CLAIMS

What is claimed is:

1. An isolated meditope-enabled antibody or fragment thereof, comprising: a heavy chain variable (VH) region and a light chain variable (VL) region, wherein:

the VL region has an amino acid sequence comprising a threonine, serine, or aspartate at position 40, a residue other than glycine at position 41, and an aspartate or asparagine at position 85, according to Kabat numbering;

the antibody or fragment does not specifically bind to the epitope of EGFR that is specifically bound by cetuximab; and

the antibody or fragment binds to a meditope, which meditope is a peptide having an amino acid sequence selected from the group consisting of the sequences set forth in SEQ ID NO: 1, 2, 16-18, 23, 29, 31, 32, 36, 39, 42, 43, 45, 46, 51, 52, 54, or 55, or a cyclic peptide derived therefrom.

2. The meditope-enabled antibody or fragment of claim 1, wherein the VH region has an amino acid sequence comprising a serine or proline at position 40 and an isoleucine, tyrosine, methionine, phenylalanine, or tryptophan at position 89, according to Kabat numbering.

3. The meditope-enabled antibody or fragment of claim 1 or 2, wherein the amino acid sequence of the VL region further comprises an isoleucine or leucine at position 10 and isoleucine at position 83, according to Kabat numbering.

4. The meditope-enabled antibody or fragment of any of claims 1-3, wherein the amino acid sequence of the VL region further comprises a valine or isoleucine at position 9 and a residue other than glutamine at position 100, according to Kabat numbering.

5. The meditope-enabled antibody or fragment of any of claims 1-4, wherein the amino acid sequence of the VL region has a threonine at position 40, an asparagine at position 41, and an aspartate at position 85, according to Kabat numbering.

6. The antibody or fragment of any of claims 1-5, wherein the amino acid sequence of the VH region has a serine at position 40 and an isoleucine at position 89, according to Kabat numbering.

7. The antibody or fragment thereof of any of claims 1-6, wherein:

the amino acid sequence of the VL region has a valine or isoleucine at position 9, an isoleucine or leucine at position 10, an arginine at position 39, a threonine at position 40, an asparagine at position 41, a glycine at position 42, a serine at position 43, an isoleucine at position 83, an aspartate at position 85, and an alanine at position 100, according to Kabat numbering; and

the amino acid sequence of the VH region has a serine at position 40 and an isoleucine at position 89, according to Kabat numbering.

8. An isolated antibody or fragment thereof, comprising: a heavy chain variable (VH) region and a light chain variable (VL) region, wherein:

the VL region has an amino acid sequence comprising a light chain framework region (FR) 1 (FR-L1), an FR-L2, an FR-L3, and an FR-L4 of the light chain sequence set forth in SEQ ID NO: 71 or SEQ ID NO: 61, and at least one CDR that is distinct from the CDRs of the light chain sequence set forth in SEQ ID NO: 71; and

the VH region has an amino acid sequence having a heavy chain FR1 (FR-H1), an FR-H2, an FR-H3, and an FR-H4, of the heavy chain sequence set forth in SEQ ID NO: 72 or SEQ ID NO: 63, and at least one CDR that is distinct from the CDRs of the heavy chain sequence set forth in SEQ ID NO: 72.

9. The antibody or fragment of claim 8, wherein:

the at least one CDR that is distinct from the CDRS of the light chain sequence set forth in SEQ ID NO: 71 includes a CDR of the light chain sequence set forth in SEQ ID NO: 61; and

the at least one CDR that is distinct from the CDRS of the heavy chain sequence set forth in SEQ ID NO: 72 includes a CDR of the heavy chain sequence set forth in SEQ ID NO: 63.

10. The antibody or fragment of claim 8, wherein the VL comprises the amino acid sequence of SEQ ID NO: 76 and the VH comprises the amino acid sequence of SEQ ID NO: 77.

11. An isolated antibody or fragment thereof, comprising: a heavy chain variable (VH) region and a light chain variable (VL) region, wherein:

the VL region has an amino acid sequence comprising a light chain framework region (FR) 1 (FR-L1), an FR-L2, an FR-L3, and an FR-L4 of the light chain sequence set forth in SEQ ID NO: 9; and

the VH region has an amino acid sequence having a heavy chain FR1 (FR-H1), an FR-H2, an FR-H3, and an FR-H4 of the heavy chain sequence set forth in SEQ ID NO: 6.

12. The antibody or fragment thereof of claim 11, wherein:

the VL region comprises at least one complementarity determining region (CDR) that is distinct from the CDRs of the VL sequence set forth in SEQ ID NO: 9; and

the VH region comprises at least one CDR that is distinct from the CDRs of the VH sequence set forth in SEQ ID NO: 6.

13. The antibody of claim 11, wherein:

the VL region comprises the amino acid sequence of SEQ ID NO: 73; and

the VH region comprises the amino acid sequence of SEQ ID NO: 74.

14. An isolated antibody or fragment thereof, comprising: a heavy chain variable (VH) region and a light chain variable (VL) region, wherein:

the VL region has an amino acid sequence comprising a light chain framework region (FR) 1 (FR-L1), an FR-L2, an FR-L3, and an FR-L4 of the light chain sequence set forth in SEQ ID NO: 68.

15. The antibody or fragment thereof of claim 14, wherein:

the VL region comprises at least one complementarity determining region (CDR) that is distinct from the CDRs of the light chain sequence set forth in SEQ ID NO: 69; and

the VH region comprises at least one CDR that is distinct from the CDRs of the heavy chain sequence set forth in SEQ ID NO: 70.

16. The antibody of claim 14, wherein the VL region comprises the amino acid sequence of SEQ ID NO: 75.

17. The antibody or fragment of any of claims 8-16, wherein the antibody or fragment binds to a meditope having an amino acid sequence selected from the group consisting of the sequences set forth in SEQ ID NO: 1, 2, 16-18, 23, 29, 31, 32, 36, 39, 42, 43, 45, 46, 51, 52, 54, or 55, or a cyclic peptide derived therefrom.

18. The antibody or fragment of any of claims 1-7 and 17, wherein the antibody or fragment binds to the meditope with a dissociation constant of less than 10 μM, as determined by surface plasmon resonance (SPR).

19. The antibody or fragment thereof of claim 18, wherein the dissociation constant is less than 5 μM.

20. The antibody or fragment of claim 19, wherein the dissociation constant is less than 2 μM.

21. The antibody or fragment of any of claims 1-7 and 17-20, wherein the meditope is a cyclic peptide derived from a peptide of the amino acid sequence set forth in SEQ ID NO: 1 or 2.

22. An isolated antibody or fragment thereof, comprising: a heavy chain variable (VH) region and a light chain variable (VL) region, wherein:

the antibody binds to a meditope with a dissociation constant of less than 10 μM, as determined by SPR, wherein the meditope is a cyclic peptide derived from a peptide having an amino acid sequence of SEQ ID NO: 1 or 2; and

the antibody does not specifically bind to the epitope of an EGFR that is specifically bound by cetuximab.

23. The antibody or fragment of claim 22, wherein the VL region does not contain a P at position 40, a G at position 41, or a T at position 85, according to Kabat numbering, and the VH region does not contain an N or A at position 40 or a V at position 89, according to Kabat numbering.

24. The antibody or fragment thereof of claim 22 or 23, wherein the VL region does not contain an S at position 10, a P at position 40, a G at position 41, an F at position 83, or a T at position 85, according to Kabat numbering, and the VH region does not contain an N or A at position 40 or a V at position 89, according to Kabat numbering.

25. The antibody or fragment thereof of any of claims 1-24, further comprising a human constant region.

26. The antibody or fragment thereof of any of claims 1-25, wherein the antibody or fragment competes for antigen binding with or binds to the same epitope as an antibody or antibody fragment selected from the group consisting of abagovomab, abciximab, adalimumab, adecatumumab, alemtuzumab, altumomab, altumomab pentetate, anatumomab, anatumomab mafenatox, arcitumomab, atlizumab, basiliximab, bectumomab, ectumomab, belimumab, benralizumab, bevacizumab, brentuximab, canakinumab, capromab, capromab pendetide, catumaxomab, certolizumab, clivatuzumab tetraxetan, daclizumab, denosumab, eculizumab, edrecolomab, efalizumab, etaracizumab, ertumaxomab, fanolesomab, Fbta05, fontolizumab, gemtuzumab, girentuximab, golimumab, ibritumomab, igovomab, infliximab, ipilimumab, labetuzumab, mepolizumab, muromonab, muromonab-CD3, natalizumab, necitumumab nimotuzumab, ofatumumab, omalizumab, oregovomab, palivizumab, panitumumab, ranibizumab, rituximab, satumomab, sulesomab, ibritumomab, ibritumomab tiuxetan, tocilizumab, tositumomab, trastuzumab, Trbs07, ustekinumab, visilizumab, votumumab, zalutumumab, brodalumab, anrukinzumab, bapineuzumab, dalotuzumab, demcizumab, ganitumab, inotuzumab, mavrilimumab, moxetumomab pasudotox, rilotumumab, sifalimumab, tanezumab, tralokinumab, tremelimumab, the antibody produced by the hybridoma 10B5, and urelumab.

27. The antibody or fragment thereof of any of claims 1-25, wherein the antibody or fragment contains at least one complementarity determining region (CDR) of an antibody or antibody fragment selected from the group consisting of: abagovomab, abciximab, adalimumab, adecatumumab, alemtuzumab, altumomab, altumomab pentetate, anatumomab, anatumomab mafenatox, arcitumomab, atlizumab, basiliximab, bectumomab, ectumomab, belimumab, benralizumab, bevacizumab, brentuximab, canakinumab, capromab, capromab pendetide, catumaxomab, certolizumab, clivatuzumab tetraxetan, daclizumab, denosumab,

eculizumab, edrecolomab, efalizumab, etaracizumab, ertumaxomab, fanolesomab, Fbta05, fontolizumab, gemtuzumab, girentuximab, golimumab, ibritumomab, igovomab, infliximab, ipilimumab, labetuzumab, mepolizumab, muromonab, muromonab-CD3, natalizumab, necitumumab, nimotuzumab, ofatumumab, omalizumab, oregovomab, palivizumab, panitumumab, ranibizumab, rituximab, satumomab, sulesomab, ibritumomab, ibritumomab tiuxetan, tocilizumab, tositumomab, Trbs07, ustekinumab, visilizumab, votumumab, zalutumumab, brodalumab, anrukinzumab, bapineuzumab, dalotuzumab, demcizumab, ganitumab, inotuzumab, mavrilimumab, moxetumomab pasudotox, rilotumumab, sifalimumab, tanezumab, tralokinumab, tremelimumab, the antibody produced by the hybridoma 10B5, and urelumab.

