light chain sequence variant, and b) the corresponding starting antibodies (e.g., the starting MET-binding monoclonal antibody) light chain or heavy chain, respectively, using methods known to the art. After allowing for a period of protein expression, cell culture supernatants are collected, quantified, and the pH dependence of the variant is evaluated using biolayer interferometry (BLI) or other methods known to the art. Briefly, cell culture supernatants are normalized to an antibody expression level of 50 μg/mL, and captured on an anti-human Fc sensor (Forte Bio). A baseline is established using 1X kinetics buffer (Forte Bio), and the sensor is associated with 100 nM of MET in 1X PBS at pH 7.4 for 300 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor is exposed to 1X PBS at either pH 5.5 or pH 7.4 for 300-500 sec. Association and dissociation phase curves are examined for the starting antibody and each corresponding

antibody variant at pH 5.5 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.5 due to histidine or alanine substitution compared to the starting antibody, and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.5 in the antibody variant itself and with the starting antibody. Variants that show either enhanced dissociation at pH 5.5 or reduced dissociation at pH 7.4 or both are selected for further analysis. It is also noted that while some histidine and alanine mutations obliterate MET binding, others are tolerated with little (e.g., less than 1-fold change in KD or dissociation rate) or no change in MET binding kinetics. Especially because histidine is a large, positively charged amino acid, these histidine variants and alanine variants with no change are noted as positions that may tolerate a wide range of mutations and lead to antibodies with different sequence but similar binding properties, a designation that is not otherwise apparent. The variants selected for further analysis are expressed at a larger scale and purified using protein A affinity chromatography. Binding kinetics (kon and koff) of the purified starting antibody and variant antibodies are measured at pH 5.5 and pH 7.4 using Biacore (GE Healthcare). The ratio of the antibody's rate of dissociation (koff at pH 7.4 divided by koff at pH 5.5) is also used as a quantitative assessment of pH-dependent binding; similarly, the dissociation constant KD is calculated at both pH 5.5 and pH 7.4 as koff divided by kon and the ratio of the antibody's dissociation constant (KD at pH 7.4 divided by KD at pH 5.5) is also used as a quantitative assessment of pH-dependent binding. Antibodies with a rate of dissociation ratio less than that of the starting antibody and/or a dissociation constant ratio less than that of the starting antibody are selected for further assessment of combinatorial substitutions. Favorable histidine and/or alanine amino acid positions can also be combined to enhance pH dependence; this can be done by, e.g., combinatorially or rationally combining histidine and/or alanine substitutions on a given heavy or light chain that individually improve pH dependence, by, e.g., combinatorially or rationally combining modified heavy and light chains such that histidine and/or alanine substitutions are present on both chains, or combinations thereof. Such combinatorial variants are generated and tested/analyzed for differential pH dependence using the methods and protocols described herein, or others known to the art. Antibody variants that have the lowest rate of dissociation ratios and/or dissociation constant ratios are selected as candidates for further analysis (hereafter referred to as "pH-engineered antibodies specific for MET").

The second method for selection of pH-engineered antibodies specific for MET involves either screening libraries to identify de novo pH-dependent antibodies specific for MET or antibodies that could serve as templates for engineering pH-dependent binding as described herein. Two types of libraries can be used for these selections: naive phage/yeast display antibody libraries (e.g., Fab, scFv, VHH, VL, or others known to the art) or phage/yeast display libraries where CDRs have been mutated to express a subset of amino acid residues. Libraries are screened against soluble recombinant MET extracellular domains using methods known to the art with positive selection for variants that bind weakly (e.g., are eluted from beads) at pH 5.0 and bind strongly (e.g., are bound to beads) at pH 7.4. Three rounds of selections are performed. The final round of binders are screened using ELISA for binding to human MET and cyno MET and mouse MET or via mean fluorescence intensity in flow cytometric analysis. If more binders with cyno or murine cross-reactivity are desired, the final selection round can instead be performed on cyno MET or murine MET. Selected binding proteins are subcloned into mammalian expression vectors and expressed as either full IgG proteins or Fc fusions in Expi293 cells. BLI analysis is performed as described herein for selection of pH-dependent binder variants and confirmed using Biacore.

**Example 2. In vitro demonstration of pH-dependent binding to MET, pH-dependent release of MET, enhanced endolysosomal delivery in MET+ cells, and increased MET antigen density in MET+ cells after exposure to pH-engineered antibodies specific for MET as compared to control antibodies specific for MET.**

As discussed herein, pH-engineered antibodies specific for MET exhibit the desirable property of decreased MET binding at acidic pH (e.g., pH 5.0, pH 5.5), but enhanced binding at higher pH (e.g., pH 7.4), which enhances their accumulation in endolysosomes under physiological conditions.

**pH-dependent binding to MET on cells**

To demonstrate that pH-engineered antibodies specific for MET binds cell surface MET at neutral pH, a cell surface binding assay is performed. A panel of human cells that are MET+ is assembled (e.g., Hs 746T ATCC Cat#HTB-135, NCI-H441 ATCC Cat#HTB-174, NCI-H820 ATCC Cat#HTB-181). Methods of identifying and quantifying gene expression (e.g., MET) for a

given cell line are known to the art, and include, e.g., consulting the Cancer Cell Line Encyclopedia (CCLE; https://portals.broadinstitute.org/ccle) to ascertain the expression level and/or mutation status of a given gene in a tumor cell line), rtPCR, microarray, or RNA-Seq analysis, or cell staining with antibodies known in the art (e.g. Telisotuzumab or Cell Signaling Technology Met (D1C2) XP Rabbit mAb Cat#8198, or R&D Systems Human HGFR/c-MET Antibody Clone#95106 Cat#MAB3582 for MET). Cells are seeded at approximately 5-10,000 per well in 150 μL of pH 7.4 culture medium and incubated at 37 °C for 5 minutes at several doses (e.g., a two-fold dilution series) from 1 pM to 1 μM with one of the following antibodies: a known, control antibody specific for MET (e.g., an antibody, Telisotuzumab, emibetuzumab, hucMET27Gv1.3, or P3D12), the pH-engineered antibody specific for MET, and an appropriate negative isotype control mAb (e.g., Biolegend Purified Human IgG1 Isotype Control Recombinant Antibody, Cat#403501). Prior to the onset of the experiment, the binding properties of all antibodies are validated using methods known to the art. Following the 5 minute incubation, cells are fixed with 4% formaldehyde (20 min at room temperature) and incubated with an appropriate fluorophore-labeled secondary antibody (e.g., ThermoFisher Mouse anti-Human IgG1 Fc Secondary Antibody, Alexa Fluor 488, Cat#A-10631) for 60 minutes. Unbound reagents are washed with a series of PBS washes, and the cell panels are imaged using confocal microscopy. Upon analysis of the images, significant fluorescence can be observed on the surface of cells bound with the known, control antibody specific for MET as well as the pH-engineered antibody specific for MET, but little surface binding can be observed for the isotype negative control. To isolate the effect of pH on surface binding, the same experiment is repeated twice, with the primary antibody incubation taking place at sequentially lower pH (e.g., pH 6.5 and 5.5 and 5.0). Analysis of the resulting confocal microscopy images can show significant fluorescence on the surface of cells bound with all mAbs tested, excepting the isotype negative control, and that this fluorescence decreases for the pH-engineered antibody specific for MET as the pH decreases. Alternatively, cells are analyzed for mean fluorescent intensity by flow cytometry using methods known in the art. A dissociation constant KD on cells at neutral pH of the antibodies analyzed is determined by nonlinear regression methods known in the art (e.g., a Scatchard plot). Taken together, the results can show that the pH engineering process results in the creation of a pH-engineered antibody specific for MET that is pH-dependent in its binding properties and that it more effectively binds at neutral pH as

compared to more acidic pH. Other methods of assessing the pH dependence of the pH-engineered antibodies specific for MET are known in the art and include, e.g., using flow cytometry to measure antibody surface binding.

**pH-dependent release of MET on cells**

To demonstrate that pH-engineered antibodies specific for MET are capable of releasing MET at low pH after binding at a neutral pH, a variant of the cell surface binding assay described above is performed using methods known to the art (e.g., as generally described in Gera N. (2012) PLoS ONE 7(11): e48928). Briefly, an appropriate MET+ cell line (passage number less than 25) is harvested and 50,000 cells per well are plated in a U-Bottomed 96-well microplate. Three conditions are tested; binding and secondary staining at pH 7.4, binding and secondary staining at pH 5.0, and binding at pH 7.4 followed by release at pH 5.0 for 30 minutes and secondary staining at pH 7.4. Both pH-engineered antibodies specific for MET as well as a control antibody specific for MET are tested. The cells are washed two times with 200 µL of FACS buffer (1x PBS containing 3% Fetal Bovine Serum) at either pH 7.4 or 5.0 depending on the condition being tested. The purified protein samples are diluted into FACS buffer of the appropriate pH and added to the cells and allowed to bind for one hour on ice. After incubation with the primary antibodies the pH 7.4 and pH 5.0 conditions are washed twice as before, and then 100 µl of secondary rat anti-human Fc AF488 (BioLegend 410706) or other appropriate antibody, diluted 1:50, or anti Myc-Tag mouse mAb-AF488 (Cell Signaling Technologies 2279S) diluted 1:50 is added in FACS buffer of the appropriate pH, and incubated for 30 minutes on ice. The pH 5.0 release condition is washed twice with FACS buffer pH 7.4 and then resuspended in 100 µl of FACS buffer pH 5.0 and incubated on ice for 30 minutes, followed by secondary staining in FACS buffer pH 7.4 as described for the other conditions. The plates are washed twice as before and resuspended in 1% paraformaldehyde in the appropriate FACS buffer to fix them for flow cytometry analysis. All conditions are read on a flow cytometer (Accuri C6, BD Biosciences). Binding is observed as a shift in the FLl signal (as a mean fluorescence intensity) versus secondary alone. Upon analysis of the data, it can be determined that both the pH-engineered antibody specific for MET as well as the control antibody specific for MET effectively bind the surface of MET+ cells at neutral pH, but the pH-engineered

antibody specific for MET binds poorly at pH 5.0; similarly, it can be determined that the pH-engineered antibody specific for MET binds effectively at pH 7.4, but then releases/unbinds MET at pH 5.0.

**Enhanced endolysosomal delivery in MET+ cells of pH-engineered antibodies specific for MET as compared to control antibodies specific for MET (pHrodo)**

To verify and demonstrate that antibodies specific for MET achieve endolysosomal localization following cellular uptake, an internalization assay is performed using methods known to the art (e.g., Mahmutefendic et al., Int. J. Biochem. Cell Bio., 2011). Briefly, as described herein, a panel of human cells that express MET highly is assembled using methods known to the art. Cells are plated, washed three times with PBS, and incubated at 37 degrees C for 60 minutes in media at neutral pH, with added concentrations of 2 micrograms per milliliter of a known, control antibody specific for MET (e.g., as described herein), the pH-engineered antibody specific for MET, and an appropriate negative isotype control mAb (e.g., as described herein). In a subset of cells, validation of antibody internalization and endosomal localization is performed using methods known to the art; e.g., cells are fixed in 4% formaldehyde as described herein, permeabilized using TWEEN 20 or other methods known to the art (Jamur MC et al (2010) Permeabilization of cell membranes, Methods Mol Biol. 588:63-6), additionally stained with an endosomal marker, e.g., a fluorescent RAB11 antibody (RAB11 Antibody, Alexa Fluor 488, 3H18L5, ABfinity™ Rabbit Monoclonal), stained with an appropriate fluorescently labeled anti-human secondary antibody (e.g., as described herein), and imaged using confocal fluorescence microscopy, as described herein. Analysis of the confocal images can be used to show that both the pH-engineered antibody specific for MET as well as the control antibody specific for MET are internalized and accumulate in the endolysosomes.

To demonstrate that pH-engineered antibodies specific for MET achieve enhanced endolysosomal accumulation relative to a control antibody specific for MET, a pHrodo-based internalization assay is performed using both a known, control antibody specific for MET (e.g., as described herein) as well as the pH-engineered antibody specific for MET. The assay makes use of pHrodo™ iFL (P36014, ThermoFisher), a dye whose fluorescence increases with decreasing pH, such that its level of fluorescence outside the cell at neutral pH is lower than its

level of fluorescence inside the acidic pH environment of endolysosomes. Briefly, an appropriate MET+ cell line (less than passage 25) is suspended in its recommended media (e.g., by cell banks or cell bank databases ATCC, DSMZ, or ExPASy Cellosaurus) and plated in a 24-well plate at a density of 2,000,000 cells/mL, 1 mL per well. While keeping the cells on ice, 1 mL of 2x pHrodo iFL-labeled antibody (prepared in accordance with the manufacturer's instructions) is added to each well, the well is pipetted/mixed five times, and the plate is incubated in a light-protected environment for 45 minutes, on ice. An identical but separate plate is also incubated on ice that is meant as a no-internalization negative control. Following this incubation, the experimental plate is moved to a 37 degree C incubator, the negative control plate is kept on ice to slow or block internalization, and samples are taken at designated time points to create an internalization time course. Samples are placed into a U-bottom 96-well plate, and internalization is quenched via addition of 200 µL/well of ice-cold FACS buffer. The plates are spun down at 2000xg for 2 minutes, resuspended in 200 µL ice-cold FACS buffer, spun down again, and resuspended in FACS buffer a second time. Finally, the samples are loaded into a flow cytometer for read-out of cellular pHrodo fluorescence using excitation and emission wavelengths consistent with the excitation and emission maxima of the pHrodo iFL Red dye (566 nm and 590 nm, respectively). Upon completion of the flow cytometry experiment and analysis of the data, it can be observed that cells treated with the pH-engineered antibody specific for MET have a higher pHrodo iFL signal relative to a known, control antibody specific for MET, indicating that pH-engineered antibodies specific for MET achieve enhanced endolysosomal accumulation relative to a control antibody specific for MET.

Alternatively, to demonstrate that pH-engineered antibodies specific for MET achieve enhanced endolysosomal accumulation relative to a control antibody specific for MET, a variation of the above-described experiment is performed. MET+ cells are plated, washed three times with PBS, and incubated at 37 degrees C for 60 minutes in media at neutral pH with added concentrations of 2 µg/mL of either pH-engineered antibody specific for MET or control antibody specific for MET. Following incubation, cells are washed three times with PBS, fixed and permeabilized, and stained with a panel of appropriately selected antibodies that bind late endosomal markers as well as lysosomes (e.g., RAB7, and LAMP1; Cell Signaling Technology, Endosomal Marker Antibody Sampler Kit #12666; AbCam, Anti-LAMP2 antibody [GL2A7], ab13524). After primary antibody staining, cells are stained with an appropriate mixture of

fluorescently labeled secondary antibodies (e.g., Goat Anti-Human IgG (H&L) Secondary Antibody (Alexa Fluor 647), Cat#A-21445, and Abcam Goat Anti-Rabbit IgG H&L (Alexa Fluor 488), Cat#ab150077), imaged using confocal fluorescence microscopy, and regions of co-localization of signal from MET-specific antibodies and endosomal markers are visualized and quantified. Upon analysis of the data, it can be revealed that there is increased co-localization of endolysosomal and MET-specific antibody signal in wells treated with the pH-engineered antibodies specific for MET as compared to wells treated with control antibody specific for MET, and can thereby demonstrate that pH-engineered antibodies specific for MET achieve enhanced endolysosomal accumulation relative to control antibody specific for MET.

**Increased MET antigen density in MET+ cells after exposure to pH-engineered antibodies specific for MET as compared to control antibodies specific for MET**

To demonstrate that treatment of cells with the pH-engineered antibodies specific for MET does not result in a detectable reduction of the level of MET on the surface of cells exposed to the pH-engineered antibodies specific for MET, or that said treatment results in less of a reduction of the level of MET on the surface of cells exposed to the pH-engineered antibody specific for MET versus a control antibody specific for MET, an antigen density study is performed using flow cytometry. Briefly, 4.0x10^5 cells that express MET are plated per well in a 96-well plate in 100 µL media. Cells are treated with a titration from 1 pM to 1 µM of i) pH-engineered antibodies specific for MET, ii) a first control antibody specific for MET, iii) an appropriate isotype control, and iv) an untreated control. Cells are incubated for 2 hours at 37 °C, at which point all cells are incubated with 200 nM of a fluorophore-labeled second control antibody specific for MET (e.g., as described herein) which has a different epitope (as determined by, e.g., competitive binding studies on cells) than either the first control antibody specific for MET or the pH-engineered antibodies specific for MET for 30 minutes at 4 °C. Following this 30-minute incubation, the mean fluorescence intensity (MFI) of all cells is read out using, e.g., flow cytometry, using methods known to one of ordinary skill in the art. In parallel, a quantitative standard curve that can be used to quantify the presence of MET on the surface of treated cells as a function of MFI is generated using a commercially available quantification kit (e.g., BD Biosciences PE Phycoerythrin Fluorescence Quantitation Kit, catalog

#340495); the quantitative standard curve is created by following the manufacturer's instructions. Other methods of determining the absolute number of MET on the cell surface are known in the art and include, e.g., use of radioisotopically labeled reagents. Upon analysis of the data, it can be revealed that at least one antibody concentration, cells treated with a control antibody specific for MET experience a reduction of the level of MET on their surface, whereas cells treated with pH-engineered antibodies specific for MET experience a significantly smaller reduction or no reduction at all, both relative to the isotype and untreated controls.

**Example 3. Conjugation of pH-engineered and control antibodies specific for MET to cytotoxic drugs**

An antibody conjugate (ADC) is made comprising the MET-binding IgG (hereafter, MET-IgG) described herein linked to monomethyl auristatin E (MMAE) via a valine-citrulline (vc) linker (hereafter, MET-IgG-DC). Conjugation of the antigen-binding protein construct with vcMMAE begins with a partial reduction of the MET-IgG followed by reaction with maleimidocaproyl-Val-Cit-PABC-MMAE (vcMMAE). The MET-IgG (20 mg/mL) is partially reduced by addition of TCEP (molar equivalents of TCEP:mAb is 2:1) followed by incubation at 0° C overnight. The reduction reaction is then warmed to 20° C. To conjugate all of the thiols, vcMMAE is added to a final vcMMAE:reduced Cys molar ratio of 1:15. The conjugation reaction is carried out in the presence of 10% v/v of DMSO and allowed to proceed at 20° C for 60 minutes.

After the conjugation reaction, excess free N(acetyl)-Cysteine (2 equivalents vs. vcMMAE charge) is added to quench unreacted vcMMAE to produce the Cys-Val-Cit-MMAE adduct. The Cys quenching reaction is allowed to proceed at 20° C for approximately 30 minutes. The Cys-quenched reaction mixture is purified as per below. The above conjugation method can also be used to conjugate maleimidocaproyl monomethylauristatin F (mcMMAF) to an antigen-binding protein construct.

The MET-IgG-DC is purified using a batch purification method. The reaction mixture is treated with the appropriate amount of water washed Bu-HIC resin (ToyoPearl; Tosoh Biosciences), i.e., seven weights of resin is added to the mixture. The resin/reaction mixture is stirred for the appropriate time, and monitored by analytical hydrophobic interaction chromatography for removal of drug conjugate products, filtered through a coarse polypropylene

filter, and washed by two bed volumes of a buffer (0.28 M sodium chloride, 7 mM potassium phosphate, pH 7). The combined filtrate and rinses are combined and analyzed for product profile by HIC HPLC. The combined filtrate and rinses are buffer exchanged by ultrafiltration/diafiltration (UF/DF) to 15 mM histidine, pH 6 with 10 diavolumes 15 nM histidine buffer.

A similar protocol can be used to conjugate DNA toxins such as SG3249 and SGD-1910 to MET-IgG (see Tiberghien AC et al (2016) Design and Synthesis of Tesirine, a Clinical Antibody−Drug Conjugate Pyrrolobenzodiazepine Dimer Payload, ACS Med Chem Lett 7:983−987). Briefly, for SG3249, MET-IgG (15 mg, 100 nanomoles) is diluted into 13.5 mL of a reduction buffer containing 10 mM sodium borate pH 8.4, 2.5 mM EDTA and a final antibody concentration of 1.11 mg/mL. A 10 mM solution of TCEP is added (1.5 molar equivalent/antibody, 150 nanomoles, 15 microliters) and the reduction mixture is heated at +37 °C for 1.5 hours in an incubator. After cooling down to room temperature, SG3249 is added as a DMSO solution (5 molar equivalent/antibody, 500 nanomoles, in 1.5 mL DMSO). The solution is mixed for 1.25 hours at room temperature, then the conjugation is quenched by addition of N-acetyl cysteine (1 micromole, 100 microliters at 10 mM), and injected into an AKTA™ Pure FPLC using a GE Healthcare HiLoadTM 26/600 column packed with Superdex 200 PG, and eluted with 2.6 mL/min of sterile-filtered phosphate-buffered saline (PBS). Fractions corresponding to the MET-IgG-DC monomer peak are pooled, concentrated using a 15mL Amicon Ultracell 50KDa MWCO spin filter, analysed and sterile-filtered. UHPLC analysis on a Shimadzu Prominence system using a Phenomenex Aeris 3.6u XB-C18 150 x 2.1 mm column eluting with a gradient of water and acetonitrile on a reduced sample of MET-IgG-DC at 280 nm and 330 nm (SG3249 specific) can show a mixture of light and heavy chains attached to several molecules of SG3249, consistent with a drug-per-antibody ratio (DAR) of 1 to 4 molecules of SG3249 per antibody. UHPLC analysis on a Shimadzu Prominence system using a Phenomenex Yarra 3u SEC-3000 300 mm x 4.60 mm column eluting with sterile-filtered SEC buffer containing 200 mM potassium phosphate pH 6.95, 250 mM potassium chloride and 10% isopropanol (v/v) on a sample of MET-IgG-DC at 280 nm can show a monomer purity of over 90% with no impurity detected. UHPLC SEC analysis allows determination of final MET-IgG-DC yield of greater than 30%.

Alternatively, methods to conjugate toxins to antibodies via lysine residues are known in the art (e.g., see Catcott KC et al (2016) Microscale screening of antibody libraries as maytansinoid antibody-drug conjugates, MAbs 8:513-23). In addition, similar methods to the above can be used to conjugate drugs and toxins to non-IgG formats with disulfide bonds, such as Vh-Fcs.

**Example 4. Demonstration of enhanced cytotoxicity of pH-engineered ADCs specific for MET in MET+ cells as compared to a control ADC specific for MET**

The cytotoxic activity of both pH-engineered ADCs specific for MET (e.g., a pH-engineered MET-IgG-DC) and control antibody ADCs specific for MET (e.g., a control antibody MET-IgG-DC) are separately evaluated on a panel of MET+ cell lines expressing a variety of antigen densities (e.g., as described herein) and a MET- cell line (e.g., T-47D ATCC Cat#HTB-133), selected using the methods described herein, and, optionally, cells expressing transgenic MET, e.g., HEK293 cells transfected with MET using methods known in the art (e.g., Expi293™ Expression System Kit ThermoFisher Catalog number: A14635). For purposes of validation, prior to use, all cell lines are tested for expression of MET using methods known to the art, e.g., qPCR, flow cytometry, mRNA RPKM, and antibody staining using anti-MET antibodies known to the art (e.g., as described herein) followed by visualization of the stain using fluorescence microscopy, immunohistochemistry, flow cytometry, ELISA, or other methods known to the art. To evaluate the cytotoxicity of compounds, cells are seeded at approximately 10-40,000 per well in 150 microliters of culture medium, then treated with graded doses of compounds from 1pM to 1 μM in quadruplicates at the initiation of the assay. Cytotoxicity assays are carried out for 96 hours after addition of test compounds. Fifty microliters of resazurin dye are added to each well during the last 4 to 6 hours of the incubation to assess viable cells at the end of culture. Dye reduction is determined by fluorescence spectrometry using the excitation and emission wavelengths of 535 nm and 590 nm, respectively. For analysis, the extent of resazurin reduction by the treated cells is compared to that of untreated control cells, and percent cytotoxicity is determined. Alternatively, a WST-8 kit is used to measure cytotoxicity per the manufacturer's instructions (e.g., Dojindo Molecular Technologies Catalog# CCK-8). IC50, the concentration at which half-maximal killing is observed, is calculated using curve-fitting methods known in the art. Upon analysis of the data, it can be determined that pH-engineered

and control antibody ADCs specific for MET are substantially cytotoxic to one or more MET+ cell line, but less toxic to MET- cells. It also can be determined that pH-engineered ADCs specific for MET are more cytotoxic to one or more MET+ cell lines than control antibody ADCs specific for MET because: a) they show greater depth of killing at one or more concentrations or, b) they show lower IC50 or, c) they show a greater ratio of their dissociation constant KD on cells at neutral pH (as described herein) divided by their IC50 on those same cells.

Additionally, the cytotoxic activity of antibodies specific for MET can be measured in a secondary ADC assay. Secondary ADC assays are known in the art (e.g., Moradec Cat# αHFc-NC-MMAF and Cat# αHFc-CL-MMAE, and associated manufacturer's instructions). Briefly, the assay is carried out as in the previous paragraph, except the antibody specific for MET is substituted for the ADC specific for MET, and to evaluate the cytotoxicity of compounds, cells are seeded at approximately 10-40,000 per well in 150 microliters of culture medium, then treated with graded doses of antibody specific for MET from 1pM to 1 μM (final concentration in culture medium, having been pre-mixed with 100nM, final concentration in culture medium, of Moradec Cat# αHFc-NC-MMAF secondary ADC reagent and pre-incubated at 37°C for 30min before addition of the mixture to the culture medium) in quadruplicates at the initiation of the assay.

The cytotoxic activity of pH-engineered ADCs specific for MET and control antibody ADCs specific for MET conjugates, as well as antibodies specific for MET in a secondary ADC assay, are additionally measured by a cell proliferation assay employing the following protocol (Promega Corp. Technical Bulletin TB288; Mendoza et al., Cancer Res. 62:5485-5488, 2002):

1. An aliquot of 100 microliters of cell culture containing about 104 cells (e.g., MET+ cells as described herein) in medium is deposited in each well of a 96-well, opaque-walled plate.
2. Control wells are prepared containing medium and without cells.
3. ADC specific for MET is added to the experimental wells at a range of concentrations from 1pM-1uM and incubated for 1-5 days. Alternatively, in a secondary ADC assay, 100nM secondary ADC reagent (final concentration in culture medium, Moradec Cat# αHFc-NC-MMAF) and antibody specific for MET at a range of concentrations from

1pM-1uM (final concentration in culture medium) are pre-mixed and pre-incubated at 37°C for 30min before addition of the mixture to the culture medium, and incubated for 1-5 days.