28. The antibody or fragment of claim 27, wherein the at least one CDR includes a heavy chain CDR 1, 2, and 3 and a light chain CDR1, 2, and 3.

29. The antibody or fragment thereof of any of claims 1-28, wherein the antibody or fragment specifically binds to an antigen selected from the group consisting of: CA-125, glycoprotein (GP) IIb/IIIa receptor, TNF-alpha, CD52, TAG-72, Carcinoembryonic antigen (CEA), interleukin-6 receptor (IL-6R), IL-2, interleukin-2 receptor a-chain (CD25), CD22, B-cell activating factor, interleukin-5 receptor (CD125), VEGF, VEGF-A, CD30, IL-1beta, prostate specific membrane antigen (PSMA), CD3, EpCAM, EGF receptor (EGFR), MUC1, human interleukin-2 receptor, Tac, RANK ligand, C5 or other complement proteins, EpCAM, CD11a, , alpha-v beta-3 integrin, vitronectin receptor alpha v beta 3 integrin, HER2, neu, CD3, CD15, CD20, Interferon gamma, CD33, CA-IX, TNF alpha, CTLA-4, carcinoembryonic antigen, IL-5, CD3 epsilon, CAM, Alpha-4-integrin, IgE, IgE Fc region, an RSV antigen, F (or fusion) protein of respiratory syncytial virus (RSV), TAG-72, NCA-90(granulocyte cell antigen), IL-6, GD2, GD3, IL-12, IL-23, IL-17, CTLA16.88, IL13, interleukin-1 beta, beta-amyloid, IGF-1 receptor (IGF-1R), delta-like ligand 4 (DLL4), , alpha subunit of granulocyte macrophage colony stimulating factor receptor, hepatocyte growth factor, IFN-alpha, nerve growth factor, IL-13, CD326, PD-L1), CD47, and CD137.

30. The antibody or fragment thereof of any of claims 1-29, wherein the antibody has a light chain having P8 , V9 or I9, I10 or L10, Q38, R39, T40, N41 G42, S43, P44, R45, D82, I83, A84, D85, Y86, Y87, G99, A100, G101, T102, K103, L104, E105, R142, S162, V163, T164, E165, Q166, D167, S168, and Y173, according to Kabat numbering, and a

heavy chain having Q6, P9, R38, Q39, S40, P41, G42, K43, G44, L45, S84, D86, T87, A88, I89, Y90, Y91, W103, G104, Q105, G106, T107, L108, V111, T110, Y147, E150, P151, V152, T173, F174, P175, A176, V177, Y185, S186, and L187, according to Kabat numbering.

31. A complex, comprising the antibody of any of claims 1-30 bound to a meditope.

32. An isolated meditope, comprising a peptide that binds to a meditope binding site of a meditope-enabled antibody, wherein the peptide is not a peptide of SEQ ID NO: 1 or 2 or cyclic peptide derived therefrom.

33. The meditope of claim 32, wherein the peptide binds to the meditope binding site with a dissociation constant of less than 10 μM, as measured by surface plasmon resonance (SPR).

34. The meditope of claim 32 or 33, wherein the meditope binding site includes residues 40, 41, 83, and 85 of the light chain of the meditope-enabled antibody, according to Kabat numbering, and residues 39, 89, 105, and 108 of the heavy chain of the meditope-enabled antibody, according to Kabat numbering.

35. The meditope of any of claims 31-34, wherein the meditope binds to a meditope-enabled antibody having:

a light chain comprising an amino acid sequence set forth in SEQ ID NO: 71 and a heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 72;

a light chain having an amino acid sequence set forth in SEQ ID NO: 9 and a heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 6; or

a light chain having an amino acid sequence set forth in SEQ ID NO: 68 and a heavy chain having an amino acid sequence set forth in SEQ ID NO: 70.

36. The meditope of any of claims 32-35, wherein the peptide is between 5 and 16 amino acids in length.

37. The meditope of any of claims 32-36, wherein the peptide has the formula:

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12 (Formula I)

wherein:

X1 = Cys, Gly, β-alanine, diaminopropionic acid, β-azidoalanine, or null;

X2 = Gln or null;

X3 = Phe, Tyr, β-β'-diphenyl-Ala, His, Asp, 2-bromo-L-phenylalanine, 3-bromo-L-phenylalanine, or 4-bromo-L-phenylalanine, Asn, Gln, a modified Phe, a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X4 = Asp or Asn;

X5 = Leu; β-β'-diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X6 = Ser or Cys;

X7 = Thr or Ser or Cys;

X8 = Arg, a modified Arg, or a hydratable carbonyl or boronic acid-containing residue;

X9 = Arg, Ala;

X10 = Leu, Gln, Glu, β-β'-diphenyl-Ala; Phe; a non-natural analog of phenylalanine, tryptophan, or tyrosine; a hydratable carbonyl-containing residue; or a boronic acid-containing residue;

X11= Lys; and

X12 = Cys, Gly, 7-aminoheptanoic acid, β-alanine, diaminopropionic acid, propargylglycine, isoaspartic acid, or null,

wherein:

the modified Arg has a structure of the formula shown in Figure 34,

the modified Phe is a Phe with one or more halogen incorporated into the phenyl ring, and

formula I is not SEQ ID NO: 1 or SEQ ID NO: 2 or a cyclic peptide derived therefrom.

38. The meditope of any of claims 32-37, wherein the peptide is a cyclic peptide.

39. The meditope of claim 38, wherein the cyclization is by disulfide bridge, a thioether bridge, a lactam linkage, cycloaddition.

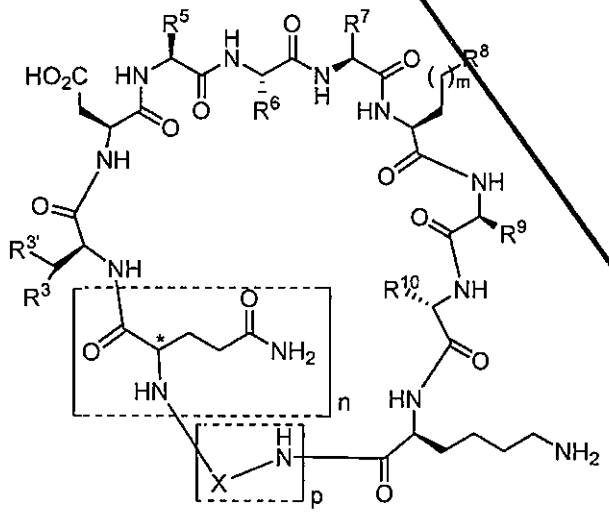
40. The meditope of claim 38 or 39, wherein the peptide is a peptide of Formula I and the cyclization is via a linkage between X1 and X12, X1 and X11, X3 and X11, X4 and X11, or X2 and X12.

41. The meditope of any of claims 37-40, wherein the peptide is a peptide of Formula I and the non-natural amino acid is β-β'-diphenyl-Ala, a branched alkyl, or an extended aromatic.

42. The peptide of any of claims 37-40, wherein the peptide is a peptide of Formula I and each of the one or more halogen is an ortho-, meta-, or para-bromo phenyl substituent.

43. The peptide of any of claims 32-42, wherein the peptide is a peptide having an amino acid selected from the group consisting of the sequences set forth in SEQ ID NO: 16-18, 23, 29, 31, 32, 36, 39, 42, 43, 45, 46, 51, 52, 54, or 55, or a cyclic peptide derived therefrom.

44. An isolated meditope, comprising the compound of Formula (X):



(X)

wherein:

the center marked with "*" is in the "R" or "S" configuration;

R^3 and $R^{3'}$ are each, independently, H or phenyl, optionally substituted with one, two, or three substituents independently selected from C_{1-4}alkyl, -OH, fluoro, chloro, bromo, and iodo;

R^5 is:

(A) C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, $-CO_2C_{1-4}$alkyl, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CONH_2$ group; or

(B) a C_{1-4}alkyl group substituted with:

a) one or two phenyl groups, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo; or

b) a naphthyl, imidazole, or indole group;

R^6 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

R^7 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

m is 0, 1, 2, 3, 4, or 5;

R^8 is:

(a) -OH, $-NR^aR^b$, $-N(R^c)C(O)R^e$, or $-N(R^c)C(=NR^d)R^e$;

wherein:

R^a is H;

R^b is H or C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, and ketal, $-B(OH)_2$, -SH, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, or $-CO_2C_{1-4}$alkyl group;

R^c is H, C_{1-8}alkyl, C_{3-8}cycloalkyl, branched alkyl, or aryl;

R^d is H or a C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, branched alkyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, halogen, oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CO_2C_{1-4}$alkyl group; and

R^e is H; $-NHR^d$; or a C_{1-12}alkyl, C_{3-8}cycloalkyl, C_{2-12}alkenyl, C_{2-8}alkynyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, oxo, C_{2-4}acetal, C_{2-4}ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, and $-CO_2C_{1-4}$alkyl group; or

(b) a C_{1-12} alkyl substituted with an oxo, acetal, ketal, $-B(OH)_2$, boronic ester, -SH, -OH, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-$C(O)C_{1-4}$alkyl, -CH=CH-CO_2C_{1-4}alkyl, or -CO_2C_{1-4}alkyl group;

R^9 is C_{1-4}alkyl or $-C_{1-2}$alkylene-R^x;

wherein R^x is -CO_2H, -$CONH_2$, -$CH_2NHC(O)NH_2$, or -$CH_2NHC(=NH)NH_2$;

R^{10} is:

(1) a C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-$C(O)C_{1-4}$alkyl, -CH=CH-CO_2C_{1-4}alkyl, -CO_2C_{1-4}alkyl, -CO_2H, and $-CONH_2$ group; or

(2) a C_{1-4}alkyl group substituted with one or two phenyl groups, or one naphthyl, imidazole, or indole group, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo;

n is 0 or 1;

p is 0 or 1;

X is C_{1-8}alkylene or C_{2-8}alkenylene, each carbon thereof optionally substituted with -CO_2H, -NH_2, or -$NHC(O)R^y$;

wherein one carbon of said alkylene is optionally replaced with -C(O)NH-, a 5-membered heteroaryl ring, or -S-S-; and

R^y is $-C_{1-4}$alkyl or $-CH(R^z)CO_2H$;

wherein R^z is –H or $-C_{1-4}$alkyl optionally substituted with –OH, -SH, or $-NH_2$;

or a pharmaceutically acceptable salt thereof,

wherein the compound is not a compound of SEQ ID NO: 1 or SEQ ID NO: 2.

45. The meditope of claim 44, wherein m is 0 or 1.

46. The meditope of claim 44, wherein R^3 is H or phenyl and R^3 is phenyl, 2-bromophenyl, 3-bromophenyl, or 4-bromophenyl.

47. The meditope of claim 44, wherein R^5 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or tert-butyl, each optionally substituted with one or more substituents selected from the group consisting of oxo, $-B(OH)_2$, -CO_2H, and

–$CONH_2$ group, or with one or two phenyl groups each optionally substituted with a bromo or chloro substituent.

48. The meditope of claim 44, wherein R^8 is -OH, -NH_2, -$N(R^c)C(O)R^e$, or -$N(R^c)C(=NR^d)R^e$.

49. The meditope of claim 48, wherein R^c is H or methyl, R^d is H or C_{1-4}alkyl, and R^e is C_{1-4}alkyl, or –$NH(C_{1-4}$alkyl).

50. The meditope of claim 44, wherein R^9 is methyl or ethyl, optionally substituted with -CO_2H, -$CONH_2$, -$CH_2NHC(O)NH_2$, or –$CH_2NHC(=NH)NH_2$.

51. The meditope of claim 44, wherein R^{10} is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, or tert-butyl, each optionally substituted with one or more substituents selected from the group consisting of oxo, -$B(OH)_2$, -CO_2H, and –$CONH_2$ group.

52. The meditope of claim 44, wherein –X-NH- is –Cys-Cys-, -Gly-Gly-, -$C(O)(CH_2)_6$-NH-, -β-Ala-β-Ala-, -$C(O)CH(NH_2)CH_2CH{=}CHCH_2CH(CO_2H)$-NH-, -$C(O)CH(NH_2)CH_2NHC(O)CH_2CH(CO_2H)$-NH-, -β-Ala-$C(O)CH_2CH(CO_2H)$-NH-, or –$C(O)CH(NH_2)CH_2$-triazinyl-$CH_2$-$CH(CO_2H)$-NH-.

53. A method for purifying a meditope-enabled antibody or fragment thereof, or a cell expressing the meditope-enabled antibody or fragment thereof, comprising:

(a) contacting a composition containing the meditope-enabled antibody, fragment, or cell with a meditope, under conditions whereby the meditope-enabled antibody or fragment binds to the peptide; and

(b) isolating the antibody or fragment or cell,

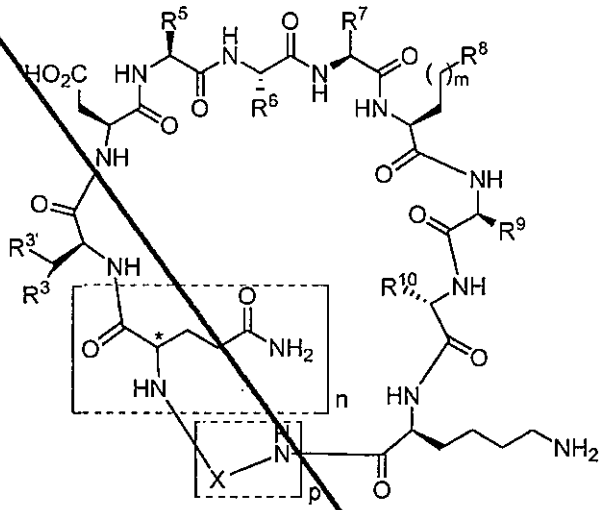
thereby purifying the antibody, fragment, or cell,

wherein the meditope is a peptide that binds to a meditope binding site of the meditope-enabled antibody.

54. The method of claim 53, wherein the peptide binds to the meditope binding site with a dissociation constant of less than 10 μM, as measured by surface plasmon resonance (SPR).

55. The method of claim 53 or 54, wherein the peptide is between 5 and 16 amino acids in length.

56. The method of any of claims 53-55, wherein the peptide is a peptide of Formula (X):



(X)

wherein:

the center marked with "*" is in the "R" or "S" configuration;

R^3 and $R^{3'}$ are each, independently, H or phenyl, optionally substituted with one, two, or three substituents independently selected from C_{1-4}alkyl, -OH, fluoro, chloro, bromo, and iodo;

R^5 is:

(A) C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, $-CO_2C_{1-4}$alkyl, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CONH_2$ group; or

(B) a C_{1-4}alkyl group substituted with:

a) one or two phenyl groups, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo; or

b) a naphthyl, imidazole, or indole group;

R^6 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

R^7 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

m is 0, 1, 2, 3, 4, or 5;

R^8 is:

(a) -OH, $-NR^aR^b$, $-N(R^c)C(O)R^c$, or $-N(R^c)C(=NR^d)R^c$;

wherein:

R^a is H;

R^b is H or C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, and ketal, $-B(OH)_2$, -SH, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, or $-CO_2C_{1-4}$alkyl group;

R^c is H, C_{1-8}alkyl, C_{3-8}cycloalkyl, branched alkyl, or aryl;

R^d is H or a C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, branched alkyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, halogen, oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CO_2C_{1-4}$alkyl group; and

R^e is H; $-NHR^d$; or a C_{1-12}alkyl, C_{3-8}cycloalkyl, C_{2-12}alkenyl, C_{2-8}alkynyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, oxo, C_{2-4}acetal, C_{2-4}ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, and $-CO_2C_{1-4}$alkyl group; or

(b) a C_{1-12} alkyl substituted with an oxo, acetal, ketal, $-B(OH)_2$, boronic ester, -SH, -OH, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, or $-CO_2C_{1-4}$alkyl group;

R^9 is C_{1-4}alkyl or $-C_{1-2}$alkylene-R^x;

wherein R^x is $-CO_2H$, $-CONH_2$, $-CH_2NHC(O)NH_2$, or $-CH_2NHC(=NH)NH_2$;

R^{10} is:

(1) a C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CONH_2$ group; or

(2) a C_{1-4}alkyl group substituted with one or two phenyl groups, or one naphthyl, imidazole, or indole group, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo;

n is 0 or 1;

p is 0 or 1;

X is C_{1-8}alkylene or C_{2-8}alkenylene, each carbon thereof optionally substituted with -CO_2H, -NH_2, or -$NHC(O)R^y$;

wherein one carbon of said alkylene is optionally replaced with -C(O)NH-, a 5-membered heteroaryl ring, or -S-S-; and

R^y is $-C_{1-4}$alkyl or $-CH(R^z)CO_2H$;

wherein R^z is –H or $-C_{1-4}$alkyl optionally substituted with –OH, -SH, or $-NH_2$;

or a pharmaceutically acceptable salt thereof.

57. The method of any of claims 53-56, wherein the meditope is coupled to a solid support.

58. The method of any of claims 53-57, wherein the isolation is effected by a change in pH.

59. A labeled meditope, comprising:

a meditope, comprising a peptide that binds to a meditope binding site of a meditope-enabled antibody; and

a therapeutic or diagnostic agent.

60. The labeled meditope of claim 59, wherein the therapeutic or diagnostic agent is selected from the group consisting of: a metal chelator bound to a metal ion, a small molecule, a chemotherapeutic agent, a therapeutic antibody or functional fragment, a toxin, a radioisotope, an enzyme, a nuclease, a hormone, an immunomodulator, an oligonucleotide, an organic or inorganic nanoparticle, an RNAi molecule, an siRNA, a chelator, a boron compound, a photoactive agent, a dye, fluorescent or luminescent substance, an enzyme, an enhancing agent, a radioactive substance, and a chelator.

61. A multivalent meditope, comprising two or more meditopes and one or more linker, wherein each of the two or more meditopes is a peptide that binds to a meditope binding site of a meditope-enabled antibody.

62. The multivalent meditope of claim 61, wherein the two or more meditopes comprise at least three meditopes.

63. The multivalent meditope of claim 61 or 62, wherein the one or more linker includes a peptide, a small chemical scaffold, a biotin-streptavidin, an organic or inorganic nanoparticle, a polynucleotide sequence, peptide nucleic acid, an organic polymer, or an immunoglobulin Fc domain.

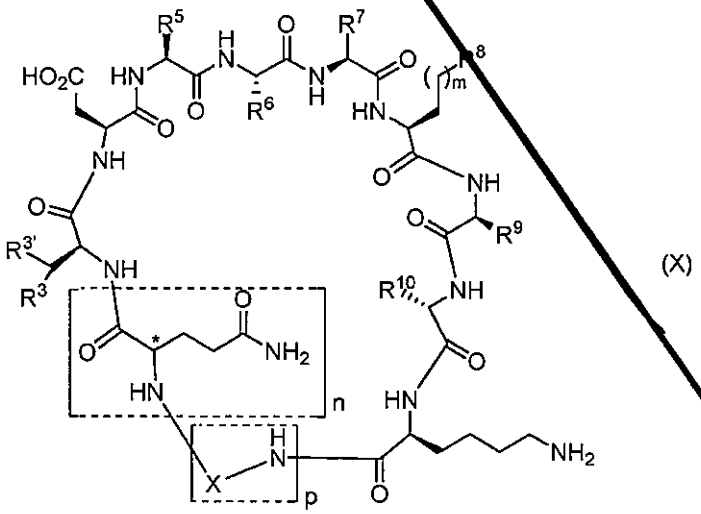
64. An isolated meditope-enabled antibody-meditope complex, comprising:

the antibody or fragment of anyone of claims 1 to 30, bound to a meditope, wherein the meditope comprises a peptide that binds to a meditope binding site of the antibody or fragment.