4. The plates are equilibrated to room temperature for approximately 30 minutes.

5. A volume of CellTiter-Glo Reagent equal to the volume of cell culture medium present in each well is added.

6. The contents are mixed for 2 minutes on an orbital shaker to induce cell lysis.

7. The plate is incubated at room temperature for 10 minutes to stabilize the luminescence signal.

8. Luminescence is recorded and reported in graphs as RLU = relative luminescence units.

**Example 5. Demonstration of enhanced toxin liberation of pH-engineered ADCs specific for MET in MET+ cells as compared to a control ADC specific for MET**

The pH-engineered ADCs specific for MET (e.g., a pH-engineered MET-IgG-DC) can also demonstrate increased toxin liberation in MET+ cells as compared to a control antibody ADC specific for MET (e.g., a control antibody MET-IgG-DC). After treatment of MET+ cells with pH-engineered and control antibody ADCs specific for MET as described herein, an LC-MS/MS method is used to quantify unconjugated (i.e., liberated) MMAE in treated MET+ cells (Singh, A.P. and Shah, D.K. Drug Metabolism and Disposition 45.11 (2017): 1120-1132.) An LC-MS/MS system with electrospray interphase and triple quadrupole mass spectrometer is used. For the detection of MMAE, a XBridge BEH Amide column (Waters, Milford, MA) is used with mobile phase A as water (with 5 mM ammonium formate and 0.1% formic acid) and mobile phase B as 95:5 acetonitrile/water (with 0.1% formic acid and 1 mM ammonium formate), using a gradient at a flow rate of 0.25 mL/min at 40 °C. The total duration of the chromatographic run is 12 minutes, where two MRM scans (718.5/686.5 and 718.5/152.1 amu) are monitored. Deuterated (d8) MMAE (MCE MedChem Express, Monmouth Junction, NJ) is used as an internal standard. First, an equation for quantifying unconjugated MMAE in a biological sample is derived by dividing the peak area for each drug standard by the peak area obtained for the internal standard. The resultant peak area ratios are then plotted as a function of the standard concentrations, and data points are fitted to the curve using linear regression. Three

QC samples are included in the low, middle, and upper ranges of the standard curve to assess the predictive capability of the developed standard curve. The standard curves obtained are then used to deduce the observed concentrations of MMAE in a biologic sample. For measurement of MMAE concentration, treated cell samples are pelleted and reconstituted in fresh media to a final concentration of 0.25 million cells/100 µL. Samples are spiked with d8-MMAE (1 ng/mL) before performing cell lysis by the addition of a 2-fold volume of ice-cold methanol followed by freeze-thaw cycle of 45 minutes at -20 °C. The final cell lysate is obtained by centrifuging the samples at 13,000 rpm for 15 minutes at 4 °C followed by collection of supernatant. For the preparation of standards and QC samples, a fresh cell suspension (0.25 million/100 µl) is spiked with known concentrations of MMAE and internal standard (d8-MMAE) before a procedure similar to the cell lysis mentioned above. The resulting cell lysates are then evaporated and reconstituted in mobile phase B before injection into LC-MS/MS. The concentration of unconjugated MMAE in lysates of MET+ cells treated with pH-engineered ADCs specific for MET is observed to be greater than that in MET+ cells treated with control antibody ADC specific for MET.

For tubulin-inhibiting toxins, toxin liberation is also assessed by monitoring of cell viability and cell cycle phase. ~2.0x10^5 MET+ cells are plated in a 96-well flat bottom plate and treated with pH-engineered and control antibody ADCs specific for MET as described herein. After treatment, cells are transferred to a 96-round bottom plate, and the plate is centrifuged at 400 rcf for 2 min to decant supernatant. Decanted cells are stained with Live/Dead eFluor 660. Cells are then centrifuged and washed with FACS buffer (PBS with 2% FBS), after which cell cycle distribution is analyzed with a BD Cycletest™ Plus DNA Kit (cat # 340242). Briefly, cells are re-suspended in 76 ul Solution A and incubated for 10 min at room temperature. 61 µL Solution B is then added, and cells are incubated for another 10 min at room temperature. Finally, 61 µL of cold Solution C is added, and cells are again incubated for 10 min at room temp. Immediately after the last incubation step, cells are analyzed by flow cytometry (without washing) at a flow rate of 10 µL/sec. Increased G2/M-phase arrest can be observed with exposure to pH-engineered ADCs specific for MET as compared to control antibody ADC specific for MET.

For DNA-damaging toxins (e.g., pyrrolobenzodiazepine or "PBD"), DNA damage is assessed by measuring the phosphorylated histone H2AX (γH2AX). H2AX is normally phosphorylated in response to double-strand breaks in DNA; however, increased levels γH2AX

may also be observed as a result of treatment with DNA-cross-linking toxins such as PBD or cisplatin (Huang, X. et al. 2004, Cytometry Part A 58A, 99–110). MET+ cells are treated with pH-engineered and control antibody ADCs specific for MET as described herein. After treatment, cells are rinsed with PBS, and then fixed in suspension in 1% methanol-free formaldehyde (Polysciences, Warrington, PA) in PBS at 0 °C for 15 min. Cells are resuspended in 70% ethanol for at least 2 h at -20°C. Cells are then washed twice in PBS and suspended in 0.2% Triton X-100 (Sigma) in a 1% (w/v) solution of BSA (Sigma) in PBS for 30 min to suppress nonspecific Ab binding. Cells are centrifuged again (200 g, 5 min) and the cell pellet is suspended in 100 µL of 1% BSA containing 1:800 diluted anti-histone γH2AX polyclonal Ab (Trevigen, Gaithersburg, MD). The cells are then incubated overnight at 4 °C, washed twice with PBS, and resuspended in 100 µL of 1:30 diluted FITC-conjugated F(ab')2 fragment of swine anti-rabbit immunoglobulin (DAKO, Carpinteria, CA) for 30 min at room temperature in the dark. The cells are then counterstained with 5 µg/mL of PI (Molecular Probes, Eugene, OR) dissolved in PBS containing 100 µg/mL of DNase-free RNase A (Sigma), for 20 min at room temperature. Cellular fluorescence of the FITC γH2AX signal and the PI counterstain are measured using flow cytometry using methods known in the art. When comparing cells within the same stage of the cell cycle (based on total DNA content), treated MET+ cells can be observed to have an increased FITC γH2AX signal relative to untreated MET+ cells (which serve as a baseline). Furthermore, MET+ cells treated with pH-engineered ADCs specific for MET can be observed to have a greater increase in levels of γH2AX over baseline than cells treated with a control antibodyADC specific for MET. In addition to the γH2AX assay, DNA cross-linking can be more directly assessed with a Comet assay (Chandna, S. (2004) Cytometry 61A, 127–133).

In addition, as disclosed herein, pH-engineered and control antibodies can be assayed using the methods in this example without direct conjugation by performing a secondary ADC assay instead of using primary conjugated ADCs.

**Example 6. Demonstration of decreased half-life of pH-engineered antibodies specific for MET as compared to a control antibody specific for MET in tumor-bearing animals**

One of the surprising aspects of the pH-engineered antibodies specific for MET described by the invention can be their ability to facilitate increased dissociation of antibodies from the

MET within the endosome or lysosome resulting in a decreased serum half-life relative to control antibodies specific for MET or antibodies that are not specific for MET in tumor-bearing animals. This decreased serum half-life is due to the enhanced frequency with which pH-engineered antibodies specific for MET are cleared from circulation due to their enhanced cellular internalization by tumor cells once bound to MET, which over time can be observed through a decrease in serum concentration of unbound pH-engineered antibody specific for MET in tumor-bearing animals. To demonstrate these properties, a series of animal studies in tumor bearing mice is performed using pH-engineered antibody specific for MET and control antibody specific for MET using methods known to the art (e.g., Gupta, P., et al. (2016), mAbs, 8:5, 991-997). Briefly, to conduct mouse studies, a single intravenous bolus (e.g., 5 mg/kg) of either pH-engineered antibody specific for MET or control antibody specific for MET is administered via tail vein to two groups of NOD SCID mice (e.g. Jackson Labs NOD.CB17-Prkdcscid/J Stock No: 001303) xenografted with a MET+ cell line (e.g., as described herein). Xenografted mice are prepared by growing 1-5 million MET+ cells in vitro and inoculating subcutaneously into the right flank of the mouse. Tumors are size matched at 300 mm3. Measurements of the length (L) and width (W) of the tumors are taken via electronic caliper and the volume is calculated according to the following equation: V=L×W^2/2. Blood samples are collected via retro-orbital bleeds from each group at each of the following time points: 15m, 30m, 1h, 8h, 24h, and 3d, 7d, 10d, 14d, 17d, 21d, and 28d. Samples are processed to collect serum, and antibody concentrations are quantified using ELISA or other methods known to the art (e.g., PAC assay or MAC assay; Fischer, S.K. et al. (2012), mAbs, 4:5, 623-631, utilizing, e.g., anti-human IgG antibody Jackson ImmunoResearch Labs, Cat# 109–006–006). Antibody concentrations of pH-engineered antibody specific for MET and control antibody specific for MET are plotted as a function of time. Upon analysis of the data, it can be observed that the pH-engineered antibody specific for MET has a significantly shorter serum half-life relative to control antibody specific for MET, thereby demonstrating the ability of the pH-engineered antibody specific for MET's pH dependence to facilitate an enhanced dissociation within the endosome or lysosome relative to other, similar binders (e.g., control antibody specific for MET) that bind the same antigen but that differ in their pH dependence.

In addition, the half-life of pH-engineered and control antibody ADCs specific for MET can be assessed using the above methods by substituting pH-engineered and control antibody

ADCs specific for MET for the pH-engineered and control antibodies specific for MET (i.e., studying the antibodies after conjugation to a drug or toxin, as described herein).

**Example 7. Increased potency of pH-engineered ADCs specific for MET vs. a control antibody ADC specific for MET in mouse xenograft models**

The enhanced anti-tumor activity of the pH-engineered ADCs specific for MET against MET+ tumors can be demonstrated in a subcutaneous xenograft model of MET+ cells. For the experiments, 1-5 million MET+ cells are grown in vitro and inoculated subcutaneously per mouse into the right flank of female immunodeficient (e.g., SCID-Beige or NOD scid) mice. Tumors are size matched at 100-200 mm3, and dosed intraperitoneally (IP) (1 dose given every ~4-7 days for a total of ~2-6 doses). Measurements of the length (L) and width (W) of the tumors are taken via electronic caliper and the volume is calculated according to the following equation: V=L×W^2/2. A bolus (e.g., 5 mg/kg) of either pH-engineered ADC specific for MET or control antibody ADC specific for MET is administered via tail vein. Tumor growth inhibition (TGI) and tumor growth delay (TGD) and survival are significantly improved with administration of pH-engineered ADC specific for MET compared to administration of control antibody ADC specific for MET at the same regimen.

Optionally, spread of tumor cells into the various tissues is determined in sacrificed animals. Metastasis is measured according to Schneider, T., et al., Clin. Exp. Metas. 19 (2002) 571-582. Briefly, tissues are harvested and human Alu sequences are quantified by real-time PCR. Higher human DNA levels, quantified by real-time PCR, correspond to higher levels of metastasis. Levels of human Alu sequences (correlating to invasion of tumor cells into secondary tissue) are significantly lower in animals treated with pH-engineered ADC specific for MET, corresponding to reduced metastasis, compared to mice treated with control antibody ADC specific for MET at the same regimen. Alternatively, the enhanced anti-tumor activity of the pH-engineered ADC specific for MET can be shown in MET+ patient-derived xenograft models (e.g., available from The Jackson Laboratory).

**Example 8. Creation of a pH-engineered bispecific MET bispecific antibody and demonstration of exemplary properties as compared to a control bispecific antibody**

To create a pH-engineered antibody specific for MET with modified toxicity and internalization properties, a bispecific antibody that binds two different epitopes on MET is constructed. It is known in the art that biparatopic antibodies can show increased antigen-dependent internalization, and are therefore useful for applications such as antibody-drug conjugates (e.g., see Li et al (2016) A Biparatopic HER2-Targeting Antibody-Drug Conjugate Induces Tumor Regression in Primary Models Refractory to or Ineligible for HER2-Targeted Therapy, Cancer Cell 29:117-29). Briefly, a pH-engineered MET x MET bispecific, biparatopic antibody specific for MET is assembled using light chain/heavy chain pairs from two different pH-engineered antibodies specific for MET, each of which binds a distinct epitope on MET that does not overlap with the other epitope. A set of pH-engineered antibodies specific for MET that bind non-overlapping epitopes are discovered, e.g., using the methods described herein, or others known to one of ordinary skill in the art. Briefly, two binders are selected on the basis that they bind substantially different epitopes on MET, as determined by, e.g., a binding competition assay as in Abdiche YN et al (2009) Exploring blocking assays using Octet, ProteOn, and Biacore biosensors, Anal Biochem 386:172-80. Alternatively, briefly, as described in herein, cell culture supernatants of cells transfected with a first antibody specific for MET are normalized to an antibody expression level of 50 μg/mL, and captured on an anti-human Fc sensor (Forte Bio). A baseline is established using 1X kinetics buffer (Forte Bio), and the sensor is associated with 50 nM of MET in 1X PBS (that has been mixed and pre-incubated for 30 min at 37 degrees C with a second antibody specific for MET transfection supernatant or the first antibody specific for MET transfection supernatant, both normalized to 50ug/mL) at pH 7.4 for 300 sec to generate an association curve. If the association rate in the presence of the second antibody specific for MET is significantly faster (as calculated by the instrument software, or as seen by an elevated level of association over time) than the association rate in the presence of the first antibody specific for MET, then the second antibody specific for MET is deemed to bind a non-overlapping epitope of MET. Optionally, each antibody is screened for its internalization properties when bound to its epitope on a cell expressing MET, and well-internalizing antibodies are selected. Assays for determining the internalization rate of a molecule present on the surface of a cell are known to the art. See, e.g., Wiley et al. (1991) J. Biol. Chem. 266: 11083-11094; and Sorkin and Duex

(2010) Curr. Protoc. Cell Biol. Chapter, Unit-15.14; Vainshtein et al. (2015) Pharm Res. 32: 286-299. Once selected, heavy and light chain constructs with engineered mutations for heavy and light chain pairing (Spiess et al., "Alternative molecular formats and therapeutic applications of bispecific antibodies," 2015) are synthesized for both arms. Bispecific antibodies specific for MET are produced by co-expression of corresponding heavy and light chain plasmids in, e.g., Expi293 cells. Cell culture supernatants are harvested and subjected to Protein A purification. Heterodimeric antibodies specific for MET are separated from homodimeric species via additional purification steps such as ion exchange chromatography, hydrophobic interaction chromatography, and mixed mode chromatography. The purified pH-engineered MET x MET bispecific, biparatopic antibodies specific for MET are characterized via mass spectrometry to confirm the purity and absence of homodimeric species and size exclusion chromatography to confirm the presence of monomeric antigen-binding protein construct species. For the product antibody, binding to the MET is confirmed via Biacore analysis. Other methods of bispecific antibody production are known to the art and could also be used to create a bispecific antibody, e.g., the MET x MET bispecific, biparatopic antibodies specific for MET described herein (e.g., Labrijn et al (2014) "Controlled Fab-arm exchange for the generation of stable bispecific IgG1" Nature Protcols 9:2450–2463, accessed at http://www.nature.com/nprot/journal/v9/n10/abs/nprot.2014.169.html), as would be apparent to one of ordinary skill in the art. Alternatively, instead of a MET x MET antibody specific for MET, a pH-engineered MET x BINDER antibody specific for MET can be constructed using similar methods apparent to one skilled in the art, where BINDER is any antibody that has been published in the art or discovered using methods like those herein or those known in the art (e.g., display-based or immunization-based methods).

Next, exemplary properties of pH-engineered MET x MET antibodies specific for MET can be demonstrated using the methods described herein, with the appropriate control being a control antibody monospecific or bispecific antibody specific for MET. Briefly, it can be shown that, as compared to a control, the pH-engineered MET x MET antibodies specific for MET: a) bind in a pH-dependent manner to cells, e.g., bind at a neutral pH but not an acidic pH and b) release from cells in a pH-dependent manner, e.g. bind at a neutral pH and release at an acidic pH and c) show enhanced endolysosomal accumulation in MET+ cells and d) show increased MET antigen density after exposure to MET+ cells and e) when conjugated to a toxin, show

increased cytotoxicity to MET+ cells and f) when conjugated to a toxin, show increased toxin liberation when incubated with MET+ cells and g) show decreased half-life when exposed to MET antigen in a relevant animal model and h) when conjugated to a toxin, show increased efficacy in a mouse xenograft model of MET+ cells. Similarly, the exemplary properties of pH-engineered MET x BINDER antibodies specific for MET can be demonstrated using the methods described herein, with the appropriate control being a control antibody MET x BINDER bispecific antibody specific for MET.

**Example 9. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding [Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000]. We selected Telisotuzumab (Heavy chain SEQ ID NO: 159, Light chain SEQ ID NO: 160) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid residues within the heavy chain CDRs were systematically substituted with a histidine, one at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with only one histidine or alanine mutation in a heavy chain CDR were generated by co-transfection of Expi293 cells with a) one heavy chain sequence variant, and b) the corresponding starting antibody light chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 384 instrument. Briefly, 15µL of cell culture supernatant was diluted into 185µL of 1x PBST pH 7.4 for loading onto the sensor tips. This resulted in a high concentration of 41.1 µg/mL, a low concentration of 13.7 µg/mL and an average concentration of 26.5 µg/mL. This diluted

supernatant was then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20) pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H, Lot No. LC11SE2008) in 1X PBST pH 7.4 for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST pH 7.4 for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST pH 5.4 throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody, (with no substitutions), and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Heavy chain variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis. It was also noted that while some histidine and alanine mutations obliterated MET binding, others were tolerated with little (e.g., less than 1-fold change in dissociation constant KD or dissociation rate) or no change in MET binding kinetics.

Especially because histidine is a large, positively charged amino acid, these variants with no change were noted as positions in the heavy chain that may tolerate a wide range of mutations and lead to antibodies with different sequence but similar binding properties, a designation that is not otherwise apparent.

**Example 10. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding [Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000]. We selected Telisotuzumab (Heavy chain SEQ ID NO: 159, Light chain SEQ ID NO: 160) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT

(Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid residues within the light chain CDRs were systematically substituted with a histidine, one at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with only one histidine or alanine mutation in a light chain CDR were generated by co-transfection of Expi293 cells with a) one light chain sequence variant, and b) the corresponding starting antibody heavy chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20) pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST pH 7.4 for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST pH 7.4 for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST pH 5.4 throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Light chain variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis (e.g., MYT2040). It was also noted that some histidine and alanine

mutations were tolerated with little (e.g., less than 1-fold change in dissociation constant KD or dissociation rate) or no change in MET binding kinetics. Especially because histidine is a large, positively charged amino acid, these variants with no change were noted as positions in the light chain that may tolerate a wide range of mutations and lead to antibodies with different sequence but similar binding properties, a designation that is not otherwise apparent.

**Example 11. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding [Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000]. We selected Telisotuzumab (Heavy chain SEQ ID NO: 159, Light chain SEQ ID NO: 160) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the heavy chain CDRs that had been previously selected for further analysis in Example 9 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the heavy chain CDRs were generated by co-transfection of Expi293 cells with a) one heavy chain combinations sequence variant, and b) the corresponding starting antibody light chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was

diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20) pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H)) in 1X PBST pH 7.4 for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST pH 7.4 for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST pH 5.4 throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Heavy chain combinations variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis.

**Example 12. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding [Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000]. We selected Telisotuzumab (Heavy chain SEQ ID NO: 159, Light chain SEQ ID NO: 160) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the light chain CDRs that had been previously selected for further analysis in Example 10 were systematically combined

two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the light chain CDRs were generated by co-transfection of Expi293 cells with a) one light chain combinations sequence variant, and b) the corresponding starting antibody heavy chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50 mM Potassium Phosphate Buffer + 150 mM NaCl + 0.05% Tween 20), pH 7.4, and the sensor was associated with MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST, pH 7.4, for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST, pH 7.4, for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST, pH 5.4, throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (e.g., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (e.g., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Light chain combinations variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis.

**Example 13. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding [Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000]. We selected Telisotuzumab (Heavy chain SEQ ID NO: 159, Light chain SEQ ID NO: 160) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy and light chains were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the heavy and light chain CDRs that had been previously selected for further analysis in Examples 9-12 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations were generated by co-transfection of Expi293 cells with a) one light chain sequence variant or light chain combinations sequence variant, and b) one heavy chain sequence variant or heavy chain combinations sequence variant using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20), pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST, pH 7.4, for 120 sec to generate an association curve. In the dissociation phase, the

antibody-antigen complex on the sensor was exposed to 1X PBST, pH 7.4, for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST, pH 5.4, throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (e.g., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (e.g., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Paired heavy and light chain variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), , were selected for further analysis (MYT3463, MYT3477, MYT3491, MYT3603, MYT3604, MYT3606, MYT3607, MYT3608, MYT3609, MYT3610, MYT3611, MYT3612, MYT3614, MYT3615, MYT4211, MYT4212, MYT4214, MYT4217, and MYT4220).

**Example 14. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding [Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000]. We selected Telisotuzumab (Heavy chain SEQ ID NO: 159, Light chain SEQ ID NO: 160) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the heavy chain CDRs that had been previously selected for further analysis in Example 9 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the heavy chain CDRs were generated by co-transfection of Expi293 cells with a) one heavy chain combinations

sequence variant containing the triple hinge (TH) and YTE mutations described in (Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000)and (Dall, WF et al "Increasing the Affinity of a Human IgG1 for the Neonatal Fc Receptor: Biological Consequences" The Journal of Immunology (2002); 169:5171-5180) respectively, and b) the corresponding starting antibody light chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, purified using protein A magnetic beads (Genscript L00273), and evaluated for endolysosomal delivery on Detroit 562 cells (ATCC CCL-138). Detroit 562 cells (ATCC; CCL-138) were collected and resuspended in EMEM medium (ATCC; 30-2003) + 10% GenClone heat inactivated fetal bovine serum (HI FBS) (Genesee Scientific; 25-514H). Cell counts were determined using trypan blue staining and the Countess II FL Automated Cell Counter (Thermofisher; AMQAF1000). Cells were then diluted to 100,000 cells/mL and 100ul was seeded into 96-well flat bottom cell culture plates and allowed to attach overnight in 37C 5% CO2. Primary antibodies were then diluted in native culture mediums to 20nM and then mixed 1:1 with 60nM Incucyte Human FabFluor-pH Red Antibody Labeling Reagent (Sartorius; 4722). The mixture was incubated for 20 minutes at room temperature, followed by addition to cells. Plates were then placed immediately into the Incucyte S3 Live-Cell Analysis System for image acquisition and analysis. Endolysosomal delivery was examined for the starting antibody (with no substitutions) and each corresponding antibody variant to inform on enhanced endolysosomal delivery due to histidine or alanine substitution compared to the starting antibody (with no substitutions). Heavy chain combinations variants that showed enhanced endolysosomal delivery (as compared to the starting antibody), e.g., as shown in Figure 1, were selected for further analysis. The pH dependence of the selected variants were evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X

PBST (50 mM Potassium Phosphate Buffer + 150 mM NaCl + 0.05% Tween 20), pH 7.4, and the sensor was associated with MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST, pH 7.4, for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST, pH 7.4 or pH 5.4, for 300-600 sec. Association and dissociation phase curves at pH 7.4 and pH 5.4 were examined for the starting antibody (with no substitutions) and each corresponding antibody variant to inform on two criteria: a) enhanced dissociation (e.g., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (e.g., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Heavy chain combinations variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), e.g., as shown in Figure 2 were selected for further analysis.

**Example 15. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding [Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000]. We selected Telisotuzumab (Heavy chain SEQ ID NO: 159, Light chain SEQ ID NO: 160) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the light chain CDRs that had been previously selected for further analysis in Example 10 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the light chain CDRs were generated by co-transfection of Expi293 cells with a) one light chain combinations sequence variant, and b) the corresponding starting antibody heavy chain containing the triple

hinge (TH) and YTE mutations described in (Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000)and (Dall, WF et al "Increasing the Affinity of a Human IgG1 for the Neonatal Fc Receptor: Biological Consequences" The Journal of Immunology (2002); 169:5171-5180) respectively using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, purified using protein A magnetic beads (Genscript L00273), and evaluated for endolysosomal delivery on Detroit 562 cells (ATCC CCL-138). Detroit 562 cells (ATCC; CCL-138) were collected and resuspended in EMEM medium (ATCC; 30-2003) + 10% GenClone heat inactivated fetal bovine serum (HI FBS) (Genesee Scientific; 25-514H). Cell counts were determined using trypan blue staining and the Countess II FL Automated Cell Counter (Thermofisher; AMQAF1000). Cells were then diluted to 100,000 cells/mL and 100ul was seeded into 96-well flat bottom cell culture plates and allowed to attach overnight in 37C 5% CO2. Primary antibodies were then diluted in native culture mediums to 20nM and then mixed 1:1 with 60nM Incucyte Human FabFluor-pH Red Antibody Labeling Reagent (Sartorius; 4722). The mixture was incubated for 20 minutes at room temperature, followed by addition to cells. Plates were then placed immediately into the Incucyte S3 Live-Cell Analysis System for image acquisition and analysis. Endolysosomal delivery was examined for the starting antibody (with no substitutions) and each corresponding antibody variant to inform on enhanced endolysosomal delivery due to histidine or alanine substitution compared to the starting antibody (with no substitutions).

**Example 16. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Feng Y et al. "MET Antibody Drug Conjugate" US Patent Application US 2020/0061204 A1 (2020)). We selected Emibetuzumab (Heavy chain SEQ ID NO: 161, Light chain SEQ ID NO: 162) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The

Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid residues within the heavy chain CDRs were systematically substituted with a histidine, one at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with only one histidine or alanine mutation in a heavy chain CDR were generated by co-transfection of Expi293 cells with a) one heavy chain sequence variant, and b) the corresponding starting antibody light chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. This diluted supernatant was then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20) pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST pH 7.4 for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST pH 7.4 for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST pH 5.4 throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody, (with no substitutions), and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Heavy chain variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis (e.g., MYT2319). It was also noted that while some histidine and alanine mutations obliterated MET binding (e.g., MYT2341), others were tolerated with little (e.g., less

than 1-fold change in dissociation constant KD or dissociation rate) or no change in MET binding kinetics.

Especially because histidine is a large, positively charged amino acid, these variants with no change were noted as positions in the heavy chain that may tolerate a wide range of mutations and lead to antibodies with different sequence but similar binding properties, a designation that is not otherwise apparent.

**Example 17. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Feng Y et al. "MET Antibody Drug Conjugate" US Patent Application US 2020/0061204 A1 (2020)). We selected Emibetuzumab (Heavy chain SEQ ID NO: 161, Light chain SEQ ID NO: 162) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid residues within the light chain CDRs were systematically substituted with a histidine, one at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with only one histidine or alanine mutation in a light chain CDR were generated by co-transfection of Expi293 cells with a) one light chain sequence variant, and b) the corresponding starting antibody heavy chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for

loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20) pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST pH 7.4 for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST pH 7.4 for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST pH 5.4 throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting ABPC (with no substitutions), and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Light chain variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis (e.g., MYT3978). It was also noted that some histidine and alanine mutations were tolerated with little (e.g., less than 1-fold change in dissociation constant KD or dissociation rate) or no change in MET binding kinetics. Especially because histidine is a large, positively charged amino acid, these variants with no change were noted as positions in the light chain that may tolerate a wide range of mutations and lead to antibodies with different sequence but similar binding properties, a designation that is not otherwise apparent.