65. The complex of claim 64, wherein the peptide binds to the meditope binding site with a dissociation constant of less than 10 μM, as measured by surface plasmon resonance (SPR).

66. The complex of claim 64 or 65, wherein the peptide is between 5 and 16 amino acids in length.

67. The complex of any of claims 64-66, wherein the peptide is a compound of Formula (X):



(X)

wherein:

the center marked with "*" is in the "R" or "S" configuration;

R^3 and $R^{3'}$ are each, independently, H or phenyl, optionally substituted with one, two, or three substituents independently selected from C_{1-4}alkyl, -OH, fluoro, chloro, bromo, and iodo;

R^5 is:

(A) C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, $-CO_2C_{1-4}$alkyl, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CONH_2$ group; or

(B) a C_{1-4}alkyl group substituted with:

a) one or two phenyl groups, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo; or

b) a naphthyl, imidazole, or indole group;

R^6 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

R^7 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

m is 0, 1, 2, 3, 4, or 5;

R^8 is:

(a) -OH, $-NR^aR^b$, $-N(R^c)C(O)R^e$, or $-N(R^c)C(=NR^d)R^e$;

wherein:

R^a is H;

R^b is H or C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, and ketal, $-B(OH)_2$, -SH, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, or $-CO_2C_{1-4}$alkyl group;

R^c is H, C_{1-8}alkyl, C_{3-8}cycloalkyl, branched alkyl, or aryl;

R^d is H or a C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, branched alkyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, halogen, oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CO_2C_{1-4}$alkyl group; and

R^e is H; $-NHR^d$; or a C_{1-12}alkyl, C_{3-8}cycloalkyl, C_{2-12}alkenyl, C_{2-8}alkynyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, oxo, C_{2-4}acetal, C_{2-4}ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, and $-CO_2C_{1-4}$alkyl group; or

(b) a C_{1-12} alkyl substituted with an oxo, acetal, ketal, $-B(OH)_2$, boronic ester, -SH, -OH, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, or -CO_2C_{1-4}alkyl group;

R^9 is C_{1-4}alkyl or $-C_{1-2}$alkylene-R^x;

wherein R^x is $-CO_2H$, $-CONH_2$, $-CH_2NHC(O)NH_2$, or $-CH_2NHC(=NH)NH_2$;

R^{10} is:

(1) a C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, -CO_2C_{1-4}alkyl, $-CO_2H$, and $-CONH_2$ group; or

(2) a C_{1-4}alkyl group substituted with one or two phenyl groups, or one naphthyl, imidazole, or indole group, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo;

n is 0 or 1;

p is 0 or 1;

X is C_{1-8}alkylene or C_{2-8}alkenylene, each carbon thereof optionally substituted with $-CO_2H$, $-NH_2$, or -$NHC(O)R^y$;

wherein one carbon of said alkylene is optionally replaced with -C(O)NH-, a 5-membered heteroaryl ring, or -S-S-; and

R^y is $-C_{1-4}$alkyl or $-CH(R^z)CO_2H$;

wherein R^z is –H or $-C_{1-4}$alkyl optionally substituted with –OH, -SH, or $-NH_2$;

or a pharmaceutically acceptable salt thereof.

68. The complex of any of claims 64-67, wherein the meditope is a multivalent meditope.

69. An isolated antibody-meditope complex, comprising:

a meditope-enabled antibody or fragment thereof bound to a meditope of any of claims 31-50, the labeled meditope of claim 59 or 60, or the multivalent meditope of any of claims 61-63.

70. A pharmaceutical composition, comprising:

the complex of any of claims 64-69; and

a pharmaceutically acceptable carrier.

71. A method of treatment, comprising administering to a subject the pharmaceutical composition of claim 70.

72. A diagnostic method, comprising:

(a) administering to a subject the antibody-meditope complex of any of claims 64-69; and

(b) detecting binding of the antibody-meditope complex to an antigen in the subject.

73. A method of treatment, comprising: administering to a subject the antibody or fragment thereof of any of claims 1 to 30.

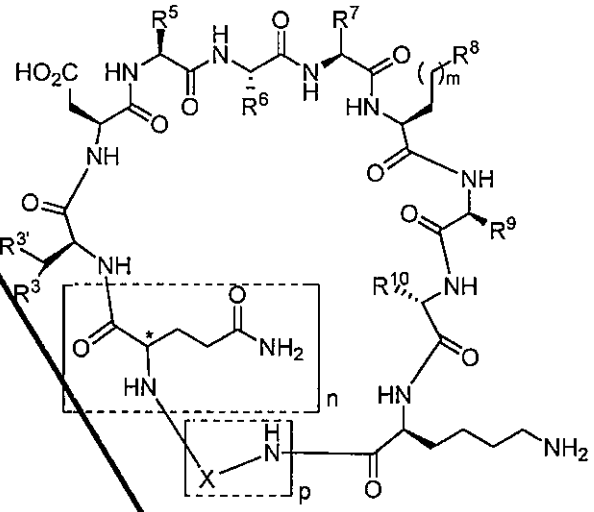
74. A method of treatment, comprising: administering to a subject a meditope-enabled antibody or fragment thereof and administering to the subject one or more meditope, wherein the meditope-enabled antibody or fragment and one or more meditope are administered sequentially or simultaneously and the one or more meditope comprises a peptide that binds to a meditope binding site of the meditope-enabled antibody or fragment.

75. The method of treatment of claim 74, wherein the meditope-enabled antibody or fragment comprises: a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VL region has an amino acid sequence comprising a threonine, serine, or aspartate at position 40, a residue other than glycine at position 41, and an aspartate or asparagine at position 85, according to Kabat numbering.

76. The method of claim 74 or 75, wherein the meditope-enabled antibody or fragment is bound to the one or more meditope, such that administration of the meditope-enabled antibody and the one or more meditope comprises administering a complex of the meditope-enabled antibody and the meditope.

77. The method of claim 74 or 75, wherein the meditope-enabled antibody is administered prior to administration of the one or more meditope.

78. The method of any of claims 74-77, wherein the peptide is a compound of Formula (X):



(X)

wherein:

the center marked with "*" is in the "R" or "S" configuration;

R^3 and $R^{3'}$ are each, independently, H or phenyl, optionally substituted with one, two, or three substituents independently selected from C_{1-4}alkyl, -OH, fluoro, chloro, bromo, and iodo;

R^5 is:

(A) C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, $-CO_2C_{1-4}$alkyl, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, $-CO_2H$, and $-CONH_2$ group; or

(B) a C_{1-4}alkyl group substituted with:

a) one or two phenyl groups, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo; or

b) a naphthyl, imidazole, or indole group;

R^6 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

R^7 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

m is 0, 1, 2, 3, 4, or 5;

R^8 is:

(a) -OH, $-NR^aR^b$, $-N(R^c)C(O)R^e$, or $-N(R^c)C(=NR^d)R^e$;

wherein:

R^a is H;

R^b is H or C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, and ketal, $-B(OH)_2$, -SH, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, or $-CO_2C_{1-4}$alkyl group;

R^c is H, C_{1-8}alkyl, C_{3-8}cycloalkyl, branched alkyl, or aryl;

R^d is H or a C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, branched alkyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, halogen, oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CO_2C_{1-4}$alkyl group; and

R^e is H; $-NHR^d$; or a C_{1-12}alkyl, C_{3-8}cycloalkyl, C_{2-12}alkenyl, C_{2-8}alkynyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, oxo, C_{2-4}acetal, C_{2-4}ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, and $-CO_2C_{1-4}$alkyl group; or

(b) a C_{1-12} alkyl substituted with an oxo, acetal, ketal, $-B(OH)_2$, boronic ester, -SH, -OH, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, or $-CO_2C_{1-4}$alkyl group;

R^9 is C_{1-4}alkyl or $-C_{1-2}$alkylene-R^x;

wherein R^x is $-CO_2H$, $-CONH_2$, $-CH_2NHC(O)NH_2$, or $-CH_2NHC(=NH)NH_2$;

R^{10} is:

(1) a C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CONH_2$ group; or

(2) a C_{1-4}alkyl group substituted with one or two phenyl groups, or one naphthyl, imidazole, or indole group, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo;

n is 0 or 1;

p is 0 or 1;

X is C_{1-8}alkylene or C_{2-8}alkenylene, each carbon thereof optionally substituted with -CO_2H, -NH_2, or -$NHC(O)R^y$;

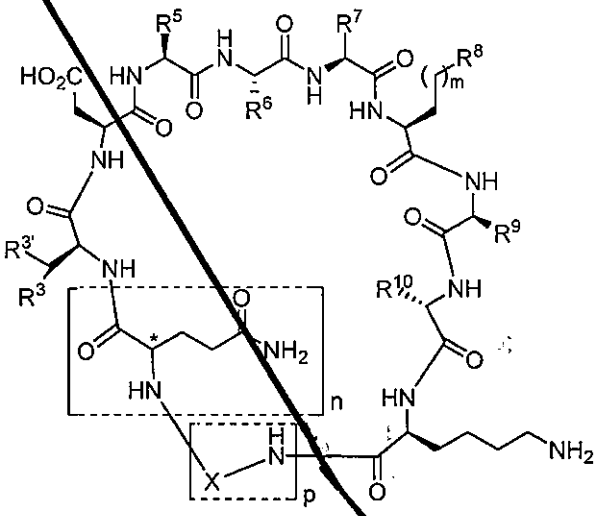
wherein one carbon of said alkylene is optionally replaced with -C(O)NH-, a 5-membered heteroaryl ring, or -S-S-; and

R^y is $-C_{1-4}$alkyl or $-CH(R^z)CO_2H$;

wherein R^z is –H or $-C_{1-4}$alkyl optionally substituted with –OH, -SH, or $-NH_2$;

or a pharmaceutically acceptable salt thereof.

79. The method of claim 73, wherein the antibody or fragment thereof is bound to one or more meditope, wherein the one or more meditope comprises a peptide of Formula (X):



(X)

wherein:

the center marked with "*" is in the "R" or "S" configuration;

R^3 and $R^{3'}$ are each, independently, H or phenyl, optionally substituted with one, two, or three substituents independently selected from C_{1-4}alkyl, -OH, fluoro, chloro, bromo, and iodo;

R^5 is:

(A) C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, -$B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CO_2C_{1-4}alkyl, -CH=CH-CHO, -CH=CH-$C(O)C_{1-4}$alkyl, -CH=CH-CO_2C_{1-4}alkyl, $-CO_2H$, and $-CONH_2$ group; or

(B) a C_{1-4}alkyl group substituted with:

a) one or two phenyl groups, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo; or

b) a naphthyl, imidazole, or indole group;

R^6 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

R^7 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

m is 0, 1, 2, 3, 4, or 5;

R^8 is:

(a) -OH, $-NR^aR^b$, $-N(R^c)C(O)R^c$, or $-N(R^c)C(=NR^d)R^c$;

wherein:

R^a is H;

R^b is H or C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, and ketal,

$-B(OH)_2$, -SH, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, $-CO_2H$, or -CO_2C_{1-4}alkyl group;

R^c is H, C_{1-8}alkyl, C_{3-8}cycloalkyl, branched alkyl, or aryl;

R^d is H or a C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, branched alkyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, halogen, oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, $-CO_2H$, and -CO_2C_{1-4}alkyl group; and

R^e is H; $-NHR^d$; or a C_{1-12}alkyl, C_{3-8}cycloalkyl, C_{2-12}alkenyl, C_{2-8}alkynyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, oxo, C_{2-4}acetal, C_{2-4}ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, and -CO_2C_{1-4}alkyl group; or

(b) a C_{1-12} alkyl substituted with an oxo, acetal, ketal, $-B(OH)_2$, boronic ester, -SH, -OH, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, or -CO_2C_{1-4}alkyl group;

R^9 is C_{1-4}alkyl or $-C_{1-2}$alkylene-R^x;

wherein R^x is -CO_2H, -$CONH_2$, -$CH_2NHC(O)NH_2$, or -$CH_2NHC(=NH)NH_2$;

R^{10} is:

(1) a C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester,

ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, -CO_2C_{1-4}alkyl, -CO_2H, and $-CONH_2$ group; or

(2) a C_{1-4}alkyl group substituted with one or two phenyl groups, or one naphthyl, imidazole, or indole group, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo;

n is 0 or 1;

p is 0 or 1;

X is C_{1-8}alkylene or C_{2-8}alkenylene, each carbon thereof optionally substituted with -CO_2H, -NH_2, or -NHC(O)R^y;

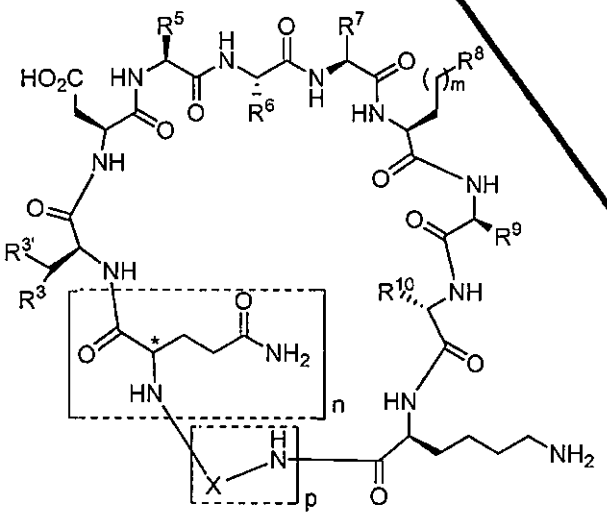
wherein one carbon of said alkylene is optionally replaced with -C(O)NH-, a 5-membered heteroaryl ring, or -S-S-; and

R^y is $-C_{1-4}$alkyl or $-CH(R^z)CO_2H$;

wherein R^z is –H or $-C_{1-4}$alkyl optionally substituted with –OH, -SH, or $-NH_2$;

or a pharmaceutically acceptable salt thereof.

80. The method of claim 73, further comprising then administering to the subject one or more meditope, wherein the one or more meditope comprises a peptide of Formula (X):



(X)

wherein:

the center marked with "*" is in the "R" or "S" configuration;

R^3 and $R^{3'}$ are each, independently, H or phenyl, optionally substituted with one, two, or three substituents independently selected from C_{1-4}alkyl, -OH, fluoro, chloro, bromo, and iodo;

R^5 is:

(A) C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, $-CO_2C_{1-4}$alkyl, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CONH_2$ group; or

(B) a C_{1-4}alkyl group substituted with:

a) one or two phenyl groups, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo; or

b) a naphthyl, imidazole, or indole group;

R^6 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

R^7 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

m is 0, 1, 2, 3, 4, or 5;

R^8 is:

(a) -OH, $-NR^aR^b$, $-N(R^c)C(O)R^e$, or $-N(R^c)C(=NR^d)R^e$;

wherein:

R^a is H;

R^b is H or C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, and ketal;

$-B(OH)_2$, -SH, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, or $-CO_2C_{1-4}$alkyl group;

R^c is H, C_{1-8}alkyl, C_{3-8}cycloalkyl, branched alkyl, or aryl;

R^d is H or a C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, branched alkyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, halogen, oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CO_2C_{1-4}$alkyl group; and

R^e is H; $-NHR^d$; or a C_{1-12}alkyl, C_{3-8}cycloalkyl, C_{2-12}alkenyl, C_{2-8}alkynyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, oxo, C_{2-4}acetal, C_{2-4}ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, and $-CO_2C_{1-4}$alkyl group; or

(b) a C_{1-12} alkyl substituted with an oxo, acetal, ketal, $-B(OH)_2$, boronic ester, -SH, -OH, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-$C(O)C_{1-4}$alkyl, -CH=CH-CO_2C_{1-4}alkyl, or -CO_2C_{1-4}alkyl group;

R^9 is C_{1-4}alkyl or $-C_{1-2}$alkylene-R^x;

wherein R^x is $-CO_2H$, $-CONH_2$, $-CH_2NHC(O)NH_2$, or $-CH_2NHC(=NH)NH_2$;

R^{10} is:

(1) a C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-$C(O)C_{1-4}$alkyl, -CH=CH-CO_2C_{1-4}alkyl, -CO_2C_{1-4}alkyl, $-CO_2H$, and $-CONH_2$ group; or

(2) a C_{1-4}alkyl group substituted with one or two phenyl groups, or one naphthyl, imidazole, or indole group, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo;

n is 0 or 1;

p is 0 or 1;

X is C_{1-8}alkylene or C_{2-8}alkenylene, each carbon thereof optionally substituted with $-CO_2H$, $-NH_2$, or $-NHC(O)R^y$;

wherein one carbon of said alkylene is optionally replaced with -C(O)NH-, a 5-membered heteroaryl ring, or -S-S-; and

R^y is $-C_{1-4}$alkyl or $-CH(R^z)CO_2H$;

wherein R^z is –H or $-C_{1-4}$alkyl optionally substituted with –OH, -SH, or $-NH_2$;

or a pharmaceutically acceptable salt thereof.

81. The method of any of claims 74-80, wherein the one or more meditope comprises a multivalent meditope.

82. The method of any of claims 74-81, wherein the one or more meditope is coupled to a therapeutic agent.

83. The method of claim 82, wherein the therapeutic agent is selected from the group consisting of: drugs, chemotherapeutic agents, therapeutic antibodies, toxins, radioisotopes, enzymes, chelators, boron compounds, photoactive agents, dyes, metals, metal alloys, and nanoparticles.

84. A diagnostic method, comprising:

(a) administering to a subject the antibody or fragment thereof of any of claims 1 to 30; and

(b) detecting binding of the antibody or fragment to an antigen in the subject.

85. A diagnostic method, comprising: administering to a subject a meditope-enabled antibody or fragment thereof and one or more meditope and detecting binding of the antibody or fragment to an antigen in the subject, wherein:

the meditope-enabled antibody or fragment and one or more meditope are administered sequentially or simultaneously; and

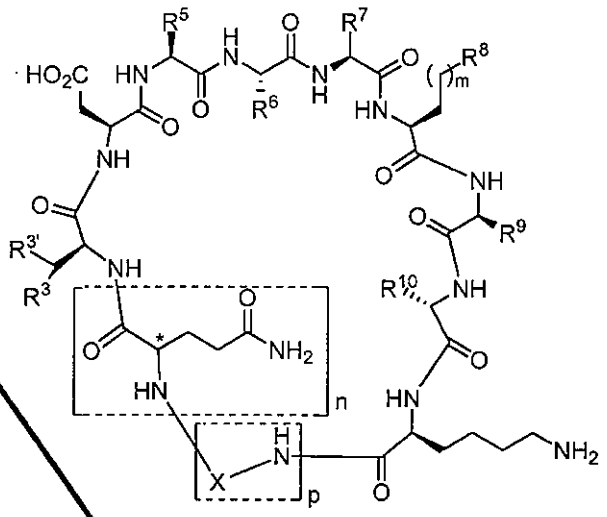
the one or more meditope comprises a peptide that binds to a meditope binding site of the meditope-enabled antibody or fragment.

86. The diagnostic method of claim 85, wherein the meditope-enabled antibody or fragment comprises: a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VL region has an amino acid sequence comprising a threonine, serine, or aspartate at position 40, a residue other than glycine at position 41, and an aspartate or asparagine at position 85, according to Kabat numbering.

87. The method of claim 85 or 86, wherein the meditope-enabled antibody or fragment is bound to the one or more meditope, such that administration of the meditope-enabled antibody and the one or more meditope comprises administering a complex of the meditope-enabled antibody and the meditope.

88. The method of claim 85 or 86, wherein the meditope-enabled antibody is administered prior to administration of the one or more meditope.