**Example 18. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Feng Y et al. “MET Antibody Drug Conjugate” US Patent Application US 2020/0061204 A1 (2020)). We selected Emibetuzumab (Heavy chain SEQ ID NO: 161, Light chain SEQ ID NO: 162) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and

IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the heavy chain CDRs that had been previously selected for further analysis in Example 16 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the heavy chain CDRs were generated by co-transfection of Expi293 cells with a) one heavy chain combinations sequence variant, and b) the corresponding starting antibody light chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20) pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) ) in 1X PBST pH 7.4 for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST pH 7.4 for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST pH 5.4 throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Heavy chain combinations variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis (e.g., MYT2850, MYT2861).

**Example 19. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Feng Y et al. "MET Antibody Drug Conjugate" US Patent Application US 2020/0061204 A1 (2020)). We selected Emibetuzumab (Heavy chain SEQ ID NO: 161, Light chain SEQ ID NO: 162) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the light chain CDRs that had been previously selected for further analysis in Example 17 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the light chain CDRs were generated by co-transfection of Expi293 cells with a) one light chain combinations sequence variant, and b) the corresponding starting antibody heavy chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50 mM Potassium Phosphate Buffer + 150 mM NaCl + 0.05% Tween 20), pH 7.4, and the sensor was associated with MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST, pH 7.4, for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST, pH 7.4, for 300-600 sec. Baseline, association, and dissociation were repeated using

1xPBST, pH 5.4, throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (e.g., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (e.g., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Light chain combinations variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis (e.g., MYT4326).

**Example 20. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Feng Y et al. "MET Antibody Drug Conjugate" US Patent Application US 2020/0061204 A1 (2020)). We selected Emibetuzumab (Heavy chain SEQ ID NO: 161, Light chain SEQ ID NO: 162) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy and light chains were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the heavy and light chain CDRs that had been previously selected for further analysis in Examples 16 - 19 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations were generated by co-transfection of Expi293 cells with a) one light chain sequence variant or light chain combinations sequence variant, and b) one heavy chain sequence variant or heavy chain combinations sequence variant using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative

expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20), pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST, pH 7.4, for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST, pH 7.4, for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST, pH 5.4, throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (e.g., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (e.g., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Paired heavy and light chain variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis (e.g., MYT3999, MYT4001, MYT4007, MYT4010, MYT4011, MYT4012, MYT4013, MYT4014, MYT4015, MYT4016, MYT4017, MYT4018, MYT4019, MYT4023, MYT4032, MYT4034, MYT4040).

**Example 21. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Feng Y et al. “MET Antibody Drug Conjugate” US Patent Application US 2020/0061204 A1 (2020)). We selected Emibetuzumab (Heavy chain SEQ ID NO: 161, Light chain SEQ ID NO: 162) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The

Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the heavy chain CDRs that had been previously selected for further analysis in Example 16 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the heavy chain CDRs were generated by co-transfection of Expi293 cells with a) one heavy chain combinations sequence variant containing the triple hinge (TH) and YTE mutations described in (Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000) and (Dall, WF et al "Increasing the Affinity of a Human IgG1 for the Neonatal Fc Receptor: Biological Consequences" The Journal of Immunology (2002); 169:5171-5180) respectively, and b) the corresponding starting antibody light chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, purified using protein A magnetic beads (Genscript L00273), and evaluated for endolysosomal delivery on Detroit 562 cells (ATCC CCL-138). Detroit 562 cells (ATCC; CCL-138) were collected and resuspended in EMEM medium (ATCC; 30-2003) + 10% GenClone heat inactivated fetal bovine serum (HI FBS) (Genesee Scientific; 25-514H). Cell counts were determined using trypan blue staining and the Countess II FL Automated Cell Counter (Thermofisher; AMQAF1000). Cells are then diluted to 100,000 cells/mL and 100ul was seeded into 96-well flat bottom cell culture plates and allowed to attach overnight in 37C 5% CO2. Primary antibodies were then diluted in native culture mediums to 20nM and then mixed 1:1 with 60nM Incucyte Human FabFluor-pH Red Antibody Labeling Reagent (Sartorius; 4722). The mixture was incubated for 20 minutes at room temperature, followed by addition to cells. Plates were then placed immediately into the Incucyte S3 Live-Cell Analysis System for image acquisition and analysis. Endolysosomal delivery was examined for the starting antibody (with no substitutions) and each corresponding antibody variant to inform on enhanced endolysosomal delivery due to histidine or alanine substitution compared to the starting antibody (with no substitutions).

**Example 22. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Hicks, SW and Lai, K "MET Antibodies and Immunoconjugates and uses thereof" International Patent Application WO 2020/014306 A1 (2020)). We selected hucMET27Gv1.3 (Heavy chain SEQ ID NO: 225, Light chain SEQ ID NO: 235) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid residues within the heavy chain CDRs were systematically substituted with a histidine, one at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with only one histidine or alanine mutation in a heavy chain CDR were generated by co-transfection of Expi293 cells with a) one heavy chain sequence variant, and b) the corresponding starting antibody light chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20) pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST pH 7.4 for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST pH 7.4 for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST pH 5.4 throughout in a separate

condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody, (with no substitutions), and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Heavy chain variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis. It was also noted that while some histidine and alanine mutations obliterated MET binding, others were tolerated with little (e.g., less than 1-fold change in dissociation constant KD or dissociation rate) or no change in MET binding kinetics.

Especially because histidine is a large, positively charged amino acid, these variants with no change were noted as positions in the heavy chain that may tolerate a wide range of mutations and lead to antibodies with different sequence but similar binding properties, a designation that is not otherwise apparent.

**Example 23. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Hicks, SW and Lai, K "MET Antibodies and Immunoconjugates and uses thereof" International Patent Application WO 2020/014306 A1 (2020)). We selected hucMET27Gv1.3 (Heavy chain SEQ ID NO: 225, Light chain SEQ ID NO: 235) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid residues within the light chain CDRs were systematically substituted with a histidine, one at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with only one histidine or alanine mutation in a light chain CDR were generated by co-transfection of Expi293

cells with a) one light chain sequence variant, and b) the corresponding starting antibody heavy chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20) pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST pH 7.4 for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST pH 7.4 for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST pH 5.4 throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Light chain variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis. It was also noted that some histidine and alanine mutations were tolerated with little (e.g., less than 1-fold change in dissociation constant KD or dissociation rate) or no change in MET binding kinetics. Especially because histidine is a large, positively charged amino acid, these variants with no change were noted as positions in the light chain that may tolerate a wide range of mutations and lead to antibodies with different sequence but similar binding properties, a designation that is not otherwise apparent.

**Example 24. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Hicks, SW and Lai, K "MET Antibodies and Immunoconjugates and uses thereof" International Patent Application WO 2020/014306 A1 (2020)). We selected hucMET27Gv1.3 (Heavy chain SEQ ID NO: 225, Light chain SEQ ID NO: 235) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the heavy chain CDRs that had been previously selected for further analysis in Example 22 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the heavy chain CDRs were generated by co-transfection of Expi293 cells with a) one heavy chain combinations sequence variant, and b) the corresponding starting antibody light chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20) pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) ) in 1X PBST pH 7.4 for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST pH 7.4 for 300-600 sec. Baseline, association, and dissociation

were repeated using 1xPBST pH 5.4 throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Heavy chain combinations variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis.

**Example 25. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Hicks, SW and Lai, K "MET Antibodies and Immunoconjugates and uses thereof" International Patent Application WO 2020/014306 A1 (2020)). We selected hucMET27Gv1.3 (Heavy chain SEQ ID NO: 225, Light chain SEQ ID NO: 235) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the light chain CDRs that had been previously selected for further analysis in Example 23 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the light chain CDRs were generated by co-transfection of Expi293 cells with a) one light chain combinations sequence variant, and b) the corresponding starting antibody heavy chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant

determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50 mM Potassium Phosphate Buffer + 150 mM NaCl + 0.05% Tween 20), pH 7.4, and the sensor was associated with MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST, pH 7.4, for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST, pH 7.4, for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST, pH 5.4, throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (e.g., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (e.g., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Light chain combinations variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis (e.g., MYT4230).

**Example 26. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Hicks, SW and Lai, K "MET Antibodies and Immunoconjugates and uses thereof" International Patent Application WO 2020/014306 A1 (2020)). We selected hucMET27Gv1.3 (Heavy chain SEQ ID NO: 225, Light chain SEQ ID NO: 235) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To

generate pH-dependent sequence variants, individual amino acid mutations within the heavy chain CDRs that had been previously selected for further analysis in Example 22 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the heavy chain CDRs were generated by co-transfection of Expi293 cells with a) one heavy chain combinations sequence variant containing the triple hinge (TH) and YTE mutations described in (Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000) and (Dall, WF et al "Increasing the Affinity of a Human IgG1 for the Neonatal Fc Receptor: Biological Consequences" The Journal of Immunology (2002); 169:5171-5180) respectively, and b) the corresponding starting antibody light chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, purified using protein A magnetic beads (Genscript L00273), and evaluated for endolysosomal delivery on Detroit 562 cells (ATCC CCL-138). Detroit 562 cells (ATCC; CCL-138) were collected and resuspended in EMEM medium (ATCC; 30-2003) + 10% GenClone heat inactivated fetal bovine serum (HI FBS) (Genesee Scientific; 25-514H). Cell counts were determined using trypan blue staining and the Countess II FL Automated Cell Counter (Thermofisher; AMQAF1000). Cells were then diluted to 100,000 cells/mL and 100ul was seeded into 96-well flat bottom cell culture plates and allowed to attach overnight in 37C 5% CO2. Primary antibodies were then diluted in native culture mediums to 20nM and then mixed 1:1 with 60nM Incucyte Human FabFluor-pH Red Antibody Labeling Reagent (Sartorius; 4722). The mixture was incubated for 20 minutes at room temperature, followed by addition to cells. Plates were then placed immediately into the Incucyte S3 Live-Cell Analysis System for image acquisition and analysis. Endolysosomal delivery was examined for the starting antibody (with no substitutions) and each corresponding antibody variant to inform on enhanced endolysosomal delivery due to histidine or alanine substitution compared to the starting antibody (with no substitutions).

**Example 27. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Hicks, SW and Lai, K "MET Antibodies and Immunoconjugates and uses thereof" International Patent Application WO 2020/014306 A1 (2020)). We selected hucMET27Gv1.3 (Heavy chain SEQ ID NO: 225, Light chain SEQ ID NO: 235) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the light chain CDRs that had been previously selected for further analysis in Example 23 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the light chain CDRs were generated by co-transfection of Expi293 cells with a) one light chain combinations sequence variant, and b) the corresponding starting antibody heavy chain containing the triple hinge (TH) and YTE mutations described in (Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000) and (Dall, WF et al "Increasing the Affinity of a Human IgG1 for the Neonatal Fc Receptor: Biological Consequences" The Journal of Immunology (2002); 169:5171-5180) respectively using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, purified using protein A magnetic beads (Genscript L00273), and evaluated for endolysosomal delivery on Detroit 562 cells (ATCC CCL-138). Detroit 562 cells (ATCC; CCL-138) were collected and resuspended in EMEM medium (ATCC; 30-2003) + 10% GenClone heat inactivated fetal bovine serum (HI FBS) (Genesee Scientific; 25-514H). Cell counts were determined using trypan blue staining and the Countess II FL Automated Cell Counter (Thermofisher; AMQAF1000). Cells were then diluted to 100,000 cells/mL and 100ul was seeded into 96-well flat bottom cell culture plates and allowed to attach overnight in 37C 5% CO2. Primary antibodies were then diluted in

native culture mediums to 20nM and then mixed 1:1 with 60nM Incucyte Human FabFluor-pH Red Antibody Labeling Reagent (Sartorius; 4722). The mixture was incubated for 20 minutes at room temperature, followed by addition to cells. Plates were then placed immediately into the Incucyte S3 Live-Cell Analysis System for image acquisition and analysis. Endolysosomal delivery was examined for the starting antibody (with no substitutions) and each corresponding antibody variant to inform on enhanced endolysosomal delivery due to histidine or alanine substitution compared to the starting antibody (with no substitutions). Light chain combinations variants that showed enhanced endolysosomal delivery (as compared to the starting antibody), were selected for further analysis. The pH dependence of the selected variants were evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50 mM Potassium Phosphate Buffer + 150 mM NaCl + 0.05% Tween 20), pH 7.4, and the sensor was associated with MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST, pH 7.4, for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST, pH 7.4 or pH 5.4, for 300-600 sec. Association and dissociation phase curves at pH 7.4 and pH 5.4 were examined for the starting antibody (with no substitutions) and each corresponding antibody variant to inform on two criteria: a) enhanced dissociation (e.g., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (e.g., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Light chain combinations variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis.

**Example 28. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Fujita, R et al (2020) A Novel Non-Agonist c-Met Antibody Drug Conjugate with Superior Potency Over a c-Met Tyrosine Kinase Inhibitor in c-Met Amplified and Non-Amplified Cancers, Cancer Biology and Therapy, 21(6):549-559). We selected P3D12 (Heavy chain SEQ ID NO: 163, Light chain SEQ ID NO: 164) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid residues within the heavy chain CDRs were systematically substituted with a histidine, one at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with only one histidine or alanine mutation in a heavy chain CDR were generated by co-transfection of Expi293 cells with a) one heavy chain sequence variant, and b) the corresponding starting antibody light chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. This diluted supernatant was then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20) pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST pH 7.4 for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST pH 7.4 for 300-600 sec. Baseline, association, and dissociation

were repeated using 1xPBST pH 5.4 throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody, (with no substitutions), and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Heavy chain variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis (e.g., MYT3698 and MYT3701). It was also noted that some histidine and alanine mutations were tolerated with little (e.g., less than 1-fold change in dissociation constant KD or dissociation rate) or no change in MET binding kinetics.

Especially because histidine is a large, positively charged amino acid, these variants with no change were noted as positions in the heavy chain that may tolerate a wide range of mutations and lead to antibodies with different sequence but similar binding properties, a designation that is not otherwise apparent.

**Example 29. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Fujita, R et al (2020) A Novel Non-Agonist c-Met Antibody Drug Conjugate with Superior Potency Over a c-Met Tyrosine Kinase Inhibitor in c-Met Amplified and Non-Amplified Cancers, Cancer Biology and Therapy, 21(6):549-559). We selected P3D12 (Heavy chain SEQ ID NO: 163, Light chain SEQ ID NO: 164) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid residues within the light chain CDRs were systematically substituted with a histidine, one at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with only one histidine

or alanine mutation in a light chain CDR were generated by co-transfection of Expi293 cells with a) one light chain sequence variant, and b) the corresponding starting antibody heavy chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20) pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST pH 7.4 for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST pH 7.4 for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST pH 5.4 throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Light chain variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis (e.g., MYT3735, and MYT3740). It was also noted that some histidine and alanine mutations were tolerated with little (e.g., less than 1-fold change in dissociation constant KD or dissociation rate) or no change in MET binding kinetics. Especially because histidine is a large, positively charged amino acid, these variants with no change were noted as positions in the light chain that may tolerate a wide range of mutations and lead to antibodies with different sequence but similar binding properties, a designation that is not otherwise apparent.

**Example 30. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Fujita, R et al (2020) A Novel Non-Agonist c-Met Antibody Drug Conjugate with Superior Potency Over a c-Met Tyrosine Kinase Inhibitor in c-Met Amplified and Non-Amplified Cancers, Cancer Biology and Therapy, 21(6):549-559). We selected P3D12 (Heavy chain SEQ ID NO: 163, Light chain SEQ ID NO: 164) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the heavy chain CDRs that had been previously selected for further analysis in Example 28 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the heavy chain CDRs were generated by co-transfection of Expi293 cells with a) one heavy chain combinations sequence variant, and b) the corresponding starting antibody light chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20) pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H)) in 1X PBST pH 7.4 for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X

PBST pH 7.4 for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST pH 5.4 throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (i.e., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (i.e., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Heavy chain combinations variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), e.g., as shown in Figures 3A-3C were selected for further analysis (e.g., MYT4313).

**Example 31. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Fujita, R et al (2020) A Novel Non-Agonist c-Met Antibody Drug Conjugate with Superior Potency Over a c-Met Tyrosine Kinase Inhibitor in c-Met Amplified and Non-Amplified Cancers, Cancer Biology and Therapy, 21(6):549-559). We selected P3D12 (Heavy chain SEQ ID NO: 163, Light chain SEQ ID NO: 164) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the light chain CDRs that had been previously selected for further analysis in Example 29 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the light chain CDRs were generated by co-transfection of Expi293 cells with a) one light chain combinations sequence variant, and b) the corresponding starting antibody heavy chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was

evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50 mM Potassium Phosphate Buffer + 150 mM NaCl + 0.05% Tween 20), pH 7.4, and the sensor was associated with MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST, pH 7.4, for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST, pH 7.4, for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST, pH 5.4, throughout in a separate condition. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (e.g., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (e.g., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Light chain combinations variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis (e.g., MYT4247).

**Example 32. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Fujita, R et al (2020) A Novel Non-Agonist c-Met Antibody Drug Conjugate with Superior Potency Over a c-Met Tyrosine Kinase Inhibitor in c-Met Amplified and Non-Amplified Cancers, Cancer Biology and Therapy, 21(6):549-559). We selected P3D12 (Heavy chain SEQ ID NO: 163, Light chain SEQ ID NO: 164) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy and light chains were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and

IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the heavy and light chain CDRs that had been previously selected for further analysis in Examples 28-31 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations were generated by co-transfection of Expi293 cells with a) one light chain sequence variant or light chain combinations sequence variant, and b) one heavy chain sequence variant or heavy chain combinations sequence variant using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50mM Potassium Phosphate Buffer + 150mM NaCl + 0.05% Tween 20), pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST, pH 7.4, for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST, pH 7.4 or pH 5.4, for 300-600 sec. Association and dissociation phase curves were examined for the starting antibody (with no substitutions) and each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on two criteria: a) enhanced dissociation (e.g., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (e.g., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Paired heavy and light chain variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), e.g., as shown in Figure 4A-4D, were selected for further

analysis (e.g., MYT5342, MYT5343, MYT5344, MYT5345, MYT5346, MYT5350, MYT5351, MYT5352, MYT5353, MYT5354, MYT5355, MYT5356, MYT5357, MYT5359, MYT5360, MYT5366, MYT5367, MYT5369, MYT5370, MYT5372, MYT5373, MYT5375, MYT5376, and MYT5381).

**Example 33. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Fujita, R et al (2020) A Novel Non-Agonist c-Met Antibody Drug Conjugate with Superior Potency Over a c-Met Tyrosine Kinase Inhibitor in c-Met Amplified and Non-Amplified Cancers, Cancer Biology and Therapy, 21(6):549-559). We selected P3D12 (Heavy chain SEQ ID NO: 163, Light chain SEQ ID NO: 164) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the heavy chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the heavy chain CDRs that had been previously selected for further analysis in Example 28 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the heavy chain CDRs were generated by co-transfection of Expi293 cells with a) one heavy chain combinations sequence variant containing the triple hinge (TH) and YTE mutations described in (Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000) and (Dall, WF et al "Increasing the Affinity of a Human IgG1 for the Neonatal Fc Receptor: Biological Consequences" The Journal of Immunology (2002); 169:5171-5180) respectively, and b) the corresponding starting antibody light chain using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, purified using protein A magnetic beads (Genscript L00273), and evaluated for endolysosomal delivery on Detroit 562 cells (ATCC CCL-138). Briefly,

Detroit 562 cells (ATCC; CCL-138) were collected and resuspended in EMEM medium (ATCC; 30-2003) + 10% GenClone heat inactivated fetal bovine serum (HI FBS) (Genesee Scientific; 25-514H). Cell counts were determined using trypan blue staining and the Countess II FL Automated Cell Counter (Thermofisher; AMQAF1000). Cells were then diluted to 100,000 cells/mL and 100ul was seeded into 96-well flat bottom cell culture plates and allowed to attach overnight in 37C 5% CO2. Primary antibodies were then diluted in native culture mediums to 20nM and then mixed 1:1 with 60nM Incucyte Human FabFluor-pH Red Antibody Labeling Reagent (Sartorius; 4722). The mixture was incubated for 20 minutes at room temperature, followed by addition to cells. Plates were then placed immediately into the Incucyte S3 Live-Cell Analysis System for image acquisition and analysis. Endolysosomal delivery was examined for the starting antibody (with no substitutions) and each corresponding antibody variant to inform on enhanced endolysosomal delivery due to histidine or alanine substitution compared to the starting antibody (with no substitutions). Heavy chain combinations variants that showed enhanced endolysosomal delivery (as compared to the starting antibody), were selected for further analysis. The pH dependence of the selected variants were evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50 mM Potassium Phosphate Buffer + 150 mM NaCl + 0.05% Tween 20), pH 7.4, and the sensor was associated with MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST, pH 7.4, for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST, pH 7.4 or pH 5.4, for 300-600 sec. Association and dissociation phase curves at pH 7.4 and pH 5.4 were examined for the starting antibody (with no substitutions) and each corresponding antibody variant to inform on two criteria: a) enhanced dissociation (e.g., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (e.g., lower koff values) compared to pH 5.4 in the antibody variant itself

and with the starting antibody (with no substitutions). Heavy chain combinations variants that showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis.

**Example 34. Construction and screening of pH-engineered MET antibodies**

Multiple MET-binding monoclonal antibodies have been described in the literature and can be used as a template for engineering pH-dependent binding (Fujita, R et al (2020) A Novel Non-Agonist c-Met Antibody Drug Conjugate with Superior Potency Over a c-Met Tyrosine Kinase Inhibitor in c-Met Amplified and Non-Amplified Cancers, Cancer Biology and Therapy, 21(6):549-559). We selected P3D12 (Heavy chain SEQ ID NO: 163, Light chain SEQ ID NO: 164) as a MET-binding monoclonal antibody for pH engineering via histidine scanning. Briefly, CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. To generate pH-dependent sequence variants, individual amino acid mutations within the light chain CDRs that had been previously selected for further analysis in Example 29 were systematically combined two or more at a time. In cases where the starting CDR residue was a histidine, it was mutated to an alanine. Antibody variants with two or more histidine or alanine mutations in the light chain CDRs were generated by co-transfection of Expi293 cells with a) one light chain combinations sequence variant, and b) the corresponding starting antibody heavy chain containing the triple hinge (TH) and YTE mutations described in (Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000) and (Dall, WF et al "Increasing the Affinity of a Human IgG1 for the Neonatal Fc Receptor: Biological Consequences" The Journal of Immunology (2002); 169:5171-5180) respectively using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, purified using protein A magnetic beads (Genscript L00273), and evaluated for endolysosomal delivery on Detroit 562 cells (ATCC CCL-138). Briefly, Detroit 562 cells (ATCC; CCL-138) were collected and resuspended in

EMEM medium (ATCC; 30-2003) + 10% GenClone heat inactivated fetal bovine serum (HI FBS) (Genesee Scientific; 25-514H). Cell counts were determined using trypan blue staining and the Countess II FL Automated Cell Counter (Thermofisher; AMQAF1000). Cells were then diluted to 100,000 cells/mL and 100ul was seeded into 96-well flat bottom cell culture plates and allowed to attach overnight in 37C 5% CO2. Primary antibodies were then diluted in native culture mediums to 20nM and then mixed 1:1 with 60nM Incucyte Human FabFluor-pH Red Antibody Labeling Reagent (Sartorius; 4722). The mixture was incubated for 20 minutes at room temperature, followed by addition to cells. Plates were then placed immediately into the Incucyte S3 Live-Cell Analysis System for image acquisition and analysis. Endolysosomal delivery was examined for the starting antibody (with no substitutions) and each corresponding antibody variant to inform on enhanced endolysosomal delivery due to histidine or alanine substitution compared to the starting antibody (with no substitutions). Light chain combinations variants that showed enhanced endolysosomal delivery (as compared to the starting antibody), were selected for further analysis. The pH dependence of the selected variants were evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50 mM Potassium Phosphate Buffer + 150 mM NaCl + 0.05% Tween 20), pH 7.4, and the sensor was associated with MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST, pH 7.4, for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST, pH 7.4 or pH 5.4, for 300-600 sec. Association and dissociation phase curves at pH 7.4 and pH 5.4 were examined for the starting antibody (with no substitutions) and each corresponding antibody variant to inform on two criteria: a) enhanced dissociation (e.g., higher koff values) at pH 5.4 due to histidine or alanine substitution compared to the starting antibody (with no substitutions), and b) reduced dissociation at pH 7.4 (e.g., lower koff values) compared to pH 5.4 in the antibody variant itself and with the starting antibody (with no substitutions). Light chain combinations variants that

showed either enhanced dissociation at pH 5.4 or reduced dissociation at pH 7.4 or both (as compared to the starting antibody), were selected for further analysis.

**Example 35. Reformatting of Anti-MET antibodies**

Select pH engineered anti-MET variants were generated as both wild-type IgG1 molecules (e.g., in Examples 9-13, 16-20, 22-25, and 28-32) and as IgG1 molecules containing the triple hinge (TH) mutations, as described by (Wang J et al (2017) ABBV-399, a c-Met Antibody-Drug Conjugate that Targets Both MET-Amplified and c-Met-Overexpressing Tumors, Irrespective of MET Pathway Dependence, Clin Cancer Res, 23:992-1000), and the YTE mutations, as described by (Dall, WF et al "Increasing the Affinity of a Human IgG1 for the Neonatal Fc Receptor: Biological Consequences" The Journal of Immunology (2002); 169:5171-5180), by transfection of Expi293 cells with a plasmid encoding for the variable heavy region fused genetically to human IgG1 Fc with or without the TH and YTE mutations. Co-transfection of Expi293 cells with a) one heavy chain sequence consisting of a variable heavy chain region and constant regions corresponding to either wild-type human IgG1 isotype or the same sequence except with TH and YTE mutations, and b) one light chain sequence, using methods known to the art. After allowing for four days of protein expression, cell culture supernatants were collected, quantified by SDS-PAGE analysis, and the pH dependence of the variant was evaluated using biolayer interferometry (BLI) on an Octet RED 96e instrument. Briefly, cell culture supernatants were diluted based on qualitative expression level of the variant determined by visual examination of SDS-PAGE gels, 5 µL of cell culture supernatant was diluted into 195 µL of 1x PBST, pH 7.4 for high expressors, 25 µL of cell culture supernatant was diluted into 175 µL of 1x PBST, pH 7.4 for medium expressors and 100 µL of cell culture supernatant was diluted into 100 µL of 1x PBST, pH 7.4 for low expressors for loading onto the sensor tips. Diluted supernatants were then captured on an anti-human Fc sensor (Forte Bio). A baseline was established using 1X PBST (50 mM Potassium Phosphate Buffer + 150 mM NaCl + 0.05% Tween 20), pH 7.4, and the sensor was associated with 50 nM of MET (cMET, Sino Biological Cat. No. 10692-H08H) in 1X PBST, pH 7.4, for 120 sec to generate an association curve. In the dissociation phase, the antibody-antigen complex on the sensor was exposed to 1X PBST, pH 7.4, for 300-600 sec. Baseline, association, and dissociation were repeated using 1xPBST, pH 5.4, throughout in a separate condition. Association and

dissociation phase curves were examined for each corresponding antibody variant at pH 5.4 and pH 7.4 to inform on three criteria: a) enhanced dissociation (e.g., higher koff values) at pH 5.4 as compared to its corresponding starting antibody, b) reduced dissociation at pH 7.4 (e.g., lower koff values) compared to pH 5.4 in the antibody variant itself, and c) comparison of the wild-type human IgG1 antibodies and their TH and YTE containing variants. Wild-type human IgG1 and reformatted human IgG1 antibodies containing the TH and YTE mutations showed broadly similar association and dissociation curves. We conclude from this data that the desirable properties of our variant variable domain sequences, including but not limited to pH dependence and endolysosomal delivery, are retained whether in IgG1 format or in IgG1 format with the TH and YTE mutations.