89. The method of any of claims 85-88, wherein the peptide is a compound of Formula (X):



(X)

wherein:

the center marked with "*" is in the "R" or "S" configuration;

R^3 and $R^{3'}$ are each, independently, H or phenyl, optionally substituted with one, two, or three substituents independently selected from C_{1-4}alkyl, -OH, fluoro, chloro, bromo, and iodo;

R^5 is:

(A) C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $B(OH)_2$, boronic ester, phosphonate ester, ortho ester, $-CO_2C_{1-4}$alkyl, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CONH_2$ group; or

(B) a C_{1-4}alkyl group substituted with:

a) one or two phenyl groups, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo; or

b) a naphthyl, imidazole, or indole group;

R^6 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

R^7 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

m is 0, 1, 2, 3, 4, or 5;

R^8 is:

(a) -OH, $-NR^aR^b$, $-N(R^c)C(O)R^e$, or $-N(R^c)C(=NR^d)R^e$;

wherein:

R^a is H;

R^b is H or C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, and ketal,

$-B(OH)_2$, -SH, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, $-CO_2H$, or -CO_2C_{1-4}alkyl group;

R^c is H, C_{1-8}alkyl, C_{3-8}cycloalkyl, branched alkyl, or aryl;

R^d is H or a C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, branched alkyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, halogen, oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, $-CO_2H$, and -CO_2C_{1-4}alkyl group; and

R^e is H; $-NHR^d$; or a C_{1-12}alkyl, C_{3-8}cycloalkyl, C_{2-12}alkenyl, C_{2-8}alkynyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, oxo, C_{2-4}acetal, C_{2-4}ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, and -CO_2C_{1-4}alkyl group; or

(b) a C_{1-12} alkyl substituted with an oxo, acetal, ketal, $-B(OH)_2$, boronic ester, -SH, -OH, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, or -CO_2C_{1-4}alkyl group;

R^9 is C_{1-4}alkyl or $-C_{1-2}$alkylene-R^x;

wherein R^x is -CO_2H, -$CONH_2$, -$CH_2NHC(O)NH_2$, or $-CH_2NHC(=NH)NH_2$;

R^{10} is:

(1) a C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, -CO_2C_{1-4}alkyl, -CO_2H, and $-CONH_2$ group; or

(2) a C_{1-4}alkyl group substituted with one or two phenyl groups, or one naphthyl, imidazole, or indole group, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo;

n is 0 or 1;

p is 0 or 1;

X is C_{1-8}alkylene or C_{2-8}alkenylene, each carbon thereof optionally substituted with -CO_2H, -NH_2, or -$NHC(O)R^y$;

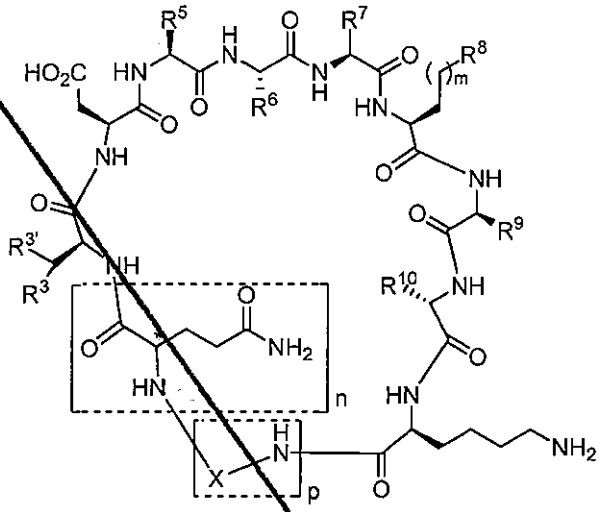
wherein one carbon of said alkylene is optionally replaced with -C(O)NH-, a 5-membered heteroaryl ring, or -S-S-; and

R^y is $-C_{1-4}$alkyl or $-CH(R^z)CO_2H$;

wherein R^z is –H or –C_{1-4}alkyl optionally substituted with –OH, -SH, or –NH_2;

or a pharmaceutically acceptable salt thereof.

90. The method of claim 84, wherein the antibody or fragment is bound to one or more meditope, wherein the one or more the meditope comprises a peptide of Formula (X):



(X)

wherein:

the center marked with "*" is in the "R" or "S" configuration;

R^3 and $R^{3'}$ are each, independently, H or phenyl, optionally substituted with one, two, or three substituents independently selected from C_{1-4}alkyl, -OH, fluoro, chloro, bromo, and iodo;

R^5 is:

(A) C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, -$B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CO_2C_{1-4}alkyl, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, –CO_2H, and –$CONH_2$ group; or

(B) a C_{1-4}alkyl group substituted with:

a) one or two phenyl groups, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo; or

b) a naphthyl, imidazole, or indole group;

R^6 is –C_{1-4}alkyl-OH or –C_{1-4}alkyl-SH;

R^7 is –C_{1-4}alkyl-OH or –C_{1-4}alkyl-SH;

m is 0, 1, 2, 3, 4, or 5;

R^8 is:

(a) -OH, $-NR^aR^b$, $-N(R^c)C(O)R^e$, or $-N(R^c)C(=NR^d)R^e$;

wherein:

R^a is H;

R^b is H or C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, and ketal, $-B(OH)_2$, -SH, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, or $-CO_2C_{1-4}$alkyl group;

R^c is H, C_{1-8}alkyl, C_{3-8}cycloalkyl, branched alkyl, or aryl;

R^d is H or a C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, branched alkyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, halogen, oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CO_2C_{1-4}$alkyl group; and

R^e is H; $-NHR^d$; or a C_{1-12}alkyl, C_{3-8}cycloalkyl, C_{2-12}alkenyl, C_{2-8}alkynyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, oxo, C_{2-4}acetal, C_{2-4}ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, and $-CO_2C_{1-4}$alkyl group; or

(b) a C_{1-12} alkyl substituted with an oxo, acetal, ketal, $-B(OH)_2$, boronic ester, -SH, -OH, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, or $-CO_2C_{1-4}$alkyl group;

R^9 is C_{1-4}alkyl or $-C_{1-2}$alkylene-R^x;

wherein R^x is $-CO_2H$, $-CONH_2$, $-CH_2NHC(O)NH_2$, or $-CH_2NHC(=NH)NH_2$;

R^{10} is:

(1) a C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CONH_2$ group; or

(2) a C_{1-4}alkyl group substituted with one or two phenyl groups, or one naphthyl, imidazole, or indole group, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo;

n is 0 or 1;

p is 0 or 1;

X is C_{1-8}alkylene or C_{2-8}alkenylene, each carbon thereof optionally substituted with $-CO_2H$, $-NH_2$, or $-NHC(O)R^y$;

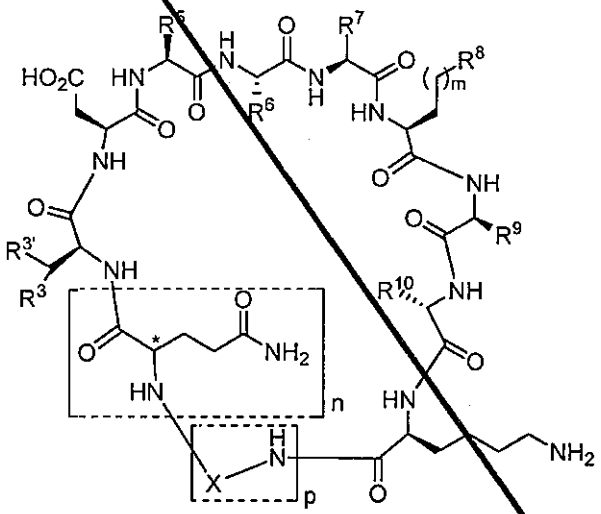
wherein one carbon of said alkylene is optionally replaced with -C(O)NH-, a 5-membered heteroaryl ring, or -S-S-; and

R^y is $-C_{1-4}$alkyl or $-CH(R^z)CO_2H$;

wherein R^z is –H or $-C_{1-4}$alkyl optionally substituted with –OH, -SH, or $-NH_2$;

or a pharmaceutically acceptable salt thereof.

91. The method of claim 84, further comprising a step (c) of administering to the subject one or more meditope, wherein the one or more meditope comprises a peptide of Formula (X):



(X)

wherein:

the center marked with "*" is in the "R" or "S" configuration;

R^3 and $R^{3'}$ are each, independently, H or phenyl, optionally substituted with one, two, or three substituents independently selected from C_{1-4}alkyl, -OH, fluoro, chloro, bromo, and iodo;

R^5 is:

(A) C_{1-8}alkyl, optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, $-CO_2C_{1-4}$alkyl, -CH=CH-CHO, $-CH=CH-C(O)C_{1-4}$alkyl, $-CH=CH-CO_2C_{1-4}$alkyl, $-CO_2H$, and $-CONH_2$ group; or

(B) a C_{1-4}alkyl group substituted with:

a) one or two phenyl groups, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo; or

b) a naphthyl, imidazole, or indole group;

R^6 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

R^7 is $-C_{1-4}$alkyl-OH or $-C_{1-4}$alkyl-SH;

m is 0, 1, 2, 3, 4, or 5;

R^8 is:

(a) -OH, $-NR^aR^b$, $-N(R^c)C(O)R^c$, or $-N(R^c)C(=NR^d)R^e$;

wherein:

R^a is H;

R^b is H or C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, and ketal, $-B(OH)_2$, -SH, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, $-CO_2H$, or -CO_2C_{1-4}alkyl group;

R^c is H, C_{1-8}alkyl, C_{3-8}cycloalkyl, branched alkyl, or aryl;

R^d is H or a C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkyl, branched alkyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, halogen, oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, $-CO_2H$, and -CO_2C_{1-4}alkyl group; and

R^e is H; $-NHR^d$; or a C_{1-12}alkyl, C_{3-8}cycloalkyl, C_{2-12}alkenyl, C_{2-8}alkynyl, or aryl group, each optionally substituted with one or more substituents selected from the group consisting of $-N_3$, $-NH_2$, -OH, -SH, oxo, C_{2-4}acetal, C_{2-4}ketal, $-B(OH)_2$, boronic ester, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, and -CO_2C_{1-4}alkyl group; or

(b) a C_{1-12} alkyl substituted with an oxo, acetal, ketal, $-B(OH)_2$, boronic ester, -SH, -OH, phosphonate ester, ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, or -CO_2C_{1-4}alkyl group;

R^9 is C_{1-4}alkyl or $-C_{1-2}$alkylene-R^x;

wherein R^x is $-CO_2H$, $-CONH_2$, $-CH_2NHC(O)NH_2$, or $-CH_2NHC(=NH)NH_2$;

R^{10} is:

(1) a C_{1-8}alkyl optionally substituted with one or more substituents selected from the group consisting of oxo, acetal, ketal, $-B(OH)_2$, boronic ester, phosphonate ester,

ortho ester, -CH=CH-CHO, -CH=CH-C(O)C_{1-4}alkyl, -CH=CH-CO_2C_{1-4}alkyl, -CO_2C_{1-4}alkyl, -CO_2H, and $-CONH_2$ group; or

(2) a C_{1-4}alkyl group substituted with one or two phenyl groups, or one naphthyl, imidazole, or indole group, wherein each phenyl is optionally substituted with one, two, or three substituents independently selected from -OH, fluoro, chloro, bromo, and iodo;

n is 0 or 1;

p is 0 or 1;

X is C_{1-8}alkylene or C_{2-8}alkenylene, each carbon thereof optionally substituted with -CO_2H, -NH_2, or -NHC(O)R^y;

wherein one carbon of said alkylene is optionally replaced with -C(O)NH-, a 5-membered heteroaryl ring, or -S-S-; and

R^y is $-C_{1-4}$alkyl or $-CH(R^z)CO_2H$;

wherein R^z is –H or $-C_{1-4}$alkyl optionally substituted with –OH, -SH, or $-NH_2$;

or a pharmaceutically acceptable salt thereof.