**Example 36. Characterization of cellular internalization and endolysosomal delivery of pH engineered anti-MET antibodies**

Selected anti-MET pH engineered antibody variants from Examples 9-13, 16-20, 22-25, and 28 - 31 were analyzed for internalization and endolysosomal delivery in U-87 MG cells (MET+), SNU-5 cells (MET+), NCI-H1373 cells (MET+), NCI-H1573 cells (MET+) and/or Detroit 562 cells (MET+). U-87 MG cells (ATCC HTB-14), Detroit 562 cells (ATCC CCL-138), NCI-H1373 cells (ATCC CRL-5866), NCI-H1573 cells (ATCC CRL-5877) or SNU-5 cells (ATCC CRL-5973) were collected and resuspended in EMEM medium (U-87 MG and Detroit 562, ATCC; 30-2003), IMDM medium (SNU-5, ATCC; 30-2005), or RPMI medium (NCI-H1373 and NCI-H1573, ATCC 30-2001) plus 5% (NCI-H1573), 10% (U-87 MG, Detroit 562, NCI-H1373) or 20% (SNU-5) GenClone heat inactivated fetal bovine serum (HI FBS) (Genesee Scientific; 25-514H). Cell counts were determined using trypan blue staining and the Countess II FL Automated Cell Counter (Thermofisher; AMQAF1000). Cells were then diluted to 2,000,000 cells/mL and 50µl/well was seeded into 96-well flat bottom cell culture plates (Genesee Scientific; 25-109). Anti-MET pH engineered antibody variants, starting antibody antibodies, control IgG1 isotype control (BP0297, Bioxcell), and vehicle control were diluted in native culture media, and then mixed 1:1 with a 3x molar ratio Zenon pHrodo iFL Human IgG Labeling Reagent (ThermoFisher; Z25611). The mixture was incubated for 20 minutes at room temperature, followed by a 1:1 addition of cells for a final volume of 100 µL. The mixture of cells, anti-MET antibody variants, and Zenon pHrodo iFL Human IgG Labeling Reagent was

incubated at 37 °C, 5% CO2 for 1-24 hours. Following incubation, 100 µL of ice cold Flow Cytometry (FC) buffer (phosphate buffered saline (PBS), pH 7.4 + 2mM ethylenediaminetetraacetic acid (EDTA) + 2% (v/v) HI FBS is added to each well. Cells were then spun down at 4°C for 2 min at 2000 rpm, washed with 200 µL ice cold FC buffer and resuspended in 100 µL ice cold FC buffer. Mean green fluorescence intensity was detected using a BD Accuri C6 flow cytometer. Data was analyzed using Flowjo analysis software. pHrodo green is a pH sensitive dye that fluoresces in the low pH environment of the endosomes and lysosomes and therefore can be used to quantify antibody internalization and endolysosomal delivery. Internalization and endolysosomal delivery of anti-MET starting antibodies and variants at concentrations, in U-87 MG (MET+), Detroit 562 (MET+), SNU-5 (MET+), NCI-H1573 (MET+), or NCI-H1373 (MET+) cells, was measured by pHrodo green mean fluorescence intensity. Several pH engineered anti-MET antibody variants showed increased mean fluorescence intensity relative to their corresponding starting antibodies demonstrating that increased dissociation at lower pH leads to enhanced internalization and endolysosomal delivery inside cells as shown by increased fluorescence or increased fluorescence as compared to IgG1 isotype control. Increased endolysosomal delivery is quantitated for each pH engineered anti-MET antibody variant on the top of each bar as a ratio of: the variant's mean fluorescence intensity minus the mean fluorescence intensity of the IgG control, then all divided by the variant's corresponding starting antibody's mean fluorescence intensity minus the mean fluorescence intensity of the IgG control. For example MYT2040, MYT3609, MYT3611, and MYT3615, antibody variants of telisotuzumab, show increased internalization and endolysosomal delivery relative to telisotuzumab (MYT0886). For example MYT2319, MYT2850, MYT2861, and MYT4326, antibody variants of emibetuzumab, show increased internalization and endolysosomal delivery relative to emibetuzumab. For example MYT3698, MYT3735, MYT3740, MYT4247, and MYT4325, an antibody variant of P3D12, shows increased internalization and endolysosomal delivery relative to P3D12. Such pH engineered anti-MET antibody variants with increased mean fluorescence intensity relative to their starting antibodies were selected for further analysis.

**Example 37. Thermal stability of anti-MET mAbs**

Protein melting temperature (Tm) was measured through the use of Differential Scanning Flourimetry (DSF). DSF visualizes protein unfolding by measuring the fluorescent signal from the molecule Sypro Orange (Thermo Scientific cat. no. S6650) as a protein unfolds due to heating. As a protein unfolds it exposes more hydrophilic regions to the Sypro Orange dye, which in turns binds to these hydrophilic regions resulting in increase in signal. The Tm for a protein is calculated as the half-maximal of the unfolding transition and can be visualized by plotting the first derivative of the Sypro Orange signal and finding a local maximum of this derivative plot. 20 µL of protein samples in 1xPBS, pH 7.4, was mixed with 5 µL of 25X Sypro Orange master mix, yielding a final concentration of 5x Sypro Orange. The samples were added to 96-well PCR plates (Thermo Scientific Cat. No. AB-2400/W) and sealed with optical covers (Thermo Scientific Cat. No. 4360954). The PCR plate was inserted into a real-time PCR machine (Thermo Scientific Quant Studio 3) and the plate temperature was stabilized for 3 minutes at 25 °C before ramping to 95 °C by 0.2 °C increments, stabilizing for 1 second before the Sypro Orange signal was measured. The melting temperature (Tm) values for anti-MET starting antibodies and variants were determined. Several variants show similar melting temperature values to their starting antibodies confirming that variants created through pH engineering can retain functionally appropriate thermal stabilities as compared to their corresponding starting antibodies (e.g., emibetuzumab, hucMET27Gv1.3 or P3D12). All variants tested had melting temperatures greater than or equal to the melting temperature of their corresponding starting antibody (e.g., mirvetuximab) minus 10 °C and so were selected for further analysis.

The discoveries herein are in contrast to similar engineering on other antigens such as CLEC12a and two other targets wherein multiple variants per target showed enhanced dissociation at low pH, however, despite the favorable pH-dependent binding properties of these variants (which specifically bound CLEC12a and the two other targets), they had less than 10% increase in cell internalization and endolysosomal delivery as compared to the corresponding starting antibody (e.g., the starting antibody). These variants (which specifically bound CLEC12a and the two other targets) also had similar biophysical characteristics (e.g., antibody expression, thermal stability, affinity at pH 7.4 etc.) to the corresponding starting antibody (e.g.,

the starting antibody) confirming that this was not specific to the biophysical properties of the tested variant (i.e. the biophysical properties unrelated to enhanced dissociation at pH 5.4).

**Example 38. Characterization of MYT5351 constant domain substitutions**

As discussed above histidine scanning was performed where CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. Certain heavy variable chain domain and light variable chain domains were selected for additional experimentation.

Additionally, various methods of conjugating a cytotoxic or cytostatic agent to an antibody are known. For example, conjugation is possible at either naturally occurring amino acid positions and/or at introduced (e.g., engineered amino acids). As discussed herein, various methods of introducing conjugation sites into an antibody are known.

Examples of engineered amino acid conjugation sites include, but are not limited to the following: a substitution to produce “a triple hinge” conjugation site (e.g., a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108 of SEQ ID NO: 155 or SEQ ID NO: 189 generates the triple hinge conjugation site, an alanine to a cysteine substitution at amino acid position 1 of SEQ ID NO: 155 or SEQ ID NO: 189, and/or a valine to cysteine substitution at amino acid position 98 of SEQ ID NO: 157.

Examples of naturally occurring amino acid conjugation sites include, but are not limited to the following: the cysteine at amino acid position 103, the cysteine of a lysine to cysteine substitution at amino acid position 105, (iii) the cysteine at amino acid position 109, and/or the cysteine at amino acid position 112 and/or the cysteine at amino acid position 107 of SEQ ID NO: 157.

The antibodies provided herein can also include modified constant regions. For example, one or more amino acid substitutions, insertion, and/or deletions can be introduced (e.g., engineered) into the constant domains (e.g., constant heavy and/or constant light) of any of the antibodies provided herein. Amino acid substitutions in the constant region can have varying effects on the antibody, including, for example extending the half-life of the antibody. Non-

limiting examples of such substitutions include the following: a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139 (e.g., "YTE" substitution) and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317 (e.g., "LS" substitution).

Thus, MYT5351 includes a variable heavy chain domain comprising SEQ ID NO: 5 and a variable light chain domain comprising SEQ ID NO: 6. Various modified constant regions (e.g., a modified heavy constant region, a modified light constant region) can be combined with variable chains described herein (e.g., SEQ ID NO: 5, SEQ ID NO: 6, respectively). The following represent the following heavy and light chain combinations as such: triple hinge conjugation only (heavy chain of SEQ ID NO: 35 and light chain of SEQ ID NO: 41); triple hinge conjugation and LS substitution (heavy chain: SEQ ID NO: 36 and a light chain: SEQ ID NO: 4)1; triple hinge substitution and YTE substitution (heavy chain of SEQ ID NO: 37 and a light chain of SEQ ID NO: 41); triple hinge conjugation and V205 substitution (heavy chain of SEQ ID NO: 35 and a light chain of SEQ ID NO: 42); a triple hinge substitution and LS substitution and V205 substitution (heavy chain of SEQ NO: 36 and a light chain of SEQ ID NO: 42); a triple hinge substitution and a YTE substitution and a V205C substitution (heavy chain of SEQ ID NO: 37 and a light chain of SEQ ID NO: 42); a triple hinge substitution and an A118C substitution (heavy chain of SEQ ID NO: 38 and a light chain of SEQ ID NO: 41); a triple hinge substitution and a LS substitution and a A118C substitution (a heavy chain of SEQ ID NO: 39 and a light chain of SEQ ID NO: 41); a triple hinge substitution and a YTE substitution and a A118C substitution (heavy chain of SEQ ID NO: 40 and a light chain of SEQ NO: 41).

The combinations above can be assessed by any of the assays described in the above examples.

**Example 39. Characterization of MYT4313 constant domain substitutions**

As discussed above histidine scanning was performed where CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and

IMGT CDR definitions were called as CDR residues. Certain heavy variable chain domain and light variable chain domains were selected for additional experimentation.

Additionally, various methods of conjugating a cytotoxic or cytostatic agent to an antibody are known. For example, conjugation is possible at either naturally occurring amino acid positions and/or at introduced (e.g., engineered amino acids). As discussed herein, various methods of introducing conjugation sites into an antibody are known.

Examples of engineered amino acid conjugation sites include, but are not limited to the following: a substitution to produce "a triple hinge" conjugation site (e.g., a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108 of SEQ ID NO: 155 or SEQ ID NO: 189 generates the triple hinge conjugation site, an alanine to a cysteine substitution at amino acid position 1 of SEQ ID NO: 155 or SEQ ID NO: 189, and/or a valine to cysteine substitution at amino acid position 98 of SEQ ID NO: 157.

Examples of naturally occurring amino acid conjugation sites include, but are not limited to the following: the cysteine at amino acid position 103, the cysteine of a lysine to cysteine substitution at amino acid position 105, (iii) the cysteine at amino acid position 109, and/or the cysteine at amino acid position 112 and/or the cysteine at amino acid position 107 of SEQ ID NO: 157.

The antibodies provided herein can also include modified constant regions. For example, one or more amino acid substitutions, insertion, and/or deletions can be introduced (e.g., engineered) into the constant domains (e.g., constant heavy and/or constant light) of any of the antibodies provided herein. Amino acid substitutions in the constant region can have varying effects on the antibody, including, for example extending the half-life of the antibody. Non-limiting examples of such substitutions include the following: a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139 (e.g., "YTE" substitution) and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317 (e.g., "LS" substitution).

Thus, MYT4313 includes a variable heavy chain domain comprising SEQ ID NO: 7 and a variable light chain domain comprising SEQ ID NO: 8. Various modified constant regions (e.g., a modified heavy constant region, a modified light constant region) can be combined with variable chains described herein (e.g., SEQ ID NO: 7, SEQ ID NO: 8, respectively). The

following represent the following heavy and light chain combinations as such: triple hinge conjugation only (heavy chain of SEQ ID NO: 43 and light chain of SEQ ID NO: 49); triple hinge conjugation and LS substitution (heavy chain: SEQ ID NO: 44 and a light chain: SEQ ID NO: 49); triple hinge substitution and YTE substitution (heavy chain of SEQ ID NO: 45 and a light chain of SEQ ID NO: 49); triple hinge conjugation and V205 substitution (heavy chain of SEQ ID NO: 43 and a light chain of SEQ ID NO: 50); a triple hinge substitution and LS substitution and V205 substitution (heavy chain of SEQ NO: 44 and a light chain of SEQ ID NO: 50); a triple hinge substitution and a YTE substitution and a V205C substitution (heavy chain of SEQ ID NO: 45 and a light chain of SEQ ID NO: 50); a triple hinge substitution and an A118C substitution (heavy chain of SEQ ID NO: 46 and a light chain of SEQ ID NO: 49); a triple hinge substitution and a LS substitution and a A118C substitution (a heavy chain of SEQ ID NO: 47 and a light chain of SEQ ID NO: 49); a triple hinge substitution and a YTE substitution and a A118C substitution (heavy chain of SEQ ID NO: 48 and a light chain of SEQ NO: 49).

The combinations above can be assessed by any of the assays described in the above examples.

**Example 40. Characterization of MYT4325 constant domain substitutions**

As discussed above histidine scanning was performed where CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. Certain heavy variable chain domain and light variable chain domains were selected for additional experimentation.

Additionally, various methods of conjugating a cytotoxic or cytostatic agent to an antibody are known. For example, conjugation is possible at either naturally occurring amino acid positions and/or at introduced (e.g., engineered amino acids). As discussed herein, various methods of introducing conjugation sites into an antibody are known.

Examples of engineered amino acid conjugation sites include, but are not limited to the following: a substitution to produce “a triple hinge” conjugation site (e.g., a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106

and 108 of SEQ ID NO: 155 or SEQ ID NO: 189 generates the triple hinge conjugation site, an alanine to a cysteine substitution at amino acid position 1 of SEQ ID NO: 155 or SEQ ID NO: 189, and/or a valine to cysteine substitution at amino acid position 98 of SEQ ID NO: 157.

Examples of naturally occurring amino acid conjugation sites include, but are not limited to the following: the cysteine at amino acid position 103, the cysteine of a lysine to cysteine substitution at amino acid position 105, (iii) the cysteine at amino acid position 109, and/or the cysteine at amino acid position 112 and/or the cysteine at amino acid position 107 of SEQ ID NO: 157.

The antibodies provided herein can also include modified constant regions. For example, one or more amino acid substitutions, insertion, and/or deletions can be introduced (e.g., engineered) into the constant domains (e.g., constant heavy and/or constant light) of any of the antibodies provided herein. Amino acid substitutions in the constant region can have varying effects on the antibody, including, for example extending the half-life of the antibody. Non-limiting examples of such substitutions include the following: a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139 (e.g., "YTE" substitution) and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317 (e.g., "LS" substitution).

Thus, MYT4325 includes a variable heavy chain domain comprising SEQ ID NO: 9 and a variable light chain domain comprising SEQ ID NO: 10. Various modified constant regions (e.g., a modified heavy constant region, a modified light constant region) can be combined with variable chains described herein (e.g., SEQ ID NO: 9, SEQ ID NO: 10, respectively). The following represent the following heavy and light chain combinations as such: triple hinge conjugation only (heavy chain of SEQ ID NO: 51 and light chain of SEQ ID NO: 57); triple hinge conjugation and LS substitution (heavy chain: SEQ ID NO: 51 and a light chain: SEQ ID NO: 57); triple hinge substitution and YTE substitution (heavy chain of SEQ ID NO: 51 and a light chain of SEQ ID NO: 57); triple hinge conjugation and V205 substitution (heavy chain of SEQ ID NO: 51 and a light chain of SEQ ID NO: 58); a triple hinge substitution and LS substitution and V205 substitution (heavy chain of SEQ NO: 52 and a light chain of SEQ ID NO: 58); a triple hinge substitution and a YTE substitution and a V205C substitution (heavy chain of SEQ ID NO: 53 and a light chain of SEQ ID NO: 58); a triple hinge substitution and an A118C

substitution (heavy chain of SEQ ID NO: 54 and a light chain of SEQ ID NO: 57); a triple hinge substitution and a LS substitution and a A118C substitution (a heavy chain of SEQ ID NO: 55 and a light chain of SEQ ID NO: 57); a triple hinge substitution and a YTE substitution and a A118C substitution (heavy chain of SEQ ID NO: 56 and a light chain of SEQ NO: 57).

The combinations above can be assessed by any of the assays described in the above examples.

**Example 41. Characterization of MYT4826 constant domain substitutions**

As discussed above histidine scanning was performed where CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. Certain heavy variable chain domain and light variable chain domains were selected for additional experimentation.

Additionally, various methods of conjugating a cytotoxic or cytostatic agent to an antibody are known. For example, conjugation is possible at either naturally occurring amino acid positions and/or at introduced (e.g., engineered amino acids). As discussed herein, various methods of introducing conjugation sites into an antibody are known.

Examples of engineered amino acid conjugation sites include, but are not limited to the following: a substitution to produce “a triple hinge” conjugation site (e.g., a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108 of SEQ ID NO: 155 or SEQ ID NO: 189 generates the triple hinge conjugation site, an alanine to a cysteine substitution at amino acid position 1 of SEQ ID NO: 155 or SEQ ID NO: 189, and/or a valine to cysteine substitution at amino acid position 98 of SEQ ID NO: 157.

Examples of naturally occurring amino acid conjugation sites include, but are not limited to the following: the cysteine at amino acid position 103, the cysteine of a lysine to cysteine substitution at amino acid position 105, (iii) the cysteine at amino acid position 109, and/or the cysteine at amino acid position 112 and/or the cysteine at amino acid position 107 of SEQ ID NO: 157.

The antibodies provided herein can also include modified constant regions. For example, one or more amino acid substitutions, insertion, and/or deletions can be introduced (e.g., engineered) into the constant domains (e.g., constant heavy and/or constant light) of any of the antibodies provided herein. Amino acid substitutions in the constant region can have varying effects on the antibody, including, for example extending the half-life of the antibody. Non-limiting examples of such substitutions include the following: a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139 (e.g., "YTE" substitution) and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317 (e.g., "LS" substitution).

Thus, MYT4826 includes a variable heavy chain domain comprising SEQ ID NO: 11 and a variable light chain domain comprising SEQ ID NO: 12. Various modified constant regions (e.g., a modified heavy constant region, a modified light constant region) can be combined with variable chains described herein (e.g., SEQ ID NO: 11, SEQ ID NO: 12, respectively). The following represent the following heavy and light chain combinations as such: triple hinge conjugation only (heavy chain of SEQ ID NO: 59 and light chain of SEQ ID NO: 65); triple hinge conjugation and LS substitution (heavy chain: SEQ ID NO: 60 and a light chain: SEQ ID NO: 65); triple hinge substitution and YTE substitution (heavy chain of SEQ ID NO: 61 and a light chain of SEQ ID NO: 65); triple hinge conjugation and V205 substitution (heavy chain of SEQ ID NO: 59 and a light chain of SEQ ID NO: 66); a triple hinge substitution and LS substitution and V205 substitution (heavy chain of SEQ NO: 60 and a light chain of SEQ ID NO: 66); a triple hinge substitution and a YTE substitution and a V205C substitution (heavy chain of SEQ ID NO: 61 and a light chain of SEQ ID NO: 66); a triple hinge substitution and an A118C substitution (heavy chain of SEQ ID NO: 62 and a light chain of SEQ ID NO: 65); a triple hinge substitution and a LS substitution and a A118C substitution (a heavy chain of SEQ ID NO: 63 and a light chain of SEQ ID NO: 65); a triple hinge substitution and a YTE substitution and a A118C substitution (heavy chain of SEQ ID NO: 64 and a light chain of SEQ NO: 65).

The combinations above can be assessed by any of the assays described in the above examples.

**Example 42. Characterization of MYT4837 constant domain substitutions**

As discussed above histidine scanning was performed where CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. Certain heavy variable chain domain and light variable chain domains were selected for additional experimentation.

Additionally, various methods of conjugating a cytotoxic or cytostatic agent to an antibody are known. For example, conjugation is possible at either naturally occurring amino acid positions and/or at introduced (e.g., engineered amino acids). As discussed herein, various methods of introducing conjugation sites into an antibody are known.

Examples of engineered amino acid conjugation sites include, but are not limited to the following: a substitution to produce “a triple hinge” conjugation site (e.g., a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108 of SEQ ID NO: 155 or SEQ ID NO: 189 generates the triple hinge conjugation site, an alanine to a cysteine substitution at amino acid position 1 of SEQ ID NO: 155 or SEQ ID NO: 189, and/or a valine to cysteine substitution at amino acid position 98 of SEQ ID NO: 157.

Examples of naturally occurring amino acid conjugation sites include, but are not limited to the following: the cysteine at amino acid position 103, the cysteine of a lysine to cysteine substitution at amino acid position 105, (iii) the cysteine at amino acid position 109, and/or the cysteine at amino acid position 112 and/or the cysteine at amino acid position 107 of SEQ ID NO: 157.

The antibodies provided herein can also include modified constant regions. For example, one or more amino acid substitutions, insertion, and/or deletions can be introduced (e.g., engineered) into the constant domains (e.g., constant heavy and/or constant light) of any of the antibodies provided herein. Amino acid substitutions in the constant region can have varying effects on the antibody, including, for example extending the half-life of the antibody. Non-limiting examples of such substitutions include the following: a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139 (e.g., “YTE”

substitution) and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317 (e.g., "LS" substitution).

Thus, MYT4837 includes a variable heavy chain domain comprising SEQ ID NO: 13 and a variable light chain domain comprising SEQ ID NO: 14. Various modified constant regions (e.g., a modified heavy constant region, a modified light constant region) can be combined with variable chains described herein (e.g., SEQ ID NO: 13, SEQ ID NO: 14, respectively). The following represent the following heavy and light chain combinations as such: triple hinge conjugation only (heavy chain of SEQ ID NO: 67 and light chain of SEQ ID NO: 73); triple hinge conjugation and LS substitution (heavy chain: SEQ ID NO: 68 and a light chain: SEQ ID NO: 73); triple hinge substitution and YTE substitution (heavy chain of SEQ ID NO: 69 and a light chain of SEQ ID NO: 73); triple hinge conjugation and V205 substitution (heavy chain of SEQ ID NO: 67 and a light chain of SEQ ID NO: 74); a triple hinge substitution and LS substitution and V205 substitution (heavy chain of SEQ NO: 68 and a light chain of SEQ ID NO: 74); a triple hinge substitution and a YTE substitution and a V205C substitution (heavy chain of SEQ ID NO: 69 and a light chain of SEQ ID NO: 74); a triple hinge substitution and an A118C substitution (heavy chain of SEQ ID NO: 70 and a light chain of SEQ ID NO: 73); a triple hinge substitution and a LS substitution and a A118C substitution (a heavy chain of SEQ ID NO: 71 and a light chain of SEQ ID NO: 73); a triple hinge substitution and a YTE substitution and a A118C substitution (heavy chain of SEQ ID NO: 72 and a light chain of SEQ NO: 73).

The combinations above can be assessed by any of the assays described in the above examples.

**Example 43. Characterization of MYT4849 constant domain substitutions**

As discussed above histidine scanning was performed where CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. Certain heavy variable chain domain and light variable chain domains were selected for additional experimentation.

Additionally, various methods of conjugating a cytotoxic or cytostatic agent to an antibody are known. For example, conjugation is possible at either naturally occurring amino acid positions and/or at introduced (e.g., engineered amino acids). As discussed herein, various methods of introducing conjugation sites into an antibody are known.

Examples of engineered amino acid conjugation sites include, but are not limited to the following: a substitution to produce "a triple hinge" conjugation site (e.g., a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108 of SEQ ID NO: 155 or SEQ ID NO: 189 generates the triple hinge conjugation site, an alanine to a cysteine substitution at amino acid position 1 of SEQ ID NO: 155 or SEQ ID NO: 189, and/or a valine to cysteine substitution at amino acid position 98 of SEQ ID NO: 157.

Examples of naturally occurring amino acid conjugation sites include, but are not limited to the following: the cysteine at amino acid position 103, the cysteine of a lysine to cysteine substitution at amino acid position 105, (iii) the cysteine at amino acid position 109, and/or the cysteine at amino acid position 112 and/or the cysteine at amino acid position 107 of SEQ ID NO: 157.

The antibodies provided herein can also include modified constant regions. For example, one or more amino acid substitutions, insertion, and/or deletions can be introduced (e.g., engineered) into the constant domains (e.g., constant heavy and/or constant light) of any of the antibodies provided herein. Amino acid substitutions in the constant region can have varying effects on the antibody, including, for example extending the half-life of the antibody. Non-limiting examples of such substitutions include the following: a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139 (e.g., "YTE" substitution) and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317 (e.g., "LS" substitution).