92. The method of any of claims 85-91, wherein the one or more meditope is a multivalent meditope.

93. The method of any of claims 85-92, wherein the meditope is coupled to a diagnostic agent.

94. The method of claim 93, wherein the diagnostic agent is an imaging agent.

95. The method of claim 94, wherein the imaging agent is selected from the group consisting of: fluorescent substances, luminescent substances, dyes, indicators, and radioactive substances.

96. The method of claim 95, wherein the imaging agent is DOTA.

97. A method of generating a meditope-enabled antibody or fragment thereof, comprising:

effecting one or more amino acid substitutions in a template antibody or fragment thereof, the substitutions including a substitution at position 40, 41, or 85 of the VL region, or position 40 or position 89 of the VH region, according to Kabat numbering,

thereby generating a meditope-enabled antibody or fragment thereof which binds to a meditope that is a peptide having an amino acid sequence selected from the group consisting of the sequences set forth in SEQ ID NO: 1, 2, 16-18, 23, 29, 31, 32, 36, 39, 42, 43, 45, 46, 51, 52, 54, and 55, or a cyclic peptide derived therefrom.

98. The method of claim 97, wherein the template antibody or fragment thereof is selected from the group consisting of: abagovomab, abciximab, adalimumab, adecatumumab, alemtuzumab, altumomab, altumomab pentetate, anatumomab, anatumomab mafenatox, arcitumomab, atlizumab, basiliximab, bectumomab, ectumomab, belimumab, benralizumab, bevacizumab, brentuximab, canakinumab, capromab, capromab pendetide, catumaxomab, certolizumab, clivatuzumab tetraxetan, daclizumab, denosumab, eculizumab, edrecolomab, efalizumab, etaracizumab, ertumaxomab, fanolesomab, Fbta05, fontolizumab, gemtuzumab, girentuximab, golimumab, ibritumomab, igovomab, infliximab, ipilimumab, labetuzumab, mepolizumab, muromonab, muromonab-CD3, natalizumab, necitumumab, nimotuzumab, ofatumumab, omalizumab, oregovomab, palivizumab, panitumumab, ranibizumab, rituximab, satumomab, sulesomab, ibritumomab, ibritumomab tiuxetan, tocilizumab, tositumomab, trastuzumab, Trbs07, ustekinumab, visilizumab, votumumab, zalutumumab, brodalumab anrukinzumab, bapineuzumab, dalotuzumab, demcizumab, ganitumab, inotuzumab, mavrilimumab, moxetumomab pasudotox, rilotumumab, sifalimumab, tanezumab, tralokinumab, tremelimumab, urelumab, B6H12.2, and the antibody produced by the hybridoma 10B5.

99. The method of claim 97 or 98, wherein the meditope-enabled antibody binds to the meditope with a dissociation constant of less than 10 μM, as measured by SPR.

100. The method of claim 99, wherein the dissociation constant is less than 5 μM.

101. The method of claim 100, wherein the dissociation constant is less than 2 μM.

102. The method of any of claims 97-101, wherein the meditope is a peptide of the amino acid sequence set forth in SEQ ID NO: 1 or 2 or cyclic peptide derived therefrom.

103. The method of any of claims 97-102, wherein each of the one or more amino acid substitutions is at a position selected from the group consisting of: position 8 , 9, 10, 38, 39, 40, 41 42, 43, 44, 45, 82, 83, 84, 85, 86, 87, 99, 100, 101, 102, 103, 104, 105, 142, 162, 163, 164, 165, 166, 167, 168, and 173 of the light chain, or 6, 9, 38, 39, 40, 41, 42, 43, 44, 45, 84, 86, 87, 88, 89, 90, 91, 103, 104, 105, 106, 107, 108, 109, 110, 147, 150, 151, 152, 173, 174, 175, 176, 177, 185, 186, and 187 of the heavy chain, according to Kabat numbering.

104. The method of claim 103, wherein the meditope-enabled antibody contains a light chain having I8 , V9 or I9, I10 or L10, Q38, R39, T40, N41 G42, S43, P44, R45, D82, I83, A84, D85, Y86, Y87, G99, A100, G101, T102, K103, L104, E105, R142, S162, V163, T164, E165, Q166, D167, S168, and Y173, according to Kabat numbering and a heavy chain having Q6, P9, R38, Q39, S40, P41, G42, K43, G44, L45, S84, D86, T87, A88, I89, Y90, Y91, W103, G104, Q105, G106, T107, L108, V111, T110, Y147, E150, P151, V152, T173, F174, P175, A176, V177, Y185, S186, and L187, according to Kabat numbering.

105. A polynucleotide, comprising a nucleotide sequence encoding the antibody or fragment thereof of any of claims 1 to 30.

106. A vector, comprising the polynucleotide of claim 105.

107. A library, comprising the vector of claim 106.

108. A screening method, comprising:

(a) expressing antibodies or fragments thereof from the library of claim 107;

(b) selecting an antibody or fragment thereof from among the expressed antibodies or fragments.

109. The screening method of claim 108, wherein the selection is based on a binding affinity, pH tolerance, pH dependence, toxicity, PK, or PD of the selected antibody or fragment thereof.

110. The method of claim 108 or 109, wherein the selection is effected by contacting the antibodies or fragments thereof with a meditope and detecting binding of one or more of the antibodies or fragments thereto.

111. A method of selecting a meditope analog or meditope variant, comprising:

(a) combining a meditope and a meditope-enabled antibody or fragment thereof, whereby the meditope non-covalently binds to the antibody or fragment thereof; and

(b) adding a candidate meditope variant or analog; and

(c) measuring displacement of the meditope by the candidate meditope variant or analog, wherein displacement of the meditope by the candidate variant or analog identifies it as the meditope variant or analog.

112. A method for modifying a meditope, comprising:

effecting one or more amino acid substitutions, insertions, or deletions, to a peptide having the sequence set forth in any of SEQ ID NOs: 1, 2, 16-18, 23, 29, 31, 32, 36, 39, 42, 43, 45, 46, 51, 52, 54, and 55,, or cyclic peptide derived therefrom, thereby altering the pH-dependence of the binding affinity of the peptide for an antibody or fragment of any of claims 1-30.

113. The method of claim 112, wherein the method decreases the binding affinity of the peptide for the antibody or fragment at a lysosomal pH level.

114. The method of claim 112 or 113, wherein the method increases the binding affinity in a hypoxic environment.

115. A method for modifying a meditope-enabled antibody, comprising: effecting one or more modificaitons at position 8 , 9, 10, 38, 39, 40, 41 42, 43, 44, 45, 82, 83, 84, 85, 86, 87, 99, 100, 101, 102, 103, 104, 105, 142, 162, 163, 164, 165, 166, 167, 168, and/or 173 of the light chain, or 6, 9, 38, 39, 40, 41, 42, 43, 44, 45, 84, 86, 87, 88, 89, 90, 91, 103, 104, 105, 106, 107, 108, 109, 110, 147, 150, 151, 152, 173, 174, 175, 176, 177, 185, 186, and/or 187 of the heavy chain, of the meditope-enabled antibody, according to Kabat numbering.

CLAIMS

1. An isolated meditope-enabled antibody or fragment thereof, comprising: a heavy chain variable (VH) region, a heavy chain constant region (CH) or portion thereof, a light chain variable (VL) region comprising a threonine, serine, or aspartate at position 40, a residue other than glycine at position 41, a residue other than phenylalanine at position 83, and an aspartate or asparagine at position 85, according to Kabat numbering, and a light chain constant region (CL) or portion thereof, wherein

the meditope-enabled antibody is a meditope-enabled variant of a human or humanized template antibody, which variant contains a plurality of framework region (FR) modifications, according to Kabat numbering, compared to the template antibody, said FR modifications being only at positions selected from the group consisting of positions 8, 9, 10, 38, 39, 40, 41, 42, 43, 44, 45, 82, 83, 84, 85, 86, 87, 99, 100, 101, 102, 103, 104, and 105 of the light chain of said template antibody, according to Kabat numbering, and positions 6, 9, 38, 39, 40, 41, 42, 43, 44, 45, 84, 86, 87, 88, 89, 90, 91, 103, 104, 105, 106, 107, 108, 109, and 110 of the heavy chain of said template antibody, according to Kabat numbering; and

the meditope-enabled antibody or fragment binds to a meditope comprising a peptide of SEQ ID NO: 1, via a meditope binding site.

2. The meditope-enabled antibody or fragment of claim 1, wherein the VH region comprises a serine or proline at position 40 and an isoleucine at position 89, according to Kabat numbering.

3. The meditope-enabled antibody or fragment of claim 1, wherein the VL region further comprises an isoleucine or leucine at position 10, according to Kabat numbering, and the residue at position 83 is an isoleucine.

4. The meditope-enabled antibody or fragment of claim 1, wherein the VL region further comprises a valine or isoleucine at position 9 and a residue other than glutamine at position 100, according to Kabat numbering.

5. The meditope-enabled antibody or fragment of claim 1, wherein the VL region has a threonine at position 40, an asparagine at position 41, and an aspartate at position 85, according to Kabat numbering.

6. The meditope-enabled antibody or fragment of claim 1, wherein the VH region has a serine at position 40 and an isoleucine at position 89, according to Kabat numbering.