Thus, MYT4849 includes a variable heavy chain domain comprising SEQ ID NO: 15 and a variable light chain domain comprising SEQ ID NO: 16. Various modified constant regions (e.g., a modified heavy constant region, a modified light constant region) can be combined with variable chains described herein (e.g., SEQ ID NO: 15, SEQ ID NO: 16, respectively). The following represent the following heavy and light chain combinations as such: triple hinge conjugation only (heavy chain of SEQ ID NO: 75 and light chain of SEQ ID NO: 81); triple

hinge conjugation and LS substitution (heavy chain: SEQ ID NO: 76 and a light chain: SEQ ID NO: 81); triple hinge substitution and YTE substitution (heavy chain of SEQ ID NO: 77 and a light chain of SEQ ID NO: 81); triple hinge conjugation and V205 substitution (heavy chain of SEQ ID NO: 75 and a light chain of SEQ ID NO: 82); a triple hinge substitution and LS substitution and V205 substitution (heavy chain of SEQ NO: 76 and a light chain of SEQ ID NO: 82); a triple hinge substitution and a YTE substitution and a V205C substitution (heavy chain of SEQ ID NO: 77 and a light chain of SEQ ID NO: 82); a triple hinge substitution and an A118C substitution (heavy chain of SEQ ID NO: 78 and a light chain of SEQ ID NO: 11); a triple hinge substitution and a LS substitution and a A118C substitution (a heavy chain of SEQ ID NO: 79 and a light chain of SEQ ID NO: 81); a triple hinge substitution and a YTE substitution and a A118C substitution (heavy chain of SEQ ID NO: 80 and a light chain of SEQ NO: 81).

The combinations above can be assessed by any of the assays described in the above examples.

**Example 44. Characterization of MYT4942 constant domain substitutions**

As discussed above histidine scanning was performed where CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. Certain heavy variable chain domain and light variable chain domains were selected for additional experimentation.

Additionally, various methods of conjugating a cytotoxic or cytostatic agent to an antibody are known. For example, conjugation is possible at either naturally occurring amino acid positions and/or at introduced (e.g., engineered amino acids). As discussed herein, various methods of introducing conjugation sites into an antibody are known.

Examples of engineered amino acid conjugation sites include, but are not limited to the following: a substitution to produce “a triple hinge” conjugation site (e.g., a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108 of SEQ ID NO: 155 or SEQ ID NO: 189 generates the triple hinge conjugation site, an

alanine to a cysteine substitution at amino acid position 1 of SEQ ID NO: 155 or SEQ ID NO: 189, and/or a valine to cysteine substitution at amino acid position 98 of SEQ ID NO: 157.

Examples of naturally occurring amino acid conjugation sites include, but are not limited to the following: the cysteine at amino acid position 103, the cysteine of a lysine to cysteine substitution at amino acid position 105, (iii) the cysteine at amino acid position 109, and/or the cysteine at amino acid position 112 and/or the cysteine at amino acid position 107 of SEQ ID NO: 157.

The antibodies provided herein can also include modified constant regions. For example, one or more amino acid substitutions, insertion, and/or deletions can be introduced (e.g., engineered) into the constant domains (e.g., constant heavy and/or constant light) of any of the antibodies provided herein. Amino acid substitutions in the constant region can have varying effects on the antibody, including, for example extending the half-life of the antibody. Non-limiting examples of such substitutions include the following: a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139 (e.g., "YTE" substitution) and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317 (e.g., "LS" substitution).

Thus, MYT4942 includes a variable heavy chain domain comprising SEQ ID NO: 17 and a variable light chain domain comprising SEQ ID NO: 18. Various modified constant regions (e.g., a modified heavy constant region, a modified light constant region) can be combined with variable chains described herein (e.g., SEQ ID NO: 17, SEQ ID NO: 18, respectively). The following represent the following heavy and light chain combinations as such: triple hinge conjugation only (heavy chain of SEQ ID NO: 83 and light chain of SEQ ID NO: 89); triple hinge conjugation and LS substitution (heavy chain: SEQ ID NO: 84 and a light chain: SEQ ID NO: 89); triple hinge substitution and YTE substitution (heavy chain of SEQ ID NO: 85 and a light chain of SEQ ID NO: 89); triple hinge conjugation and V205 substitution (heavy chain of SEQ ID NO: 83 and a light chain of SEQ ID NO: 90); a triple hinge substitution and LS substitution and V205 substitution (heavy chain of SEQ NO: 84 and a light chain of SEQ ID NO: 90); a triple hinge substitution and a YTE substitution and a V205C substitution (heavy chain of SEQ ID NO: 85 and a light chain of SEQ ID NO: 90); a triple hinge substitution and an A118C substitution (heavy chain of SEQ ID NO: 86 and a light chain of SEQ ID NO: 89); a triple hinge

substitution and a LS substitution and a A118C substitution (a heavy chain of SEQ ID NO: 87 and a light chain of SEQ ID NO: 89); a triple hinge substitution and a YTE substitution and a A118C substitution (heavy chain of SEQ ID NO: 88 and a light chain of SEQ NO: 89).

The combinations above can be assessed by any of the assays described in the above examples.

**Example 45. Characterizatoin of MYT5309 constant domain substitutions**

As discussed above histidine scanning was performed where CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. Certain heavy variable chain domain and light variable chain domains were selected for additional experimentation.

Additionally, various methods of conjugating a cytotoxic or cytostatic agent to an antibody are known. For example, conjugation is possible at either naturally occurring amino acid positions and/or at introduced (e.g., engineered amino acids). As discussed herein, various methods of introducing conjugation sites into an antibody are known.

Examples of engineered amino acid conjugation sites include, but are not limited to the following: a substitution to produce “a triple hinge” conjugation site (e.g., a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108 of SEQ ID NO: 155 or SEQ ID NO: 189 generates the triple hinge conjugation site, an alanine to a cysteine substitution at amino acid position 1 of SEQ ID NO: 155 or SEQ ID NO: 189, and/or a valine to cysteine substitution at amino acid position 98 of SEQ ID NO: 157.

Examples of naturally occurring amino acid conjugation sites include, but are not limited to the following: the cysteine at amino acid position 103, the cysteine of a lysine to cysteine substitution at amino acid position 105, (iii) the cysteine at amino acid position 109, and/or the cysteine at amino acid position 112 and/or the cysteine at amino acid position 107 of SEQ ID NO: 157.

The antibodies provided herein can also include modified constant regions. For example, one or more amino acid substitutions, insertion, and/or deletions can be introduced (e.g.,

engineered) into the constant domains (e.g., constant heavy and/or constant light) of any of the antibodies provided herein. Amino acid substitutions in the constant region can have varying effects on the antibody, including, for example extending the half-life of the antibody. Non-limiting examples of such substitutions include the following: a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139 (e.g., "YTE" substitution) and a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317 (e.g., "LS" substitution).

Thus, MYT5309 includes a variable heavy chain domain comprising SEQ ID NO: 19 and a variable light chain domain comprising SEQ ID NO: 20. Various modified constant regions (e.g., a modified heavy constant region, a modified light constant region) can be combined with variable chains described herein (e.g., SEQ ID NO: 19, SEQ ID NO: 20, respectively). The following represent the following heavy and light chain combinations as such: triple hinge conjugation only (heavy chain of SEQ ID NO: 91 and light chain of SEQ ID NO: 97); triple hinge conjugation and LS substitution (heavy chain: SEQ ID NO: 92 and a light chain: SEQ ID NO: 97); triple hinge substitution and YTE substitution (heavy chain of SEQ ID NO: 93 and a light chain of SEQ ID NO: 97); triple hinge conjugation and V205 substitution (heavy chain of SEQ ID NO: 91 and a light chain of SEQ ID NO: 98); a triple hinge substitution and LS substitution and V205 substitution (heavy chain of SEQ NO: 92 and a light chain of SEQ ID NO: 98); a triple hinge substitution and a YTE substitution and a V205C substitution (heavy chain of SEQ ID NO: 93 and a light chain of SEQ ID NO: 98); a triple hinge substitution and an A118C substitution (heavy chain of SEQ ID NO: 94 and a light chain of SEQ ID NO: 97); a triple hinge substitution and a LS substitution and a A118C substitution (a heavy chain of SEQ ID NO: 95 and a light chain of SEQ ID NO: 97); a triple hinge substitution and a YTE substitution and a A118C substitution (heavy chain of SEQ ID NO: 96 and a light chain of SEQ NO: 97).

The combinations above can be assessed by any of the assays described in the above examples.

**Example 46. Characterization of MYT5344 constant domain substitutions**

As discussed above histidine scanning was performed where CDRs in the light chain were identified using the methods described by Kabat et al (Kabat et al. (1992) Sequences of Proteins of Immunological Interest, DIANE publishing) and IMGT (Lefranc MP (1999) "The IMGT unique numbering for Immunoglobulins, T cell receptors and Ig-like domains" The Immunologist 7, 132-136), and for each CDR, residues falling under either or both Kabat and IMGT CDR definitions were called as CDR residues. Certain heavy variable chain domain and light variable chain domains were selected for additional experimentation.

Additionally, various methods of conjugating a cytotoxic or cytostatic agent to an antibody are known. For example, conjugation is possible at either naturally occurring amino acid positions and/or at introduced (e.g., engineered amino acids). As discussed herein, various methods of introducing conjugation sites into an antibody are known.

Examples of engineered amino acid conjugation sites include, but are not limited to the following: a substitution to produce “a triple hinge” conjugation site (e.g., a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108 of SEQ ID NO: 155 or SEQ ID NO: 189 generates the triple hinge conjugation site, an alanine to a cysteine substitution at amino acid position 1 of SEQ ID NO: 155 or SEQ ID NO: 189, and/or a valine to cysteine substitution at amino acid position 98 of SEQ ID NO: 157.

Examples of naturally occurring amino acid conjugation sites include, but are not limited to the following: the cysteine at amino acid position 103, the cysteine of a lysine to cysteine substitution at amino acid position 105, (iii) the cysteine at amino acid position 109, and/or the cysteine at amino acid position 112 and/or the cysteine at amino acid position 107 of SEQ ID NO: 157.

The antibodies provided herein can also include modified constant regions. For example, one or more amino acid substitutions, insertion, and/or deletions can be introduced (e.g., engineered) into the constant domains (e.g., constant heavy and/or constant light) of any of the antibodies provided herein. Amino acid substitutions in the constant region can have varying effects on the antibody, including, for example extending the half-life of the antibody. Non-limiting examples of such substitutions include the following: a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139 (e.g., “YTE”

# DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 243

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

# JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 243

NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

**WHAT IS CLAIMED IS:**

1. An antibody, wherein the antibody comprises:

(a) a heavy chain variable domain and a light chain variable domain selected from the group of:

(i) SEQ ID NO: 5 and SEQ ID NO: 6, respectively;

(ii) SEQ ID NO: 7 and SEQ ID NO: 8, respectively;

(iii) SEQ ID NO: 9 and SEQ ID NO: 10, respectively;

(iv) SEQ ID NO: 11 and SEQ ID NO: 12, respectively;

(v) SEQ ID NO: 13 and SEQ ID NO: 14, respectively;

(vi) SEQ ID NO: 15 and SEQ ID NO: 16, respectively;

(vii) SEQ ID NO: 17 and SEQ ID NO: 18, respectively;

(viii) SEQ ID NO: 19 and SEQ ID NO: 20, respectively;

(ix) SEQ ID NO: 21 and SEQ ID NO: 22, respectively;

(x) SEQ ID NO: 23 and SEQ ID NO: 24, respectively;

(xi) SEQ ID NO: 25 and SEQ ID NO: 26, respectively;

(xii) SEQ ID NO: 27 and SEQ ID NO: 28, respectively;

(xiii) SEQ ID NO: 29 and SEQ ID NO: 30, respectively;

(xiv) SEQ ID NO: 31 and SEQ ID NO: 32, respectively;

(xv) SEQ ID NO: 33 and SEQ ID NO: 34, respectively; and

(b) a heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprising one or more of the following:

(i) a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108;

(ii) a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139;

(iii) a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and

(iv) an alanine to a cysteine substitution at amino acid position 1;

and/or

a light chain $C_L$ sequence of SEQ ID NO: 157 comprising a valine to cysteine substitution at amino acid position 98.

2. The antibody of claim 1, wherein the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108.

3. The antibody of claim 2, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 35 and SEQ ID NO: 41, respectively;
(ii) SEQ ID NO: 43 and SEQ ID NO: 49, respectively;
(iii) SEQ ID NO: 51 and SEQ ID NO: 57, respectively
(iv) SEQ ID NO: 59 and SEQ ID NO: 65, respectively;
(v) SEQ ID NO: 67 and SEQ ID NO: 73, respectively;
(vi) SEQ ID NO: 75 and SEQ ID NO: 81, respectively;
(vii) SEQ ID NO: 83 and SEQ ID NO: 89, respectively;
(viii) SEQ ID NO: 91 and SEQ ID NO: 97, respectively;
(ix) SEQ ID NO: 99 and SEQ ID NO: 105, respectively;
(x) SEQ ID NO: 107 and SEQ ID NO: 113, respectively;
(xi) SEQ ID NO: 115 and SEQ ID NO: 121, respectively;
(xii) SEQ ID NO: 123 and SEQ ID NO: 129, respectively;
(xiii) SEQ ID NO: 131 and SEQ ID NO: 137, respectively;
(xiv) SEQ ID NO: 139 and SEQ ID NO: 145, respectively; or
(xv) SEQ ID NO: 147 and SEQ ID NO: 153, respectively.

4. The antibody of claim 1, wherein the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and

a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317.

5. The antibody of claim 4, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 36 and SEQ ID NO: 41, respectively;

(ii) SEQ ID NO: 44 and SEQ ID NO: 49, respectively;

(iii) SEQ ID NO: 52 and SEQ ID NO: 57, respectively;

(iv) SEQ ID NO: 60 and SEQ ID NO: 65, respectively;

(v) SEQ ID NO: 68 and SEQ ID NO: 73, respectively;

(vi) SEQ ID NO: 76 and SEQ ID NO: 81, respectively;

(vii) SEQ ID NO: 84 and SEQ ID NO: 89, respectively;

(viii) SEQ ID NO: 92 and SEQ ID NO: 97, respectively;

(ix) SEQ ID NO: 100 and SEQ ID NO: 105, respectively;

(x) SEQ ID NO: 108 and SEQ ID NO: 113, respectively;

(xi) SEQ ID NO: 116 and SEQ ID NO: 121, respectively;

(xii) SEQ ID NO: 124 and SEQ ID NO: 129, respectively;

(xiii) SEQ ID NO: 132 and SEQ ID NO: 137, respectively;

(xiv) SEQ ID NO: 140 and SEQ ID NO: 145, respectively; or

(xv) SEQ ID NO: 148 and SEQ ID NO: 153, respectively.

6. The antibody of claim 1, wherein the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and

a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139.

7. The antibody of claim 6, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 37 and SEQ ID NO: 41, respectively;

(ii) SEQ ID NO: 45 and SEQ ID NO: 49, respectively;

(iii) SEQ ID NO: 53 and SEQ ID NO: 57, respectively;

(iv) SEQ ID NO: 61 and SEQ ID NO: 65, respectively;
(v) SEQ ID NO: 69 and SEQ ID NO: 73, respectively;
(vi) SEQ ID NO: 77 and SEQ ID NO: 81, respectively;
(vii) SEQ ID NO: 85 and SEQ ID NO: 89, respectively;
(viii) SEQ ID NO: 93 and SEQ ID NO: 97, respectively;
(ix) SEQ ID NO: 101 and SEQ ID NO: 105, respectively;
(x) SEQ ID NO: 109 and SEQ ID NO: 113, respectively;
(xi) SEQ ID NO: 117 and SEQ ID NO: 121, respectively;
(xii) SEQ ID NO: 125 and SEQ ID NO: 129, respectively;
(xiii) SEQ ID NO: 133 and SEQ ID NO: 137, respectively;
(xiv) SEQ ID NO: 141 and SEQ ID NO: 145, respectively; or
(xv). SEQ ID NO: 149 and SEQ ID NO: 153, respectively.

8. The antibody of claim 1, wherein:

the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and

the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98.

9. The antibody of claim 8, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 35 and SEQ ID NO: 42, respectively;
(ii) SEQ ID NO: 43 and SEQ ID NO: 50, respectively;
(iii) SEQ ID NO: 51 and SEQ ID NO: 58, respectively;
(iv) SEQ ID NO: 59 and SEQ ID NO: 66, respectively;
(v) SEQ ID NO: 67 and SEQ ID NO: 74, respectively;
(vi) SEQ ID NO: 75 and SEQ ID NO: 82, respectively;
(vii) SEQ ID NO: 83 and SEQ ID NO: 90, respectively;
(viii) SEQ ID NO: 91 and SEQ ID NO: 98, respectively;
(ix) SEQ ID NO: 99 and SEQ ID NO: 106, respectively;

(x) SEQ ID NO: 107 and SEQ ID NO: 114, respectively;
(xi) SEQ ID NO: 115 and SEQ ID NO: 122, respectively;
(xii) SEQ ID NO: 123 and SEQ ID NO: 130, respectively;
(xiii) SEQ ID NO: 131 and SEQ ID NO: 138, respectively;
(xiv) SEQ ID NO: 139 and SEQ ID NO: 146, respectively; or
(xv) SEQ ID NO: 147 and SEQ ID NO: 154, respectively.

10. The antibody of claim 1, wherein:

the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and

a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and

the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98.

11. The antibody of claim 10, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 36 and SEQ ID NO: 42, respectively;
(ii) SEQ ID NO: 44 and SEQ ID NO: 50, respectively;
(iii) SEQ ID NO: 52 and SEQ ID NO: 58, respectively;
(iv) SEQ ID NO: 60 and SEQ ID NO: 66, respectively;
(v) SEQ ID NO: 68 and SEQ ID NO: 74, respectively;
(vi) SEQ ID NO: 76 and SEQ ID NO: 82, respectively;
(vii) SEQ ID NO: 84 and SEQ ID NO: 90, respectively;
(viii) SEQ ID NO: 92 and SEQ ID NO: 98, respectively;
(ix) SEQ ID NO: 100 and SEQ ID NO: 106, respectively;
(x) SEQ ID NO: 108 and SEQ ID NO: 114, respectively;
(xi) SEQ ID NO: 116 and SEQ ID NO: 122, respectively;
(xii) SEQ ID NO: 124 and SEQ ID NO: 130, respectively;

(xiii) SEQ ID NO: 132 and SEQ ID NO: 138, respectively;
(xiv) SEQ ID NO: 140 and SEQ ID NO: 146, respectively; or
(xv) SEQ ID NO: 148 and SEQ ID NO: 154, respectively.

12. The antibody of claim 1, wherein:

the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and

a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139; and

the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98.

13. The antibody of claim 12, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 37 and SEQ ID NO: 42, respectively;
(ii) SEQ ID NO: 45 and SEQ ID NO: 50, respectively;
(iii) SEQ ID NO: 53 and SEQ ID NO: 58, respectively;
(iv) SEQ ID NO: 61 and SEQ ID NO: 66, respectively;
(v) SEQ ID NO: 69 and SEQ ID NO: 74, respectively;
(vi) SEQ ID NO: 77 and SEQ ID NO: 82, respectively;
(vii) SEQ ID NO: 85 and SEQ ID NO: 90, respectively;
(viii) SEQ ID NO: 93 and SEQ ID NO: 98, respectively;
(ix) SEQ ID NO: 101 and SEQ ID NO: 106, respectively;
(x) SEQ ID NO: 109 and SEQ ID NO: 114, respectively;
(xi) SEQ ID NO: 117 and SEQ ID NO: 122, respectively;
(xii) SEQ ID NO: 125 and SEQ ID NO: 130, respectively;
(xiii) SEQ ID NO: 133 and SEQ ID NO: 138, respectively;
(xiv) SEQ ID NO: 141 and SEQ ID NO: 146, respectively; or

(xv) SEQ ID NO: 149 and SEQ ID NO: 154, respectively.

14. The antibody of claim 1, wherein the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

amino acid a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at positions 106 and 108; and

an alanine to a cysteine substitution at amino acid position 1.

15. The antibody of claim 14, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 38 and SEQ ID NO: 41, respectively;
(ii) SEQ ID NO: 46 and SEQ ID NO: 49, respectively;
(iii) SEQ ID NO: 54 and SEQ ID NO: 57, respectively;
(iv) SEQ ID NO: 62 and SEQ ID NO: 65, respectively;
(v) SEQ ID NO: 70 and SEQ ID NO: 73, respectively;
(vi) SEQ ID NO: 78 and SEQ ID NO: 81, respectively;
(vii) SEQ ID NO: 86 and SEQ ID NO: 89, respectively;
(viii) SEQ ID NO: 94 and SEQ ID NO: 97, respectively;
(ix) SEQ ID NO: 102 and SEQ ID NO: 105, respectively;
(x) SEQ ID NO: 110 and SEQ ID NO: 113, respectively;
(xi) SEQ ID NO: 118 and SEQ ID NO: 121, respectively;
(xii) SEQ ID NO: 126 and SEQ ID NO: 129, respectively;
(xiii) SEQ ID NO: 134 and SEQ ID NO: 137, respectively;
(xiv) SEQ ID NO: 142 and SEQ ID NO: 145, respectively; or
(xv) SEQ ID NO: 150 and SEQ ID NO: 153, respectively.

16. The antibody of claim 1, wherein the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108;

a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and

an alanine to a cysteine substitution at amino acid position 1.

17. The antibody of claim 16, wherein the antibody comprises a heavy chain and a light chain sequence selected from the group of:

(i) SEQ ID NO: 39 and SEQ ID NO: 41, respectively;

(ii) SEQ ID NO: 47 and SEQ ID NO: 49, respectively;

(iii) SEQ ID NO: 55 and SEQ ID NO: 57, respectively;

(iv) SEQ ID NO: 63 and SEQ ID NO: 65, respectively;

(v) SEQ ID NO: 71 and SEQ ID NO: 73, respectively;

(vi) SEQ ID NO: 79 and SEQ ID NO: 81, respectively;

(vii) SEQ ID NO: 87 and SEQ ID NO: 89, respectively;

(viii) SEQ ID NO: 95 and SEQ ID NO: 97, respectively;

(ix) SEQ ID NO: 103 and SEQ ID NO: 105, respectively;

(x) SEQ ID NO: 111 and SEQ ID NO: 113, respectively;

(xi) SEQ ID NO: 119 and SEQ ID NO: 121, respectively;

(xii) SEQ ID NO: 127 and SEQ ID NO: 129, respectively;

(xiii) SEQ ID NO: 135 and SEQ ID NO: 137, respectively;

(xiv) SEQ ID NO: 143 and SEQ ID NO: 145, respectively; or

(xv) SEQ ID NO: 151 and SEQ ID NO: 153, respectively.

18. The antibody of claim 1, wherein the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108;

a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139; and

an alanine to a cysteine substitution at amino acid position 1.

19. The antibody of claim 18, wherein the antibody comprises a heavy chain and a light chain sequence selected from the group of:

(i) SEQ ID NO: 40 and SEQ ID NO: 41, respectively;

(ii) SEQ ID NO: 48 and SEQ ID NO: 49, respectively;

(iii) SEQ ID NO: 56 and SEQ ID NO: 57, respectively;

(iv) SEQ ID NO: 64 and SEQ ID NO: 65, respectively;

(v) SEQ ID NO: 72 and SEQ ID NO: 73, respectively;

(vi) SEQ ID NO: 80 and SEQ ID NO: 81, respectively;

(vii) SEQ ID NO: 88 and SEQ ID NO: 89, respectively;

(viii) SEQ ID NO: 96 and SEQ ID NO: 97, respectively;

(ix) SEQ ID NO: 104 and SEQ ID NO: 105, respectively;

(x) SEQ ID NO: 112 and SEQ ID NO: 113, respectively;

(xi) SEQ ID NO: 120 and SEQ ID NO: 121, respectively;

(xii) SEQ ID NO: 128 and SEQ ID NO: 129, respectively;

(xiii) SEQ ID NO: 136 and SEQ ID NO: 137, respectively;

(xiv) SEQ ID NO: 144 and SEQ ID NO: 145, respectively; or

(xv) SEQ ID NO: 152 and SEQ ID NO: 153, respectively.

20. The antibody of any one of claims 2-19, wherein the antibody further comprises a cytotoxic drug conjugated to one or more of the following:

(a) a heavy chain CH1-CH2-CH3 of SEQ ID NO: 155 or SEQ ID NO: 189 comprising one or more of the following:

(i) the cysteine at amino acid position 103;

(ii) the cysteine of a lysine to cysteine substitution at amino acid position 105;

(iii) the cysteine at amino acid position 109;

(iv) the cysteine at amino acid position 112; and/or

(b) the cysteine at amino acid position 107 of SEQ ID NO: 157.

21. The antibody of any one of claims 8-13 and 20, wherein the antibody further comprises a cytotoxic or cytostatic agent is conjugated to the cysteine at position 98 of SEQ ID NO: 157.

22. The antibody of any one of claims 14-20, wherein the antibody further comprises a cytotoxic or cytostatic agent is conjugated to the cysteine at position 1 of SEQ ID NO: 155 or SEQ ID NO: 189.

23. The antibody of claim 20-22, wherein the cytotoxic or cytostatic agent is a conjugated toxin, a radioisotope, drug, or a small molecule.

24. The antibody of any one of claims 1-23,

wherein:

(a) the dissociation rate of the antibody 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 antibody 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.

25. The antibody of any one of claims 20-24, wherein a composition comprising the antibody:

provides for one or more of:

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

an increase in target mammalian cell killing as compared to a composition comprising the same amount of a control antibody; and

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

26. The antibody of any one of claims 1-25, wherein a composition comprising the antibody:

results in a less of a reduction in the level of MET presented on the surface of a target mammalian cell as compared to a composition comprising the same amount of a control antibody; or

does not result in a detectable reduction in the level of MET presented on the surface of the target mammalian cell.

27. The antibody of claim 25 or 26, wherein the antibody is degraded in a target mammalian cell following internalization of the antibody by a target mammalian cell.

28. The antibody of any one of claims 25-27, wherein the target mammalian cell is a cancer cell.

29. The antibody of any one of claims 25-28, wherein the antibody is cytotoxic or cytostatic to the target mammalian cell.

30. The antibody of any one of claims 1-29, wherein the antibody has an avidity that results in increased selectivity for cancer cells over non-cancerous cells.

31. The antibody of any one of claims 1-30, wherein the antibody is:

cross-reactive with a non-human primate MET and human MET; or

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

32. The antibody of any one of claims 1-31, wherein the half-life of the antibody in vivo is increased as compared to the half-life of a control antibody in vivo.

33. A pharmaceutical composition comprising an effective amount of any one of the antibodies of claims 1-32.

34. A kit comprising at least one dose of the antibody of any one of claims 1-32 or the pharmaceutical composition of claim 33.

35. A method of treating a cancer characterized by having a population of cancer cells that have MET or an epitope of MET presented on their surface, the method comprising:

administering a therapeutically effective amount of the antibody of any one of claims 1-32 or the pharmaceutical composition of claim 33 to a subject identified as having a cancer characterized by having the population of cancer cells.

36. 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 MET or an epitope of MET presented on their surface, the method comprising:

administering a therapeutically effective amount of the antibody of any one of claims 1-32 or the pharmaceutical composition of claim 33 to a subject identified as having a cancer characterized by having the population of cancer cells.

37. A method of inducing cell death in a cancer cell in a subject, wherein the cancer cell has MET or an epitope of MET presented on its surface, wherein the method comprises:

administering a therapeutically effective amount of the antibody of any one of claims 1-32 or the pharmaceutical composition of claim 33 to a subject identified as having a cancer characterized by having a population of the cancer cells.

38. 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 MET or an epitope of MET presented on their surface the method comprising:

administering a therapeutically effective amount of the antibody of any one of claims 1-32 or the pharmaceutical composition of claim 33 to a subject identified as having a cancer characterized by having the population of cancer cells.

39. An antibody, wherein the antibody comprises:

(a) heavy chain variable domain and a light chain variable domain selected from the group consisting of:

(i) SEQ ID NO: 159 and SEQ ID NO: 160, respectively;

(ii) SEQ ID NO: 161 and SEQ ID NO: 162, respectively;

(iii) SEQ ID NO: 163 and SEQ ID NO: 164; respectively;

(b) a heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprising one or more of the following substitution(s):

(i) a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine amino acid at positions 106 and 108;

(ii) a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139;

(iii) a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and

(iv) an alanine to cysteine substitution at amino acid position 1;

and/or

a light chain $C_L$ sequence of SEQ ID NO: 157 comprising a valine to cysteine substitution at position 98.

40. The antibody of claim 39, wherein the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108.

41. The antibody of claim 40, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 165 and SEQ ID NO: 171, respectively;

(ii) SEQ ID NO: 173 and SEQ ID NO: 179, respectively; or

(iii) SEQ ID NO: 181 and SEQ ID NO: 187, respectively.

42. The antibody of claim 39, wherein the heavy CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108;

a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317.

43. The antibody of claim 42, wherein antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 166 and SEQ ID NO: 171, respectively;

(ii) SEQ ID NO: 174 and SEQ ID NO: 179, respectively; or

(iii) SEQ ID NO: 182 and SEQ ID NO: 187, respectively.

44. The antibody of claim 39, wherein the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and

a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139.

45. The antibody of claim 44, wherein the antibody comprises a heavy chain and a light chain sequence selected from the group of:

(i) SEQ ID NO: 167 and SEQ ID NO: 171, respectively;

(ii) SEQ ID NO: 175 and SEQ ID NO: 179, respectively; or

(iii) SEQ ID NO: 183 and SEQ ID NO: 187, respectively.

46. The antibody of claim 39, wherein:

the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and

the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98.

47. The antibody of claim 46, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 165 and SEQ ID NO: 172, respectively;

(ii) SEQ ID NO: 173 and SEQ ID NO: 180, respectively; or

(iii) SEQ ID NO: 181 and SEQ ID NO: 188, respectively.

48. The antibody of claim 39, wherein:

the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and

a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and

the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98.

49. The antibody of claim 48, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 166 and SEQ ID NO: 172, respectively;

(ii) SEQ ID NO: 174 and SEQ ID NO: 180, respectively; or

(iii) SEQ ID NO: 182 and SEQ ID NO: 188, respectively.

50. The antibody of claim 39, wherein:

the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and

a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139; and

the light chain $C_L$ sequence of SEQ ID NO: 157 comprises a valine to cysteine substitution at amino acid position 98.

51. The antibody of claim 50, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 167 and SEQ ID NO: 172, respectively;

(ii) SEQ ID NO: 175 and SEQ ID NO: 180, respectively; or

(iii) SEQ ID NO: 183 and SEQ ID NO: 188, respectively.

52. The antibody of claim 39, wherein the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108; and

an alanine to a cysteine substitution at amino acid position 1.

53. The antibody of claim 52, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 168 and SEQ ID NO: 171, respectively;

(ii) SEQ ID NO: 176 and SEQ ID NO: 179, respectively; or

(iii) SEQ ID NO: 184 and SEQ ID NO: 187, respectively.

54. The antibody of claim 39, wherein the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108;

a methionine to leucine substitution at amino acid position 311 and an asparagine to serine substitution at amino acid position 317; and

an alanine to a cysteine substitution at amino acid position 1.

55. The antibody of claim 54, wherein the antibody comprises a heavy chain and a light chain sequence selected from the group of:

(i) SEQ ID NO: 169 and SEQ ID NO: 171, respectively;

(ii) SEQ ID NO: 177 and SEQ ID NO: 179, respectively; or

(iii) SEQ ID NO: 185 and SEQ ID NO: 187, respectively.

56. The antibody of claim 39, wherein the heavy chain CH1-CH2-CH3 sequence of SEQ ID NO: 155 or SEQ ID NO: 189 comprises:

a lysine to cysteine substitution at amino acid position 105 and deletion of a threonine at amino acid positions 106 and 108;

a methionine to tyrosine substitution at amino acid position 135, a serine to threonine substitution at amino acid position 137, and a threonine to glutamic acid substitution at amino acid position 139; and

an alanine to a cysteine substitution at amino acid position 1.

57. The antibody of claim 56, wherein the antibody comprises heavy chain and light chain sequences selected from the group of:

(i) SEQ ID NO: 170 and SEQ ID NO: 171, respectively;

(ii) SEQ ID NO: 178 and SEQ ID NO: 179, respectively; or

(iii) SEQ ID NO: 186 and SEQ ID NO: 187, respectively.

58. The antibody of any one of claims 40-57, wherein the antibody further comprises a cytotoxic drug conjugated to one or more of the following:

(a) a heavy chain CH1-CH2-CH3 of SEQ ID NO: 155 or SEQ ID NO: 189 comprising one or more of the following:

(i) the cysteine at amino acid position 103;

(ii) the cysteine of a lysine to cysteine substitution at amino acid position 105;

(iii) the cysteine at amino acid position 109; and

(iv) the cysteine at amino acid position 112; and/or

(b) the cysteine at amino acid position 107 of SEQ ID NO: 157.

59. The antibody of any one of claims 46-51 and 58, wherein the antibody further comprises a cytotoxic or cytostatic agent is conjugated to the cysteine at position 98 of SEQ ID NO: 157.

60. The antibody of any one of claims 52-58, wherein the antibody further comprises a cytotoxic or cytostatic agent is conjugated to the cysteine at position 1 of SEQ ID NO: 155 or SEQ ID NO: 189.

61. The antibody of any one of claims 58-60, wherein the cytostatic or cytotoxic agent is a conjugated toxin, a radioisotope, drug, or a small molecule.

62. The antibody of any one of claims 58-61, wherein the antibody is cytotoxic or cytostatic to a target mammalian cell.

63. The antibody of any claim 62, wherein the antibody is degraded in the target mammalian cell following internalization of the antibody by the target mammalian cell.

64. The antibody of claim 62 or 63, wherein the target mammalian cell is a cancer cell.

65. The antibody of any one of claims 39-64, wherein the antibody has an avidity that results in increased selectivity for cancer cells over non-cancerous cells.

66. The antibody of any one of claims 39-65, wherein the antibody is:

cross-reactive with a non-human primate MET and human MET; or

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

67. The antibody of any one of claims 39-66, wherein the half-life of the antibody in vivo is increased as compared to the half-life of a control antibody in vivo.

68. The antibody of claim 62-64, wherein the target mammalian cell is a cancer cell.

69. A pharmaceutical composition comprising an effective amount of any one of the antibodies of claims 39-68.

70. A kit comprising at least one dose of the antibody of any one of 39-68 or the pharmaceutical composition claim 69.

71. A method of treating a cancer characterized by having a population of cancer cells that have MET or an epitope of MET presented on their surface, the method comprising:

administering a therapeutically effective amount of the antibody of any one of claims 39-68 or the pharmaceutical composition of claim 69 to a subject identified as having a cancer characterized by having the population of cancer cells.

72. 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 MET or an epitope of MET presented on their surface, the method comprising:

administering a therapeutically effective amount of the antibody of any one of claims 39-68 or the pharmaceutical composition of claim 69 to a subject identified as having a cancer characterized by having the population of cancer cells.

73. A method of inducing cell death in a cancer cell in a subject, wherein the cancer cell has MET or an epitope of MET presented on its surface, wherein the method comprises:

administering a therapeutically effective amount of the antibody of any one of claims 39-68 or the pharmaceutical composition of claim 69 to a subject identified as having a cancer characterized by having a population of the cancer cells.

74. 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 MET or an epitope of MET presented on their surface the method comprising:

administering a therapeutically effective amount of the antibody of any one of claims 39-68 or the pharmaceutical composition of claim 69 to a subject identified as having a cancer characterized by having the population of cancer cells.

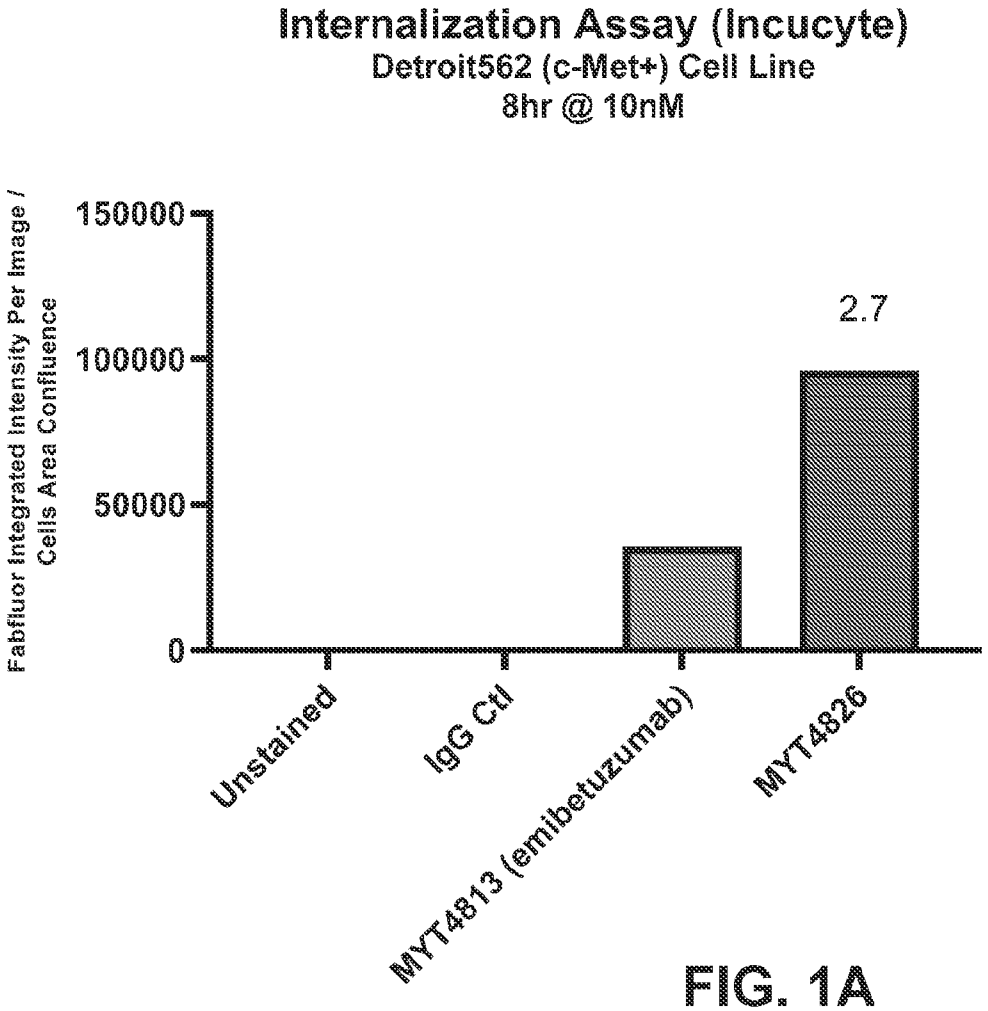

Internalization Assay (Incucyte)
Detroit562 (c-Met+) Cell Line
8hr @ 10nM
Fabfluor Integrated Intensity Per Image / Cells Area Confluence
150000
100000
50000
0
2.7
Unstained
IgG Ctl
MYT4813 (emibetuzumab)
MYT4826

FIG. 1A

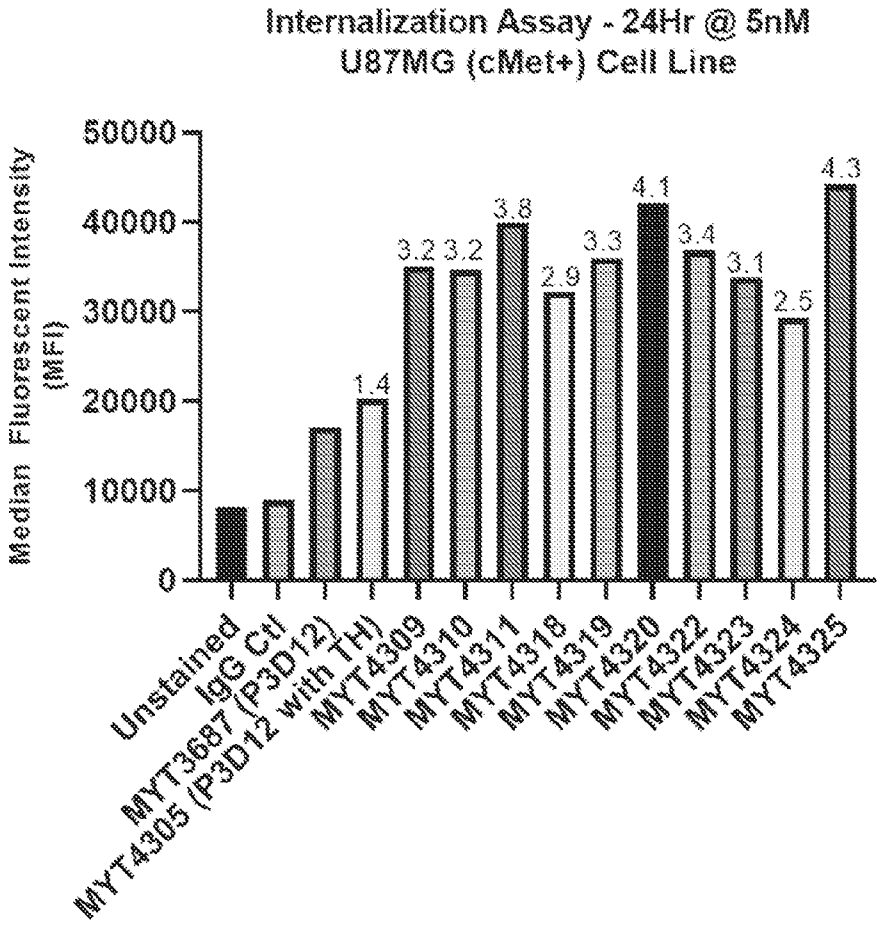

Internalization Assay - 24Hr @ 5nM
U87MG (cMet+) Cell Line
Median Fluorescent Intensity (MFI)
50000
40000
30000
20000
10000
0
1.4
3.2
3.2
3.8
2.9
3.3
4.1
3.4
3.1
2.6
4.3
Unstained
IgG Ctl
MYT3687 (P3D12)
MYT4305 (P3D12 with TH)
MYT4309
MYT4310
MYT4311
MYT4318
MYT4319
MYT4320
MYT4322
MYT4323
MYT4324
MYT4325

FIG. 1B

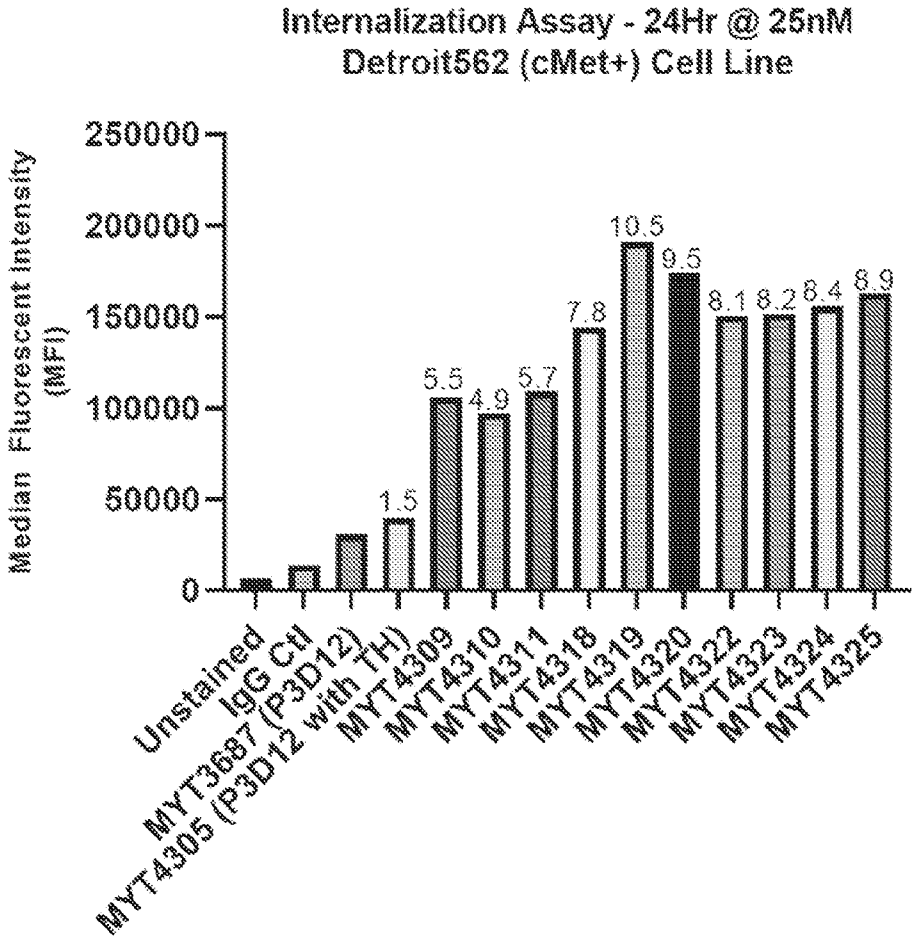

Internalization Assay - 24Hr @ 25nM
Detroit562 (cMet+) Cell Line
Median Fluorescent Intensity (MFI)
250000
200000
150000
100000
50000
0
1.5
5.5
4.9
5.7
7.8
10.5
9.5
8.1
8.2
8.4
8.9
Unstained
IgG Ctl
MYT3687 (P3D12)
MYT4305 (P3D12 with TH)
MYT4309
MYT4310
MYT4311
MYT4318
MYT4319
MYT4320
MYT4322
MYT4323
MYT4324
MYT4325

FIG. 1C

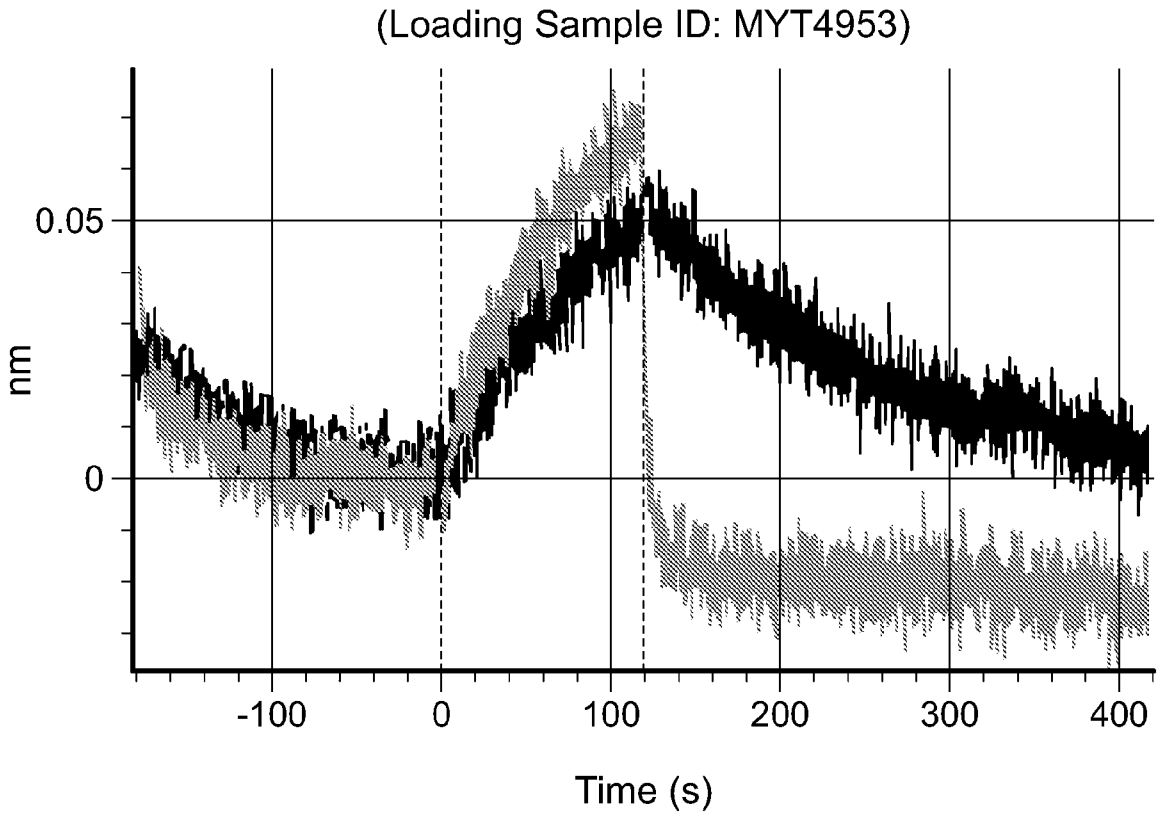



FIG. 2

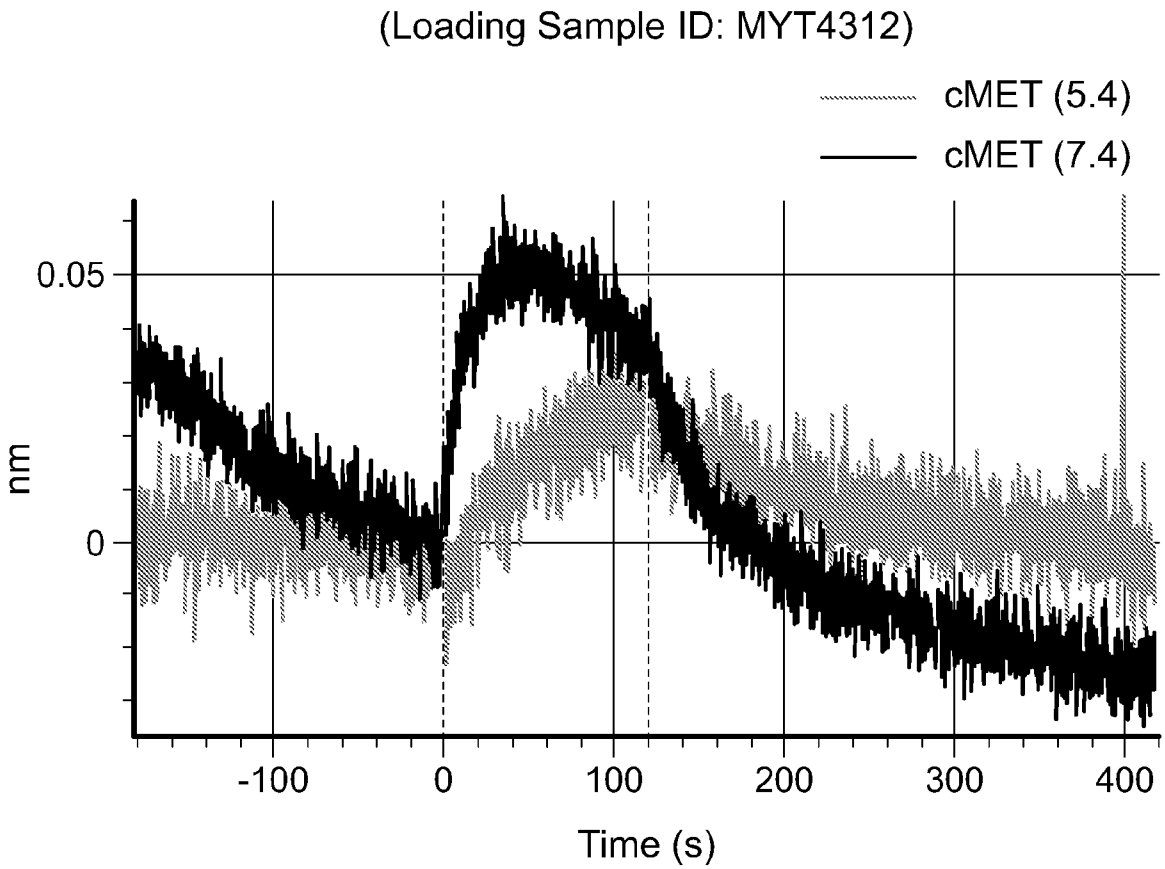

(Loading Sample ID: MYT4312)
cMET (5.4)
cMET (7.4)
0.05
0
nm
-100
0
100
200
300
400
Time (s)

FIG. 3A

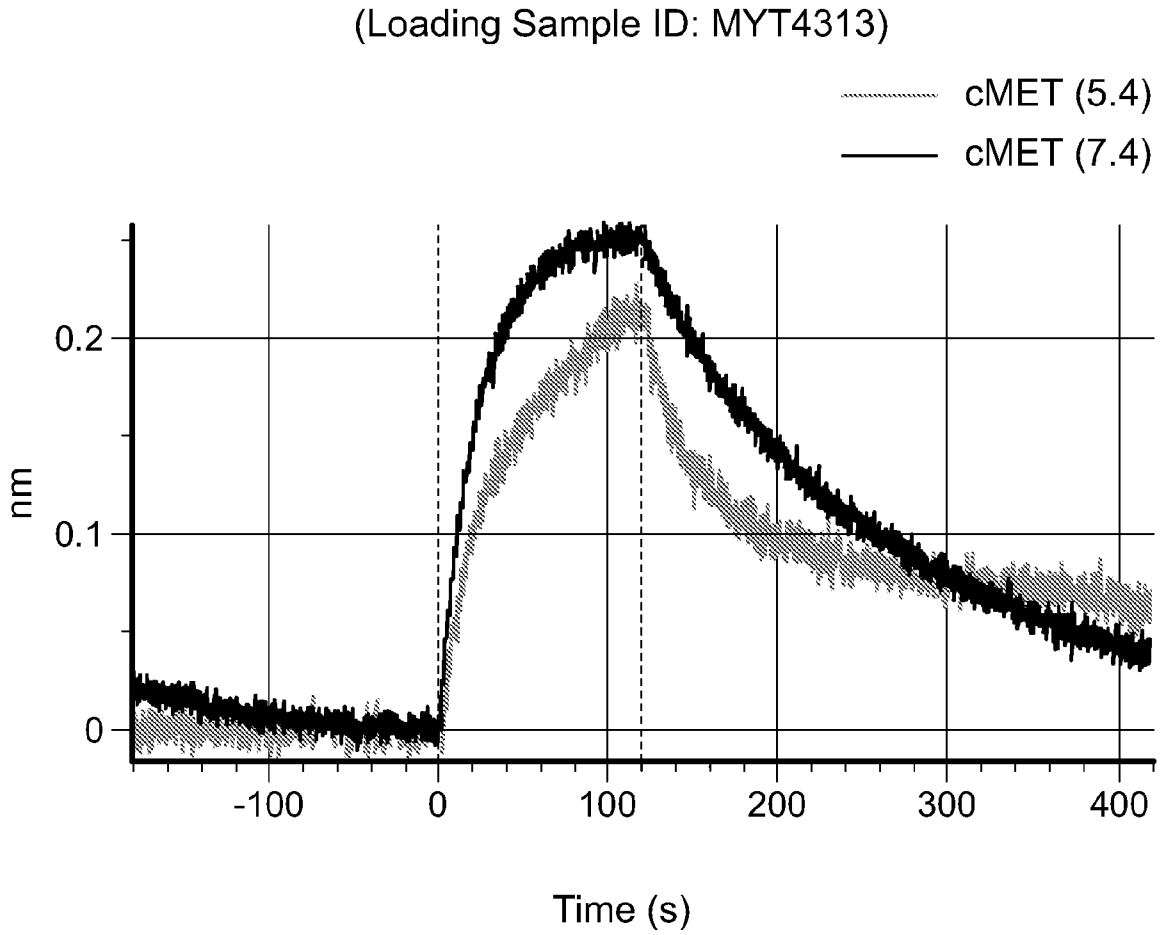

(Loading Sample ID: MYT4313)
cMET (5.4)
cMET (7.4)
nm
0.2
0.1
0
-100
0
100
200
300
400
Time (s)