7. The meditope-enabled antibody or fragment of claim 1, wherein the peptide is a cyclic peptide.

8. The meditope-enabled antibody or fragment of claim 1, wherein the meditope binds to the antibody or fragment with a dissociation constant of less than 10 μM, as measured by surface plasmon resonance (SPR).

9. The meditope-enabled antibody or fragment of claim 1, wherein the meditope binds to residues 40, 41, 83, and 85 of the VL region of the meditope-enabled antibody or fragment, according to Kabat numbering, and residues 39, 89, 105, and 108 of the VH region of the meditope-enabled antibody or fragment, according to Kabat numbering.

10. The meditope-enabled antibody or fragment of claim 1, comprising a light chain comprising the amino acid sequence set forth in SEQ ID NO:9 and a heavy chain comprising the amino acid sequence set forth in SEQ ID NO:6.

11. The meditope-enabled antibody or fragment of claim 1, wherein the FR modifications are at positions selected from the group consisting of positions 9, 10, 39, 40, 41, 42, 43, 83, and 85 of the light chain of said template antibody, according to Kabat numbering, and positions 40, 89, and 105 of the heavy chain of said template antibody, according to Kabat numbering.

12. An isolated meditope-enabled antibody or fragment thereof, comprising: a heavy chain variable (VH) region, a heavy chain constant region (CH) or portion thereof, a light chain

variable (VL) region comprising a threonine or serine at position 40, an asparagine at position 41, a residue other than phenylalanine at position 83, and an aspartate or asparagine at position 85, and a light chain constant region (CL) or portion thereof, wherein:

the meditope-enabled antibody is a meditope-enabled variant of a human or humanized template antibody, which variant contains a plurality of framework region (FR) modifications, according to Kabat numbering, compared to the template antibody, said FR modifications being only at positions selected from the group consisting of positions 8, 9, 10, 38, 39, 40, 41, 42, 43, 44, 45, 82, 83, 84, 85, 86, 87, 99, 100, 101, 102, 103, 104, and 105 of the light chain of said template antibody, according to Kabat numbering, and positions 6, 9, 38, 39, 40, 41, 42, 43, 44, 45, 84, 86, 87, 88, 89, 90, 91, 103, 104, 105, 106, 107, 108, 109, and 110 of the heavy chain of said template antibody, according to Kabat numbering; and

the antibody or fragment binds to a meditope comprising a peptide of SEQ ID NO: 1 via a meditope binding site and does not specifically bind to the epitope of EGFR that is specifically bound by cetuximab.

13. The isolated meditope-enabled antibody or fragment of claim 1, wherein the VL region comprises the amino acid sequence of SEQ ID NO: 73.

14. The isolated meditope-enabled antibody or fragment of claim 1, wherein the VH region comprises the amino acid sequence of SEQ ID NO: 74.

15. The isolated meditope-enabled antibody or fragment of claim 1, wherein the VL region comprises the amino acid sequence of SEQ ID NO: 75.

16. The isolated meditope-enabled antibody or fragment of claim 1, wherein:

The VL region has a light chain framework (FR-L)1, an FR-L2, an FR-L3, and an FR-L4 of the light chain sequence set forth as SEQ ID NO: 9; and

the VH region has a heavy chain framework (FR-H)1, an FR-H2, an FR-H3, and an FR-H4 of the heavy chain sequence set forth as SEQ ID NO: 6.

17. An isolated meditope-enabled antibody or fragment thereof, comprising: a heavy chain variable (VH) region, a heavy chain constant region (CH) or portion thereof, a light chain variable (VL) region comprising a valine or isoleucine at position 9, a threonine, serine, or aspartate at position 40, a residue other than glycine at position 41, a residue other than phenylalanine at position 83, and an aspartate or asparagine at position 85, according to Kabat numbering, and a light chain constant region (CL) or portion thereof, wherein:

the meditope-enabled antibody is a meditope-enabled variant of a template antibody, wherein the template antibody is a human or humanized antibody and the meditope-enabled antibody contains a plurality of framework region (FR) modifications, according to Kabat numbering, compared to the template antibody, said FR modifications being only at positions selected from the group consisting of positions 8, 9, 10, 38, 39, 40, 41, 42, 43, 44, 45, 82, 83, 84, 85, 86, 87, 99, 100, 101, 102, 103, 104, and 105 of the light chain of said template antibody, according to Kabat numbering, and positions 6, 9, 38, 39, 40, 41, 42, 43, 44, 45, 84, 86, 87, 88, 89, 90, 91, 103, 104, 105, 106, 107, 108, 109, and 110 of the heavy chain of said template antibody, according to Kabat numbering; and

the meditope-enabled antibody or fragment binds to a meditope comprising a peptide of SEQ ID NO: 1, via a meditope binding site and does not specifically bind to the epitope of EGFR that is specifically bound by cetuximab.

18. The meditope-enabled antibody or fragment thereof of claim 1, wherein:

the meditope-enabled antibody or fragment competes for antigen binding with, binds to the same epitope as an antibody or antigen-binding fragment thereof selected from the group consisting of abagovomab, abciximab, adalimumab, adecatumumab, alemtuzumab, altumomab, altumomab pentetate, anatumomab, anatumomab mafenatox, arcitumomab, atlizumab, basiliximab, bectumomab, ectumomab, belimumab, benralizumab, bevacizumab, brentuximab, canakinumab, capromab, capromab pendetide, catumaxomab, certolizumab, clivatuzumab tetraxetan, daclizumab, denosumab, eculizumab, edrecolomab, efalizumab, etaracizumab, ertumaxomab, fanolesomab, ~~Fbta05,~~ fontolizumab, gemtuzumab, girentuximab, golimumab, ibritumomab, igovomab, infliximab, ipilimumab, labetuzumab, mepolizumab, muromonab, muromonab-CD3, natalizumab, necitumumab nimotuzumab, ofatumumab, omalizumab, oregovomab, palivizumab, panitumumab, ranibizumab, rituximab, satumomab, sulesomab, ibritumomab, ibritumomab tiuxetan, tocilizumab, tositumomab, trastuzumab, Trbs07, ustekinumab, visilizumab, votumumab, zalutumumab, brodalumab, anrukinzumab, bapineuzumab, dalotuzumab, demcizumab, ganitumab, inotuzumab,

mavrilimumab, moxetumomab pasudotox, rilotumumab, sifalimumab, tanezumab, tralokinumab, tremelimumab, the antibody produced by the hybridoma 10B5, and urelumab; or

the meditope-enabled antibody or fragment specifically binds to an antigen selected from the group consisting of: CA-125, glycoprotein (GP) IIb/IIIa receptor, TNF-alpha, CD52, TAG-72, Carcinoembryonic antigen (CEA), interleukin-6 receptor (IL-6R), IL-2, interleukin-2 receptor a-chain (CD25), CD22, B-cell activating factor, interleukin-5 receptor (CD125), VEGF, VEGF-A, CD30, IL-1beta, prostate specific membrane antigen (PSMA), CD3, EpCAM, EGF receptor (EGFR), MUC1, human interleukin-2 receptor, Tac, RANK ligand, C5 or other complement proteins, CD11a, alpha-v beta-3 integrin, HER2, neu, CD15, CD20, Interferon gamma, CD33, CA-IX, CTLA-4, IL-5, CD3 epsilon, CAM, Alpha-4-integrin, IgE, IgE Fc region, an RSV antigen, F (or fusion) protein of respiratory syncytial virus (RSV), NCA-90 (granulocyte cell antigen), IL-6, GD2, GD3, IL-12, IL-23, IL-17, CTAA16.88, beta-amyloid, IGF-1 receptor (IGF-1R), delta-like ligand 4 (DLL4), alpha subunit of granulocyte macrophage colony stimulating factor receptor, hepatocyte growth factor, IFN-alpha, nerve growth factor, IL-13, CD326, PD-L1, CD47, and CD137.

19. An isolated meditope-enabled antibody or fragment thereof, comprising:-a heavy chain variable (VH) region, a heavy chain constant region (CH) or portion thereof, a light chain variable (VL) region comprising an isoleucine or leucine at position 10, a threonine, serine, or aspartate at position 40, a residue other than glycine at position 41, an isoleucine at position 83, and an aspartate or asparagine at position 85, according to Kabat numbering, and a light chain constant region (CL) or portion thereof, wherein:

the meditope-enabled antibody is a meditope-enabled variant of a template antibody, wherein the template is a human or humanized antibody and the meditope-enabled antibody contains a plurality of framework region (FR) modifications, according to Kabat numbering, compared to the template antibody, said FR modifications being only at positions selected from the group consisting of positions 8, 9, 10, 38, 39, 40, 41, 42, 43, 44, 45, 82, 83, 84, 85, 86, 87, 99, 100, 101, 102, 103, 104, and 105 of the light chain of said template antibody, according to Kabat numbering, and positions 6, 9, 38, 39, 40, 41, 42, 43, 44, 45, 84, 86, 87, 88, 89, 90, 91, 103, 104, 105, 106, 107, 108, 109, and 110 of the heavy chain of said template antibody, according to Kabat numbering; and

the meditope-enabled antibody or fragment binds to a peptide meditope comprising SEQ ID NO: 1 via a meditope binding site and does not specifically bind to the epitope of EGFR that is specifically bound by cetuximab.

20. The isolated meditope-enabled antibody of claim 1, wherein the VL region comprises an isoleucine or leucine at position 10, a threonine at position 40, an asparagine at position 41, an isoleucine at position 83, and an aspartate at position 85, according to Kabat numbering; and the VH region comprises an isoleucine at position 89, according to Kabat numbering.

21. The isolated meditope-enabled antibody of claim 1, wherein the VL region comprises an isoleucine or valine at position 9, an isoleucine or leucine at position 10, an arginine at position 39, a threonine at position 40, an asparagine at position 41, a glycine at position 42, a serine at position 43, an isoleucine at position 83, an aspartate at position 85, and an alanine at position 100, according to Kabat numbering; and the VH region comprises a serine at position 40 and an isoleucine at position 89, according to Kabat numbering.

22. The meditope-enabled antibody or fragment thereof of claim 1, wherein the VH region comprises an isoleucine, tyrosine, methionine, phenylalanine, or tryptophan at position 89, according to Kabat numbering.