FIG. 3B

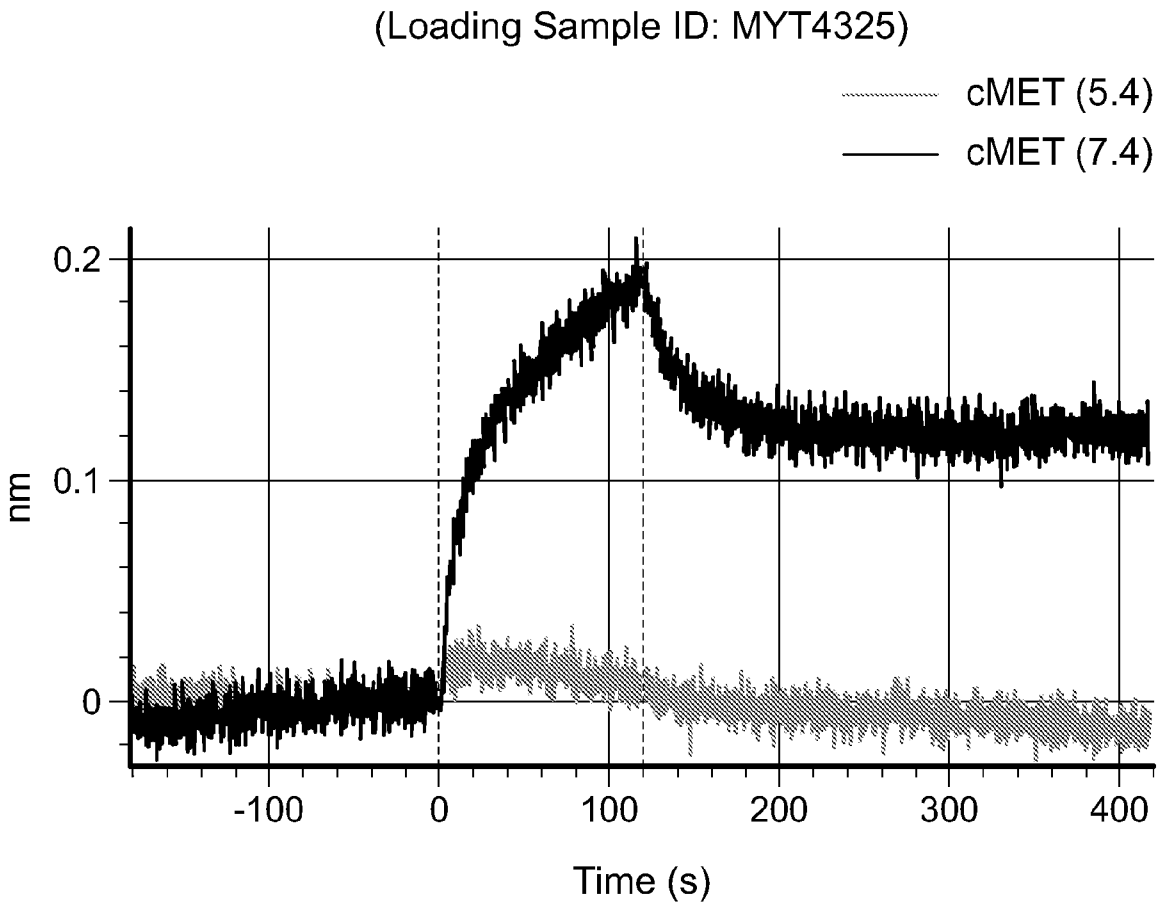

(Loading Sample ID: MYT4325)
cMET (5.4)
cMET (7.4)
0.2
0.1
0
nm
-100
0
100
200
300
400
Time (s)

FIG. 3C

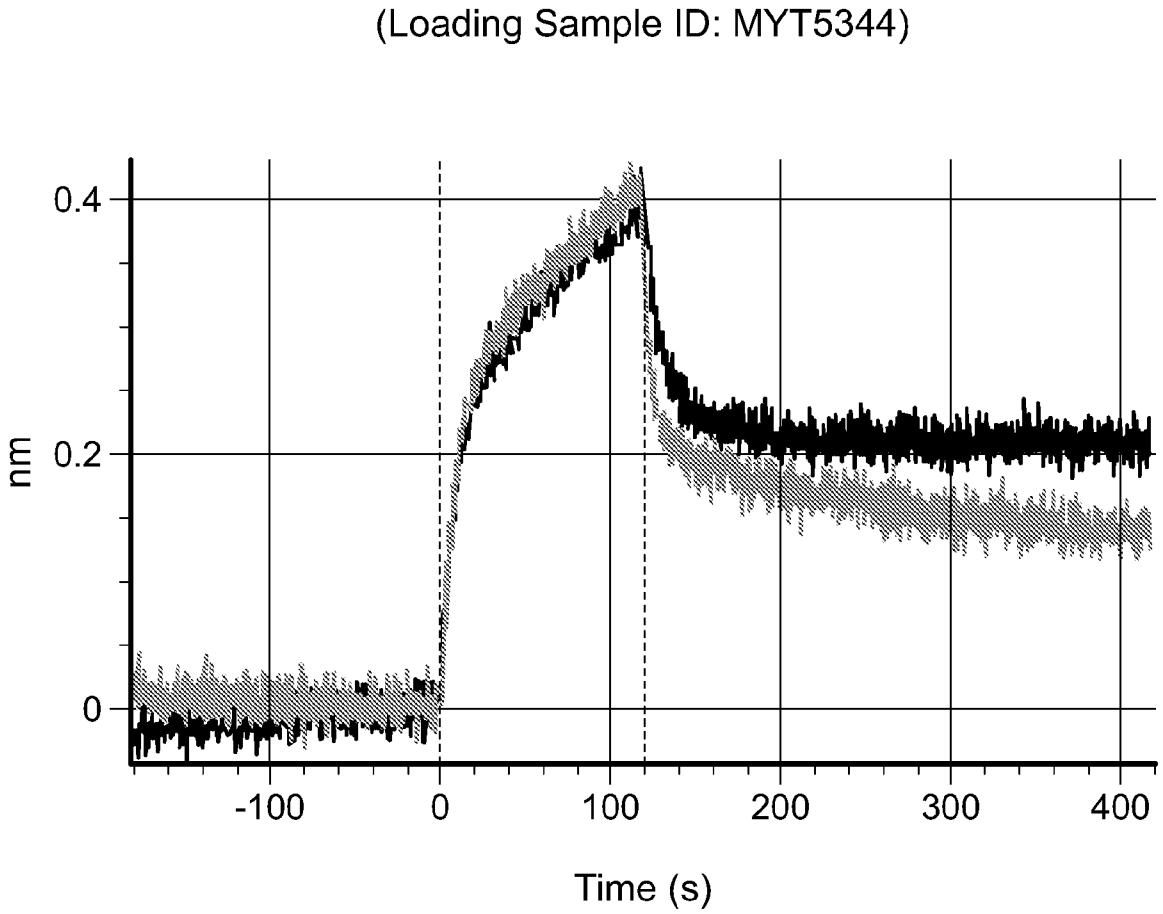

(Loading Sample ID: MYT5344)
0.4
0.2
0
nm
-100
0
100
200
300
400
Time (s)

FIG. 4A

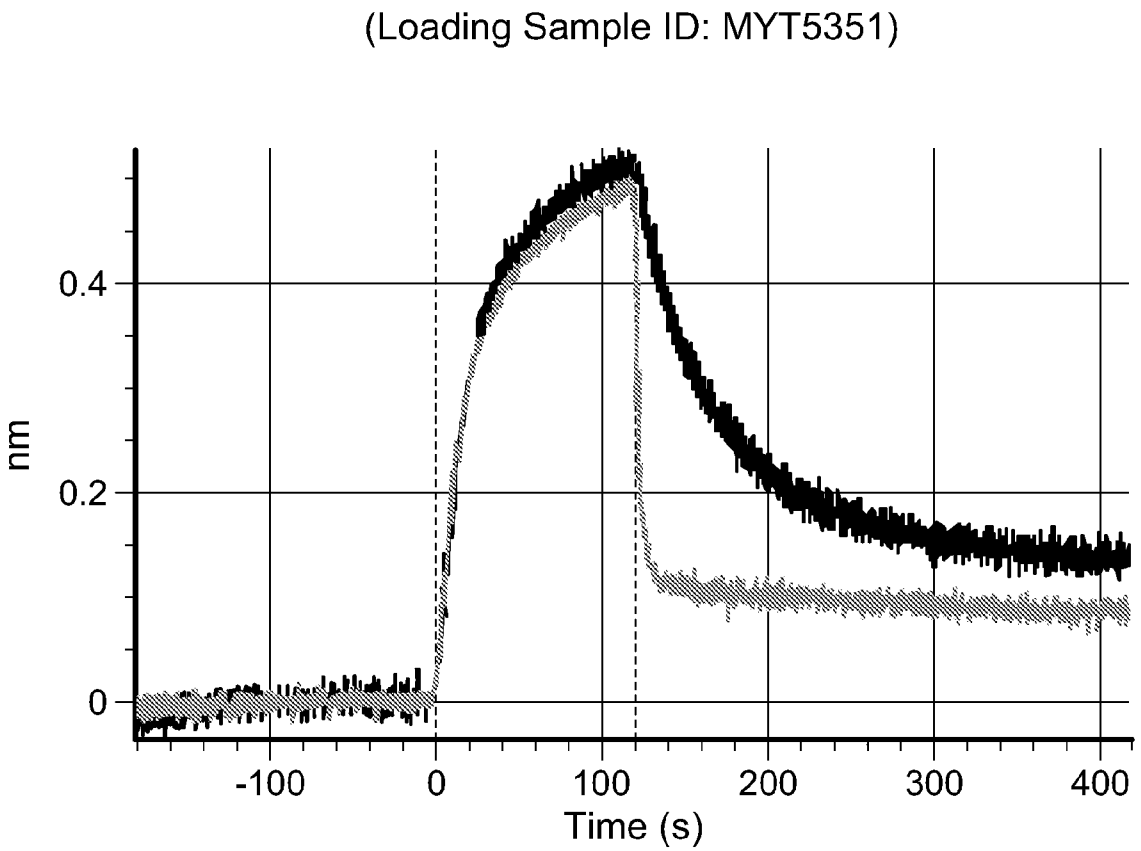

(Loading Sample ID: MYT5351)
nm
0.4
0.2
0
-100
0
100
200
300
400
Time (s)

FIG. 4B

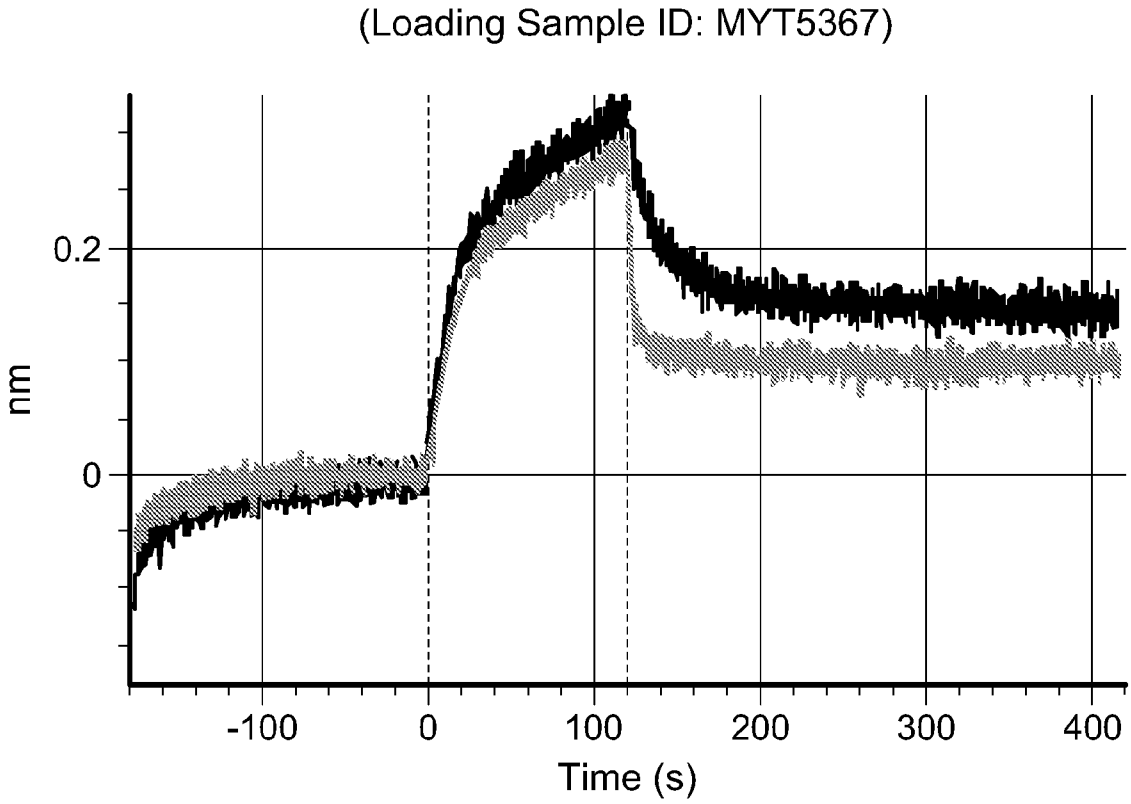

(Loading Sample ID: MYT5367)
0.2
0
nm
-100
0
100
200
300
400
Time (s)

FIG. 4C

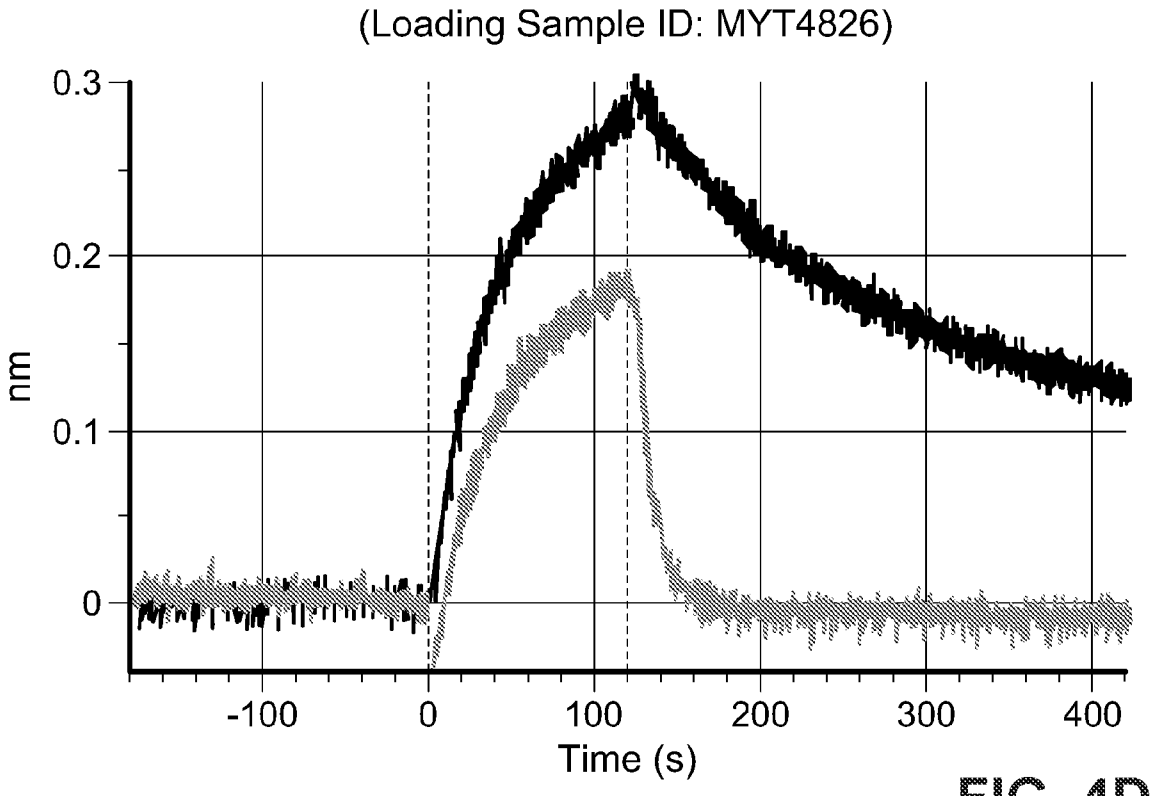

(Loading Sample ID: MYT4826)
0.3
0.2
0.1
0
nm
-100
0
100
200
300
400
Time (s)

FIG. 4D

| MYT # | Variable Heavy | Variable Light |
|---|---|---|
| MYT5351 | SEQ ID NO: 5 | SEQ ID NO: 6 |
| MYT4313 | SEQ ID NO: 7 | SEQ ID NO: 8 |
| MYT4325 | SEQ ID NO: 9 | SEQ ID NO: 10 |
| MYT4826 | SEQ ID NO: 11 | SEQ ID NO: 12 |
| MYT4837 | SEQ ID NO: 13 | SEQ ID NO: 14 |
| MYT4849 | SEQ ID NO: 15 | SEQ ID NO: 16 |
| MYT4942 | SEQ ID NO: 17 | SEQ ID NO: 18 |
| MYT5309 | SEQ ID NO: 19 | SEQ ID NO: 20 |
| MYT5344 | SEQ ID NO: 21 | SEQ ID NO: 22 |
| MYT5367 | SEQ ID NO: 23 | SEQ ID NO: 24 |
| MYT4827 | SEQ ID NO: 25 | SEQ ID NO: 26 |
| MYT4312 | SEQ ID NO: 27 | SEQ ID NO: 28 |
| MYT4953 | SEQ ID NO: 29 | SEQ ID NO: 30 |
| MYT4940 | SEQ ID NO: 31 | SEQ ID NO: 32 |
| MYT4888 | SEQ ID NO: 33 | SEQ ID NO: 34 |
| MYT2040 | SEQ ID NO: 159 | SEQ ID NO: 18 |
| MYT3463 | SEQ ID NO: 17 | SEQ ID NO: 190 |
| MYT3477 | SEQ ID NO: 17 | SEQ ID NO: 191 |
| MYT3491 | SEQ ID NO: 17 | SEQ ID NO: 192 |
| MYT3603 | SEQ ID NO: 17 | SEQ ID NO: 193 |
| MYT3604 | SEQ ID NO: 194 | SEQ ID NO: 193 |
| MYT3605 | SEQ ID NO: 195 | SEQ ID NO: 193 |
| MYT3606 | SEQ ID NO: 196 | SEQ ID NO: 193 |
| MYT3607 | SEQ ID NO: 197 | SEQ ID NO: 193 |
| MYT3608 | SEQ ID NO: 198 | SEQ ID NO: 193 |
| MYT3609 | SEQ ID NO: 199 | SEQ ID NO: 193 |
| MYT3610 | SEQ ID NO: 200 | SEQ ID NO: 193 |
| MYT3611 | SEQ ID NO: 31 | SEQ ID NO: 193 |
| MYT3612 | SEQ ID NO: 201 | SEQ ID NO: 193 |
| MYT3613 | SEQ ID NO: 202 | SEQ ID NO: 193 |
| MYT3614 | SEQ ID NO: 203 | SEQ ID NO: 193 |
| MYT3615 | SEQ ID NO: 17 | SEQ ID NO: 193 |
| MYT3616 | SEQ ID NO: 204 | SEQ ID NO: 193 |
| MYT4211 | SEQ ID NO: 17 | SEQ ID NO: 205 |
| MYT4212 | SEQ ID NO: 17 | SEQ ID NO: 206 |
| MYT4213 | SEQ ID NO: 17 | SEQ ID NO: 207 |
| MYT4214 | SEQ ID NO: 17 | SEQ ID NO: 208 |
| MYT4215 | SEQ ID NO: 17 | SEQ ID NO: 209 |
| MYT4216 | SEQ ID NO: 17 | SEQ ID NO: 210 |
| MYT4217 | SEQ ID NO: 17 | SEQ ID NO: 211 |
| MYT4218 | SEQ ID NO: 17 | SEQ ID NO: 212 |
| MYT4219 | SEQ ID NO: 17 | SEQ ID NO: 213 |
| MYT4220 | SEQ ID NO: 17 | SEQ ID NO: 214 |
| MYT2319 | SEQ ID NO: 19 | SEQ ID NO: 12 |
| MYT3978 | SEQ ID NO: 15 | SEQ ID NO: 20 |

FIG. 5

| | | |
|---|---|---|
| MYT2850 | SEQ ID NO: 11 | SEQ ID NO: 12 |
| MYT2861 | SEQ ID NO: 13 | SEQ ID NO: 12 |
| MYT4326 | SEQ ID NO: 15 | SEQ ID NO: 16 |
| MYT3999 | SEQ ID NO: 19 | SEQ ID NO: 215 |
| MYT4001 | SEQ NO: 11 | SEQ ID NO: 215 |
| MYT4007 | SEQ ID NO: 13 | SEQ ID NO: 215 |
| MYT4010 | SEQ ID NO: 19 | SEQ ID NO: 20 |
| MYT4011 | SEQ ID NO: 216 | SEQ ID NO: 20 |
| MYT4012 | SEQ ID NO: 11 | SEQ ID NO: 20 |
| MYT4013 | SEQ ID NO: 25 | SEQ ID NO: 20 |
| MYT4014 | SEQ ID NO: 217 | SEQ ID NO: 20 |
| MYT4015 | SEQ ID NO: 218 | SEQ ID NO: 20 |
| MYT4016 | SEQ ID NO: 219 | SEQ ID NO: 20 |
| MYT4017 | SEQ ID NO: 220 | SEQ ID NO: 20 |
| MYT4018 | SEQ ID NO: 13 | SEQ ID NO: 20 |
| MYT4019 | SEQ ID NO: 221 | SEQ ID NO: 20 |
| MYT4020 | SEQ ID NO: 222 | SEQ ID NO: 20 |
| MYT4021 | SEQ ID NO: 19 | SEQ ID NO: 223 |
| MYT4023 | SEQ ID NO: 11 | SEQ ID: NO: 223 |
| MYT4029 | SEQ ID NO: 13 | SEQ ID NO: 223 |
| MYT4032 | SEQ ID NO: 19 | SEQ ID NO: 224 |
| MYT4034 | SEQ ID NO: 11 | SEQ ID NO: 224 |
| MYT4040 | SEQ ID NO: 13 | SEQ ID NO: 224 |
| MYT4230 | SEQ ID NO: 225 | SEQ ID NO: 226 |
| MYT3698 | SEQ ID NO: 5 | SEQ ID NO: 8 |
| MYT3701 | SEQ ID NO: 21 | SEQ ID NO: 8 |
| MYT3735 | SEQ ID NO: 163 | SEQ ID NO: 22 |
| MYT3740 | SEQ ID NO: 163 | SEQ ID NO: 6 |
| MYT4313 | SEQ ID NO: 7 | SEQ ID NO: 8 |
| MYT4325 | SEQ ID NO: 9 | SEQ ID NO: 10 |
| MYT4247 | SEQ ID NO: 163 | SEQ ID NO: 24 |
| MYT5342 | SEQ ID NO: 227 | SEQ ID NO: 22 |
| MYT5343 | SEQ ID NO: 5 | SEQ ID NO: 22 |
| MYT5344 | SEQ ID NO: 21 | SEQ ID NO: 22 |
| MYT5345 | SEQ ID NO: 228 | SEQ ID NO: 22 |
| MYT5346 | SEQ ID NO: 229 | SEQ ID NO: 22 |
| MYT5347 | SEQ ID NO: 230 | SEQ ID NO: 22 |
| MYT5348 | SEQ ID NO: 231 | SEQ ID NO: 22 |
| MYT5349 | SEQ ID NO: 9 | SEQ ID NO: 22 |
| MYT5350 | SEQ ID NO: 227 | SEQ ID NO: 6 |
| MYT5351 | SEQ ID NO: 5 | SEQ ID NO: 6 |
| MYT5352 | SEQ ID NO: 21 | SEQ ID NO: 6 |
| MYT5353 | SEQ ID NO: 228 | SEQ ID NO: 6 |
| MYT5354 | SEQ ID NO: 229 | SEQ ID NO: 6 |
| MYT5355 | SEQ ID NO: 230 | SEQ ID NO: 6 |
| MYT5356 | SEQ ID NO: 231 | SEQ ID NO: 6 |

**FIG. 5 (CONT)**

| | | |
|---|---|---|
| MYT5357 | SEQ ID NO: 9 | SEQ ID NO: 6 |
| MYT5359 | SEQ ID NO: 5 | SEQ ID NO: 232 |
| MYT5360 | SEQ ID NO: 21 | SEQ ID NO: 232 |
| MYT5365 | SEQ ID NO: 9 | SEQ ID NO: 232 |
| MYT5366 | SEQ ID NO: 227 | SEQ ID NO: 24 |
| MYT5367 | SEQ ID NO: 5 | SEQ ID NO: 24 |
| MYT5368 | SEQ ID NO: 21 | SEQ ID NO: 24 |
| MYT5369 | SEQ ID NO: 228 | SEQ ID NO: 24 |
| MYT5370 | SEQ ID NO: 229 | SEQ ID NO: 24 |
| MYT5371 | SEQ ID NO: 230 | SEQ ID NO: 24 |
| MYT5372 | SEQ ID NO: 231 | SEQ ID NO: 24 |
| MYT5373 | SEQ ID NO: 9 | SEQ ID NO: 24 |
| MYT5375 | SEQ ID NO: 5 | SEQ ID NO: 233 |
| MYT5376 | SEQ ID NO: 21 | SEQ ID NO: 233 |
| MYT5381 | SEQ ID NO: 9 | SEQ ID NO: 233 |
| MYT4894 | SEQ ID NO: 159 | SEQ ID NO: 160 |
| MYT4970 | SEQ ID NO: 234 | SEQ ID NO: 160 |
| MYT3617 | SEQ ID NO: 225 | SEQ ID NO: 235 |

**FIG. 5 (CONT)**

| Candidate Name | Protein yield after purification from 50mL culture (mg) | Fold-change from corresponding control antibody in Internalization Assay (24h, 10nM antibody, Detroit 562 Cells) |
|---|---|---|
| MYT4826 | 0.52 | 5.00 |
| MYT4827 | 0.53 | 4.49 |
| MYT4837 | 0.54 | 4.22 |
| MYT4325 | 0.75 | 4.19 |
| MYT5351 | 0.33 | 3.82 |
| MYT4312 | 0.29 | 3.81 |
| MYT5309 | 0.42 | 3.52 |
| MYT4849 | 1.68 | 3.06 |
| MYT4888 | 0.40 | 3.01 |
| MYT5344 | 1.21 | 2.96 |
| MYT4313 | 0.58 | 2.94 |
| MYT5367 | 0.22 | 2.86 |
| MYT4942 | 0.73 | 2.03 |
| MYT4953 | 1.26 | 1.95 |
| MYT4940 | 0.57 | 1.79 |

FIG. 6

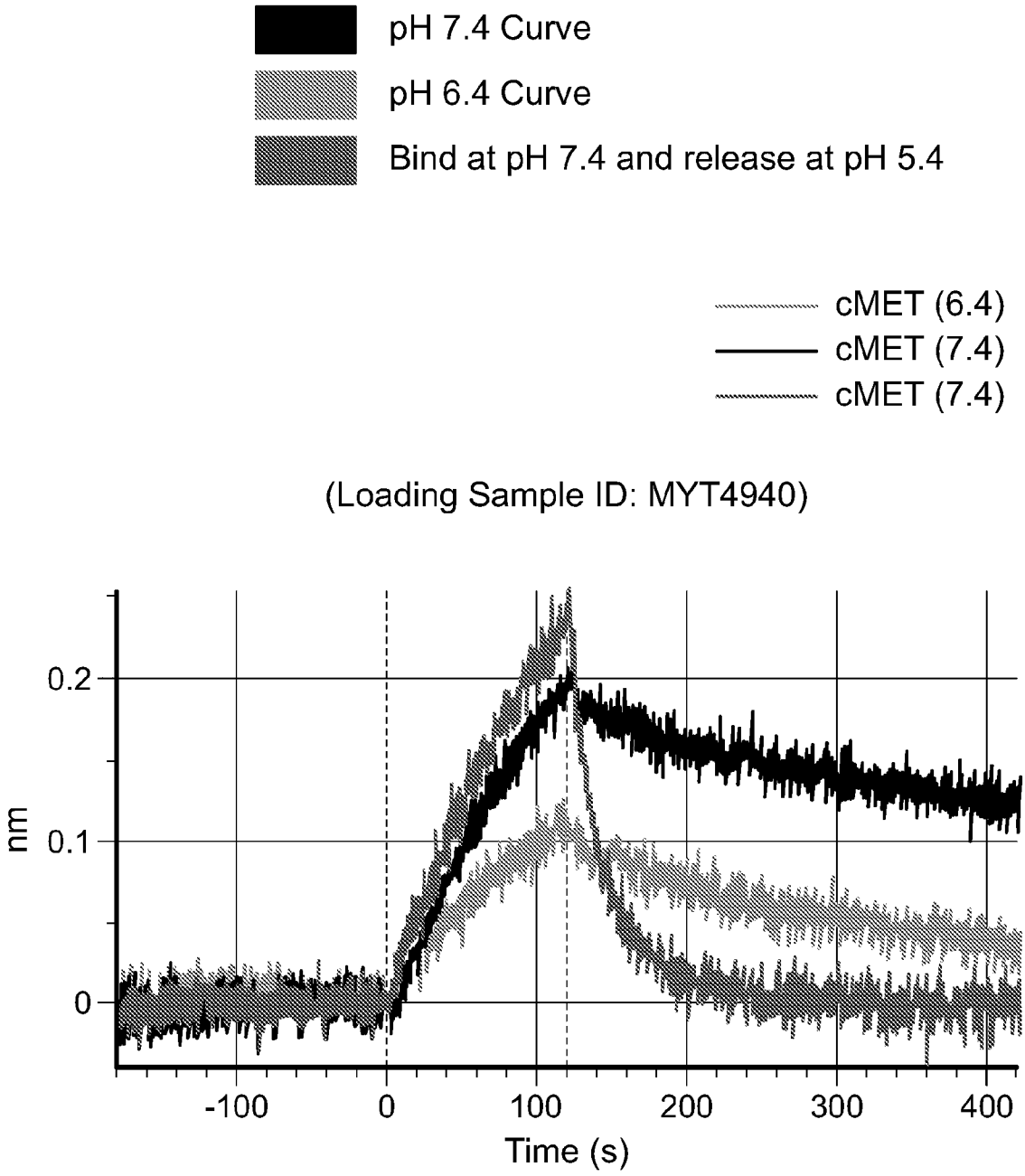

pH 7.4 Curve
pH 6.4 Curve
Bind at pH 7.4 and release at pH 5.4
cMET (6.4)
cMET (7.4)
cMET (7.4)
(Loading Sample ID: MYT4940)
nm
0.2
0.1
0
-100
0
100
200
300
400
Time (s)

FIG. 7A

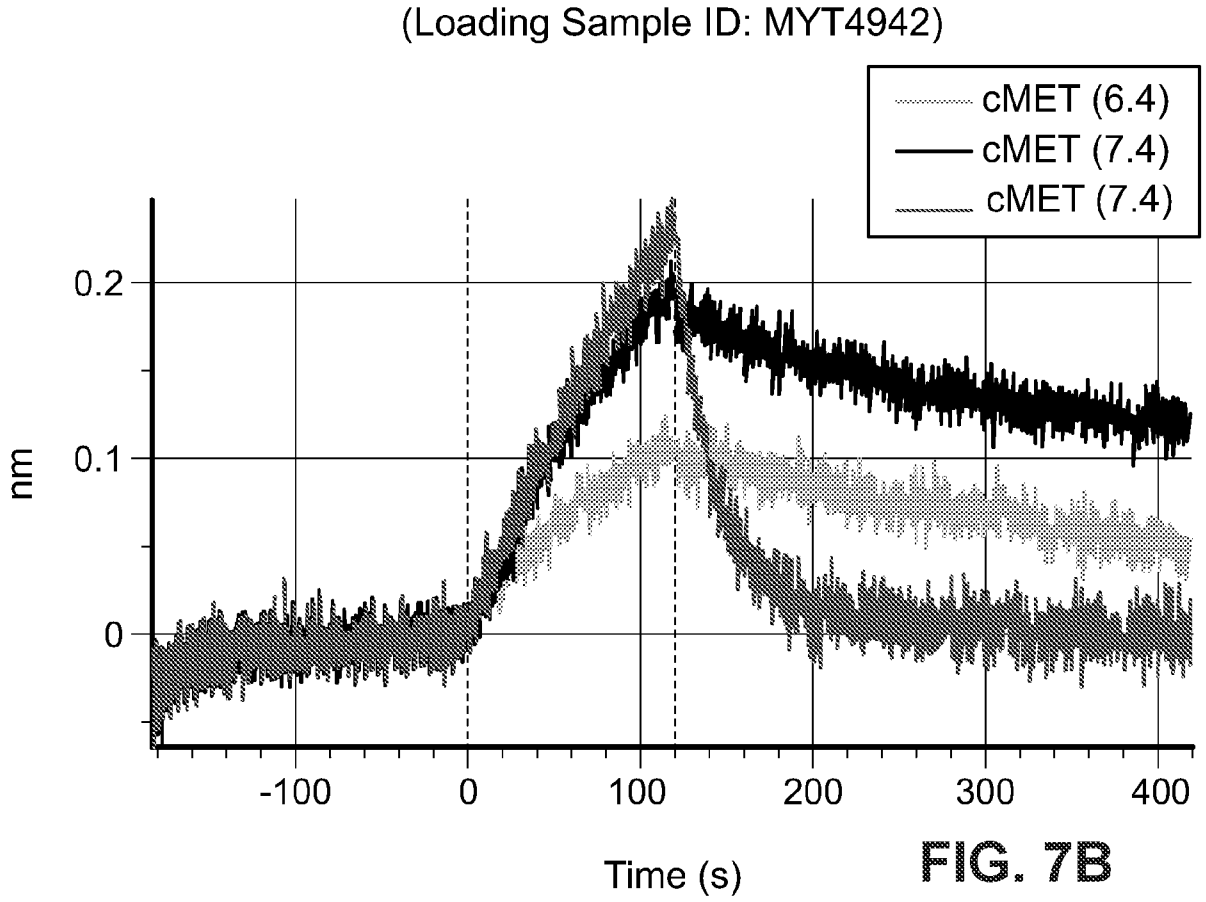

(Loading Sample ID: MYT4942)
cMET (6.4)
cMET (7.4)
cMET (7.4)
nm
0.2
0.1
0
-100
0
100
200
300
400
Time (s)

FIG. 7B

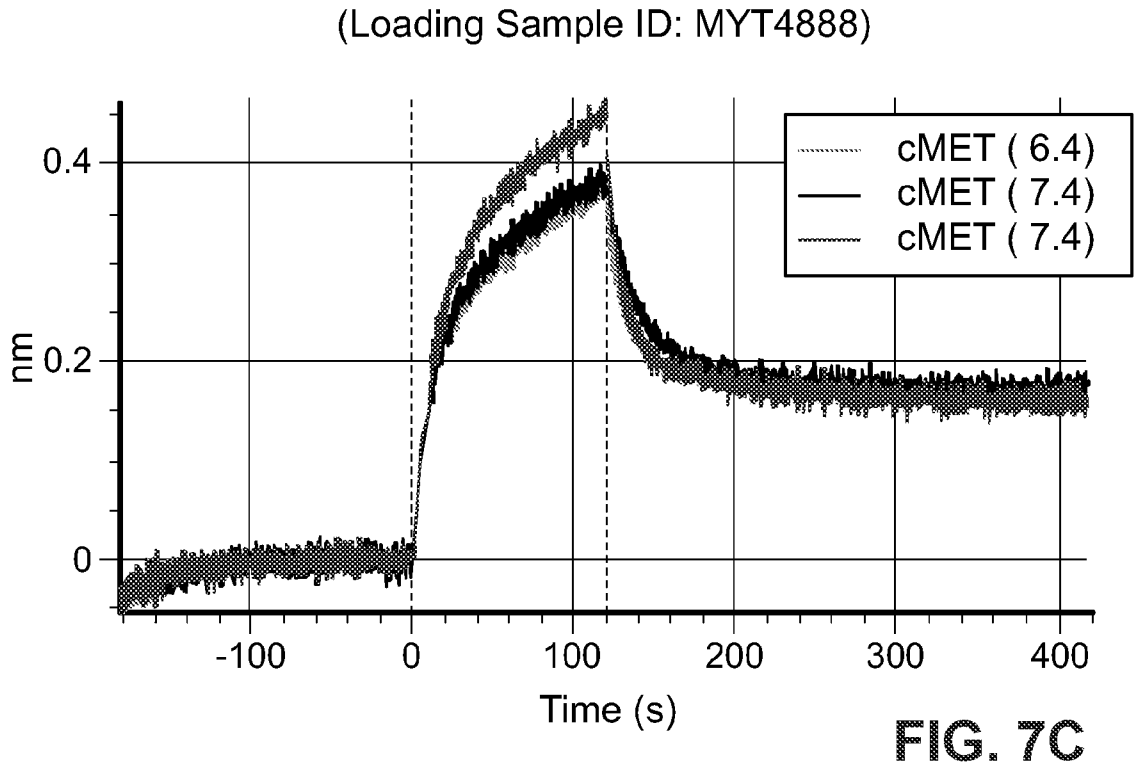

(Loading Sample ID: MYT4888)
cMET ( 6.4)
cMET ( 7.4)
cMET ( 7.4)
nm
0.4
0.2
0
-100
0
100
200
300
400
Time (s)

FIG. 7C

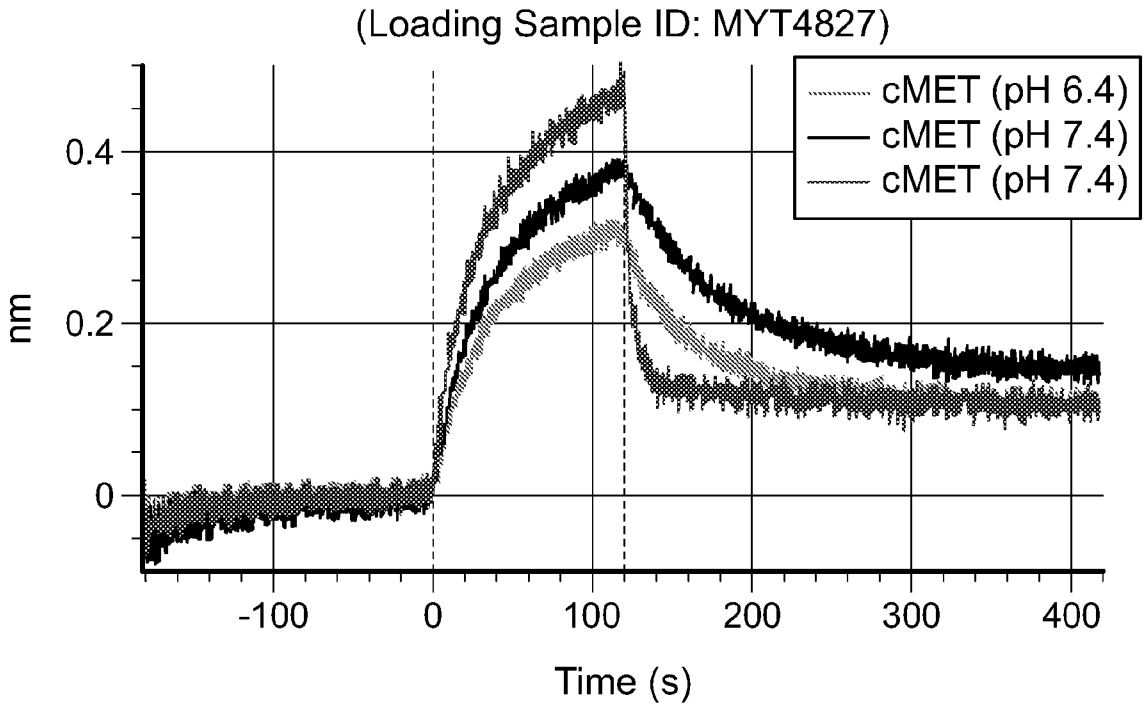

(Loading Sample ID: MYT4827)
cMET (pH 6.4)
cMET (pH 7.4)
cMET (pH 7.4)
nm
0.4
0.2
0
-100
0
100
200
300
400
Time (s)

FIG. 7D

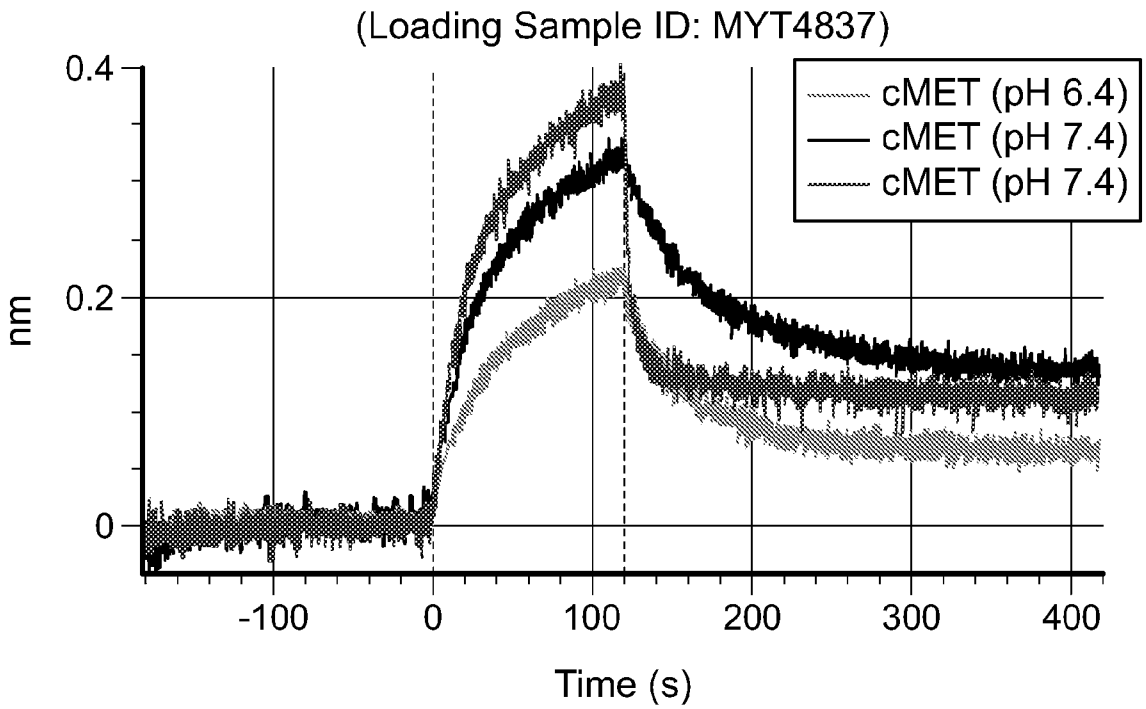

(Loading Sample ID: MYT4837)
cMET (pH 6.4)
cMET (pH 7.4)
cMET (pH 7.4)
nm
0.4
0.2
0
-100
0
100
200
300
400
Time (s)

FIG. 7E

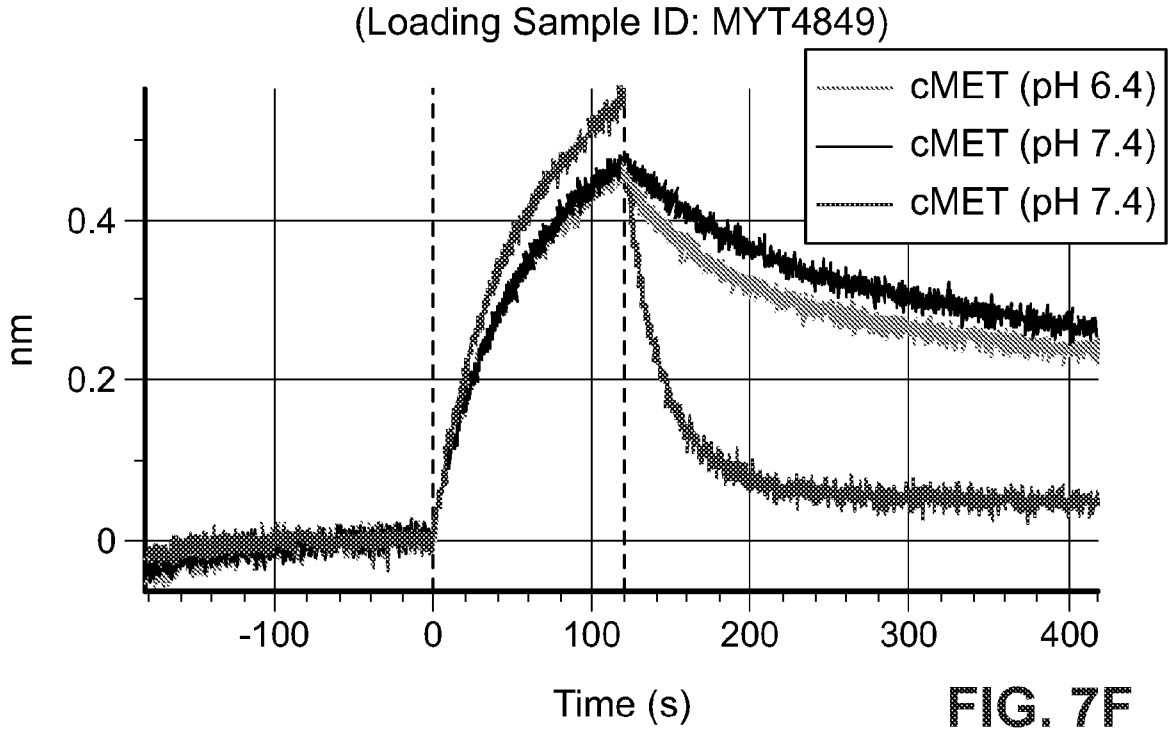

(Loading Sample ID: MYT4849)
cMET (pH 6.4)
cMET (pH 7.4)
cMET (pH 7.4)
nm
0.4
0.2
0
-100
0
100
200
300
400
Time (s)

FIG. 7F

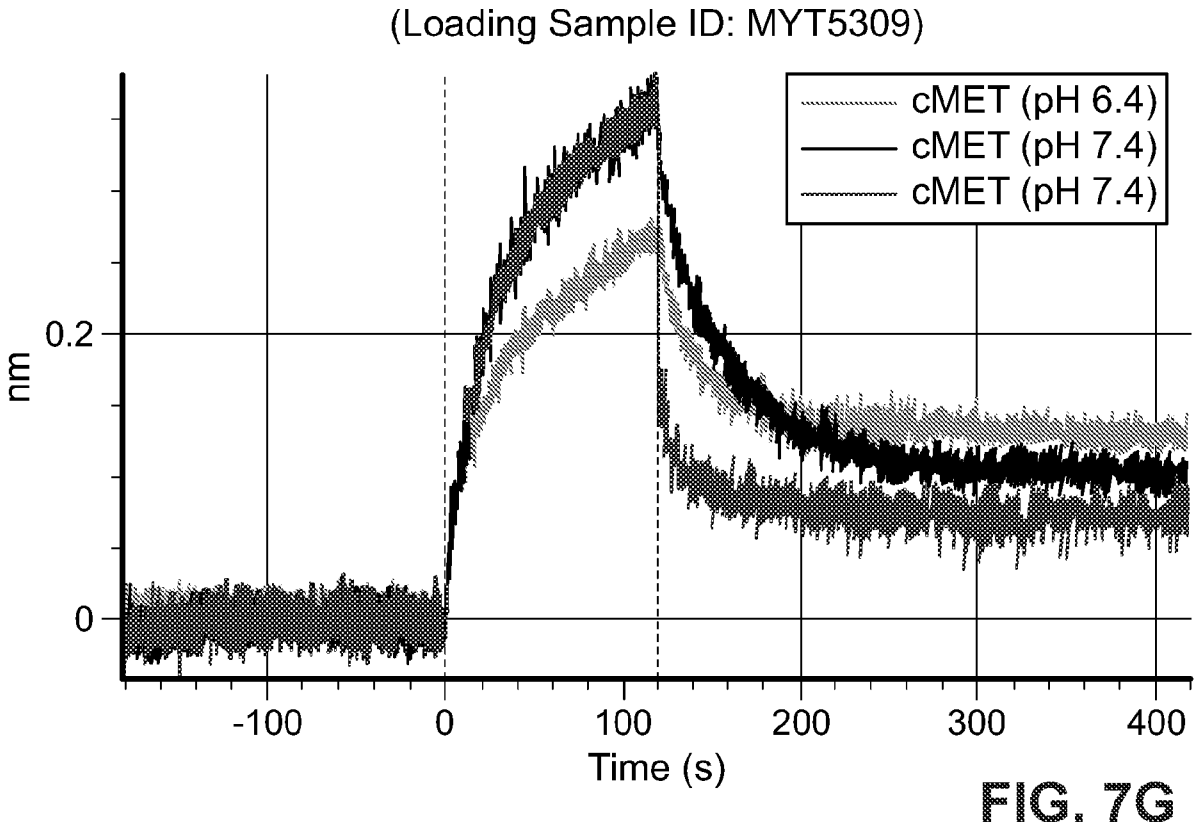

(Loading Sample ID: MYT5309)
cMET (pH 6.4)
cMET (pH 7.4)
cMET (pH 7.4)
nm
0.2
0
-100
0
100
200
300
400
Time (s)

FIG. 7G

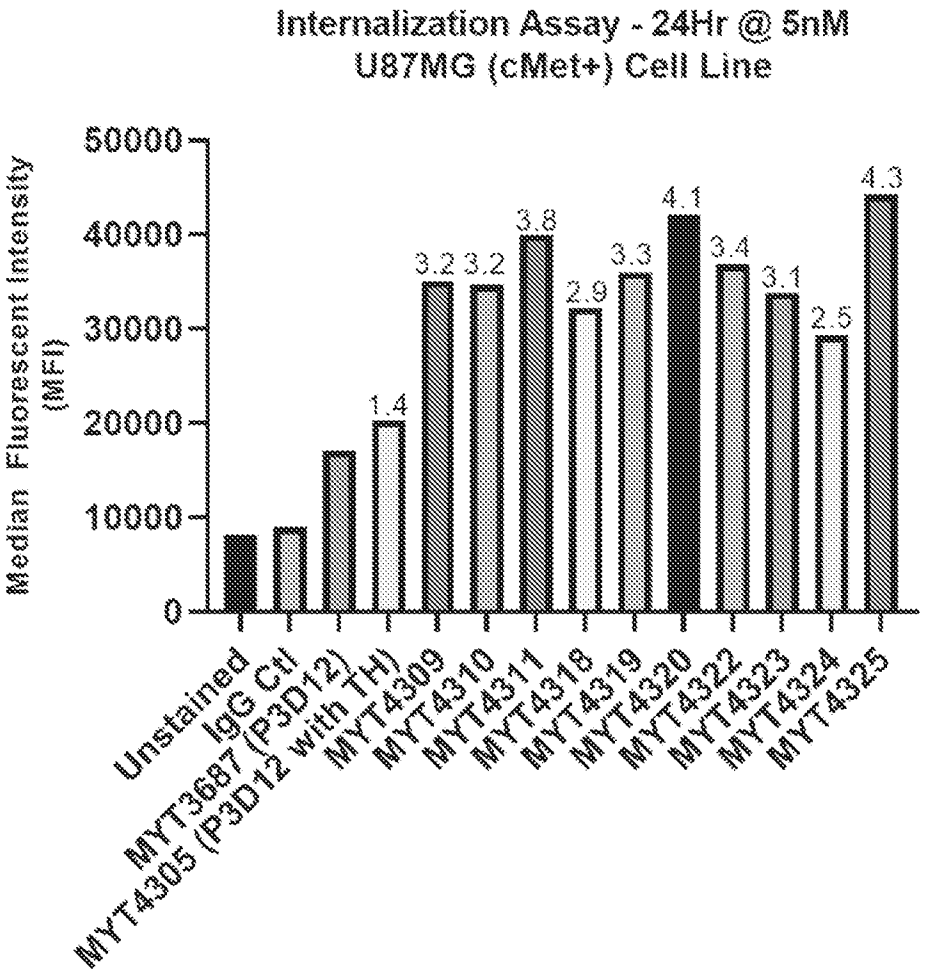

Internalization Assay - 24Hr @ 5nM
U87MG (cMet+) Cell Line
Median Fluorescent Intensity (MFI)
50000
40000
30000
20000
10000
0
1.4
3.2
3.2
3.8
2.9
3.3
4.1
3.4
3.1
2.5
4.3
Unstained
IgG Ctl
MYT3687 (P3D12)
MYT4305 (P3D12 with TH)
MYT4309
MYT4310
MYT4311
MYT4318
MYT4319
MYT4320
MYT4322
MYT4323
MYT4324
MYT4325

FIG. 1B